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2-Iodoxybenzoic acid (IBX): an efficient hypervalent iodine reagent

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Dedicated with deep respect and love to Professor Moses Lee, Dean of Natural and Applied Sciences, Hope College, MI, USA

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1. Introduction

In the past decade, the chemistry of hypervalent iodine compounds (λ^3- and λ^5-iodanes) has experienced an unprecedented growth.[1] Large atomic size and low ionization potential compared to other halogens make iodine a suitable candidate for forming polycoordinate compounds. A broad variety of polyvalent iodine reagents have been prepared for new, highly useful synthetic transformations. These multivalent iodine reagents are now used extensively in organic synthesis as a mild, safe, and economic alternative to heavy-metal reagents such as lead(IV), thallium(III), mercury(II), chromium(VI), etc. Hypervalent iodine reagents based on the heterocyclic system of benziodoxole represent an especially important class of iodanes with rich and synthetically useful chemistry. In particular, the heterocyclic λ^5-iodane, 1-hydroxy-1-oxo-1*H*-1λ^5-benzo[*d*][1,2]iodoxol-3-one, commonly referred as 2-iodoxybenzoic acid (IBX), finds widespread applications in organic synthesis as a highly efficient and mild oxidant that can be used for the selective oxidation of primary and secondary alcohols and for a variety of other important oxidative transformations. Structure (**1a**) gives the correct representation for the actual structure of IBX, while (**1b**) represents its tautomeric form (Fig. 1). This has been confirmed by X-ray crystallographic analysis, which also indicates a polymeric structure for IBX, due to an extended linkage of intermolecular secondary I···O bonding interactions.[2] The polymeric structure of IBX renders it essentially insoluble in all nonreactive media.

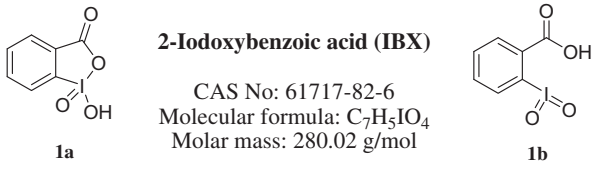
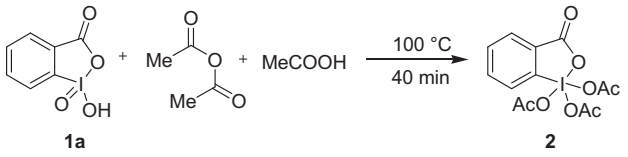


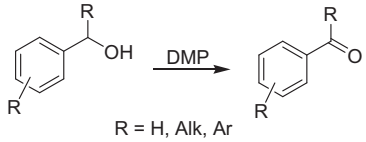
Figure 1. Structure of 2-iodoxybenzoic acid (IBX).

IBX was discovered by Hartmann and Meyer in 1893.[3] Athough known since 1893, this valuable reagent was forgotten for almost a century, probably due to its remarkable insolubility in most organic solvents and water and its potentially explosive nature. Several research groups have tried to improve IBX by structurally modifying it or by developing polymer-supported analogues. The most important derivative of IBX is the commercially available triacetate (**2**), commonly known as Dess–Martin periodinane. In 1983, Dess and Martin reported that IBX could be transformed into the far more soluble periodinane (**2**), 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one, by heating it in an acetic anhydride–acetic acid mixture (Scheme 1).[4]



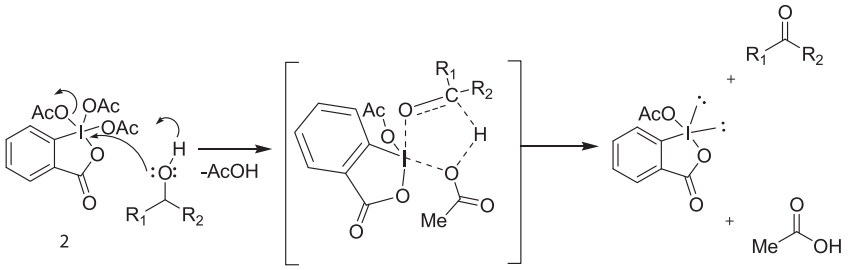
Scheme 1. Synthesis of Dess–Martin periodinane (DMP).

This more soluble derivative of IBX, usually abbreviated as DMP, became very popular in organic synthesis, as one of the most convenient reagents available for the smooth and selective transformation of alcohols into carbonyl compounds (Scheme 2).[5] DMP has found wide utility as a selective oxidant in sensitive, highly functionalized intermediates commonly encountered in the synthesis of natural products and related complex molecules.[5f,h–j] In the case of epimerization-sensitive substrates, DMP allows clean oxidation with virtually no loss of epimeric excess.[5k] DMP has also been used for the conversion of primary and secondary alcohol groups in organotrifluoroborates into an aldehyde or ketone, while retaining the valuable carbon–boron bond.[6]



Scheme 2.

DMP has several advantages over other commonly employed oxidizing agents such as chromium(VI)-based reagents and DMSO-based oxidation reagents including nearly ideal stoichiometry, mild, non-acidic or mildly acidic reaction conditions, shorter reaction times, relative ease in the preparation and storage of the reagent, simplified workups with easy removal of the by-products of oxidation, ease of safe disposal of residues, and lower toxicity of the by-products [relative to chromium(VI) reagents, in particular]. Scheme 3 depicts the mechanism of oxidation of alcohols by DMP. DMP is currently commercially available from Sigma–Aldrich and other chemical companies. The synthetic applications of DMP are highlighted in some reviews.[7] DMP is, however, moisture-sensitive, which imposes certain restrictions on the storage and handling of this useful reagent.

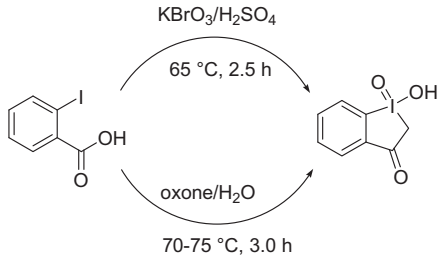


Scheme 3. Mechanism of oxidation of alcohols by Dess–Martin periodinane (DMP).

Since the innovative work carried out by Dess and Martin, modern explorations into the chemistry of hypervalent iodine(V) compounds have rapidly become the subject of burgeoning interest. In 1994, Frigero and Santagostino[8] reported that IBX, which is a cheaper and much more stable alternative to DMP, could also be utilized in the oxidation of alcohols in DMSO. Since then, IBX, which was used as a precursor of DMP, has seen a dramatic increase in its use as a reagent. IBX has proved to have a unique set of properties, which can be appropriately exploited to manipulate the course of a reaction. A number of literature reports have revealed IBX as a reagent capable of: (1) oxidizing primary and secondary alcohols to the corresponding aldehydes and ketones, (2) oxidizing oximes and tosylhydrazones to the corresponding carbonyl compounds, (3) affecting the oxidation of benzylic sites, (4) facilitating the cyclization of functionalized anilide systems to their heterocyclic counterparts, (5) dehydrogenating aldehydes, ketones, and silyl enol ethers to their corresponding α,β-unsaturated carbonyl compounds, and (6) oxidizing phenols to *o*-quinones. In this review article, we present a full account of the discovery, preparation, scope, and development of IBX as a versatile oxidation reagent and highlight its significance in synthetic chemistry.

2. Preparation of IBX

IBX can be prepared by the oxidation of 2-iodobenzoic acid with potassium bromate in 0.73 M sulfuric acid, as reported by Dess and Martin.[4,5a] Synthetic methods for the preparation of IBX from 2-iodo-[9] or 2-iodosobenzoic[10] acid have been described, but these procedures deliver a reagent of poor quality that requires tedious purification. In the light of these studies, the procedure reported by Dess and Martin gives optimal yields and somewhat better purity, and represent the state-of-the-art procedure for the synthesis of IBX. An improved procedure for the preparation of IBX using potassium bromate ($KBrO_3$) and sulfuric acid was reported by Boeckman et al. (Scheme 4).[11] However, these $KBrO_3$-based oxidation methods are unappealing for the user as $KBrO_3$ is classified as a carcinogen (R-45) in the international classification of substance toxicity, and obnoxious bromine vapors are copiously evolved (62 g/mol of IBX) from the reaction mixture, causing personal and environmental hazards. In addition, incomplete oxidation of 2-iodobenzoic acid cannot be totally avoided. The purity of the reagent varies between 90 and 95%, the major contaminants being 2-iodobenzoic acid (1–3%) and 2-iodosobenzoic acid (5–10%).



Scheme 4. Preparation of IBX.

A superior protocol for the oxidation of 2-iodobenzoic acid to IBX was developed by Santagostino et al.[12] (Scheme 4). Their method is extremely simple to perform and requires the commercially available, inexpensive oxone [$2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$] and water as solvent, thus eliminating the risks posed by dangerous contaminants like $KBrO_3$ or bromine. The procedure involves the addition of 2-iodobenzoic acid to the solution of oxone (1.3 equiv) in water (0.45 M solution) and stirring the reaction mixture at 70–75 °C for 3 h. IBX can be recovered easily from the reaction mixture in high yield (79–81%) by cooling, filtering, and washing the crystals with water and acetone. Crystalline IBX with purity ≥95% can be obtained consistently by this method. Moreover, if the reaction is performed at a slightly higher dilution at 70 °C using excess oxone (3.0 equiv), a clear solution is obtained after 1 h, from which IBX crystallizes upon cooling the reaction mixture in 77% yield and ≥99% purity. Environmentally safe sulfate salts are the only by-products formed in this method.

3. Solubility and acidity of IBX

IBX is virtually insoluble in organic solvents like ethanol, acetone, acetonitrile, chloroform, methylene dichloride, THF, and sulfolane. The insolubility of IBX in most organic solvents may be attributed to its polymeric nature. However, it dissolves readily in DMSO and clear solutions of up to 1.5 M in DMSO are easily obtained. Therefore, almost all organic transformations using IBX are carried out in DMSO. Very often, various co-solvents such as THF, acetone, toluene or fluorobenzene are used for the oxidation of compounds, which do not dissolve readily in DMSO or when a reaction temperature of below 15 °C is required. DMF can be a convenient alternative to DMSO as a solvent.[13] IBX dissolves slowly in DMF. The suspension of crystalline IBX in DMF (30 mg/ml) dissolves partially (10 mg/ml in supernatant) on stirring for 3 h at 23 °C and forms a clear solution after 12 h with an IBX concentration of 0.1 mol/dm^3. IBX has a measurable, but low, solubility in 2-methyl-2-propanol (*tert*-butanol).[14] *tert*-Butanol can be an effective solvent for IBX oxidation of primary alcohols to the corresponding aldehydes, particularly where a hydroxylic solvent is necessary for dissolution of the substrate.

The chemical name, *o*-iodoxybenzoic acid, implies that this molecule must display a certain level of Brønsted acidity. Williams et al.[15] investigated the acidity of IBX in both aqueous media and DMSO. Solution-phase acidity determinations revealed that an aqueous pK_a value for IBX is 2.40. The pK_a value of IBX in DMSO was found to be 6.65. These calculations suggest that IBX has an acidity in water similar to that of 2-nitrobenzoic acid, (pK_a in water=2.18) and an acidity in DMSO similar to that of dichloroacetic acid (pK_a in DMSO=6.4).

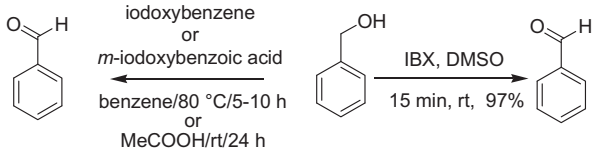
4. Handling and storage of IBX

IBX was reported to be explosive under excessive heating (>200 °C) or impact.[16] Later, it was found that the sample in question was contaminated with residual bromine, which is likely to have contributed significantly to this negative feature.[5a] However, heating this reagent above 200 °C is still not recommended, as it decomposes vigorously with a flame and a bang. IBX can be stored at 25 °C for an excess of six months with no significant degradation, provided light is excluded from the container. In contrast to Dess–Martin periodinane, it is stable to moisture, and oxidation can be performed in an open flask without any particular precautions such as an inert atmosphere and dry solvents.

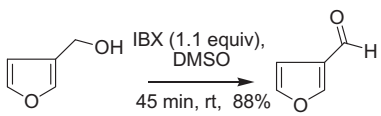
5. Synthetic applications of IBX

5.1. Oxidation of alcohols to carbonyl compounds using IBX

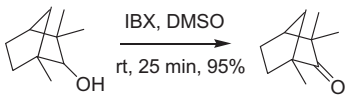
The oxidation of an alcoholic group to a carbonyl moiety is a central reaction in organic chemistry. Several methods are available for this transformation, covering a variety of experimental conditions. However, this reaction, due to its pivotal role in synthetic chemistry, still continues to receive great attention, in order to discover new oxidants with peculiar features.[17] A number of reagents, including hypervalent iodines, have been reported to effect this transformation smoothly. Among them, IBX has been prolifically explored as a mild and chemoselective reagent for alcohol oxidation. The facile oxidation of primary and secondary alcohols to the corresponding carbonyl compounds is one of the prominent features of IBX. The oxidant properties of IBX are markedly different from those of its close analogues, iodoxybenzene and *m*-iodoxybenzoic acid.[18] Thus, while the latter analogues oxidize benzyl alcohols to benzaldehydes only at high temperature (benzene/80 °C/5–10 h) or in acetic acid (rt/24 h), IBX in DMSO oxidizes benzyl alcohol to benzaldehyde in 15 min at room temperature (Scheme 5).[8] Primary alcohols are oxidized by IBX in DMSO to the corresponding aldehydes at room temperature without overoxidation to the acids (Scheme 6). Sterically hindered alcohols, too, are easily oxidized at room temperature in high yields (Scheme 7).



Scheme 5.

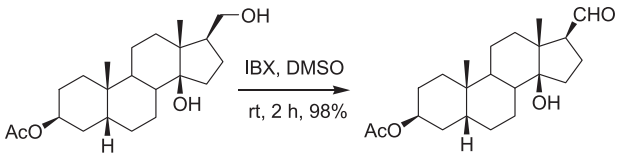


Scheme 6.

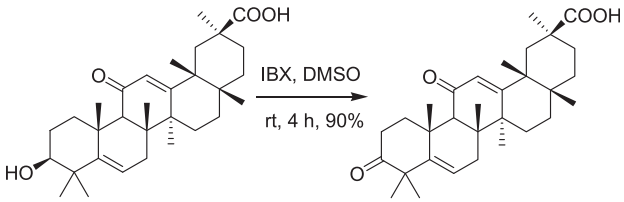


Scheme 7.

The chiral primary alcohols are oxidized without epimerization (Scheme 8) and double bonds, both conjugated and isolated, remain unaffected by IBX in DMSO (Scheme 9).

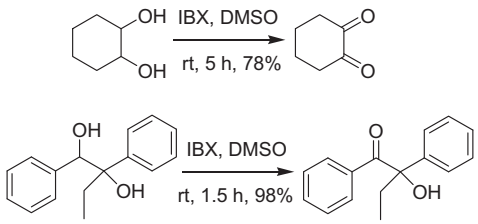


Scheme 8.



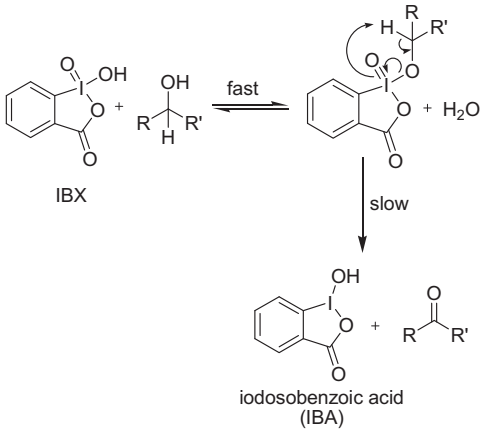
Scheme 9.

The oxidation of 1,2-diols to α-ketols or α-diketones represents a transformation that always has to overcome the problem of the oxidative cleavage of the glycol C–C bond and only a few methods are available for such reactions.[19] Interestingly, Frigerio and Santagostino[8] reported that IBX, in contrast to DMP and iodoxybenzene derivatives, smoothly oxidizes 1,2-glycols to α-ketols or α-diketones without cleaving the glycol C–C bond (Scheme 10).



Scheme 10.

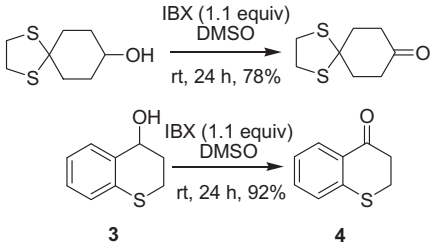
A possible mechanism for the oxidation of alcohols by IBX involves the equilibrium shown in Scheme 11.



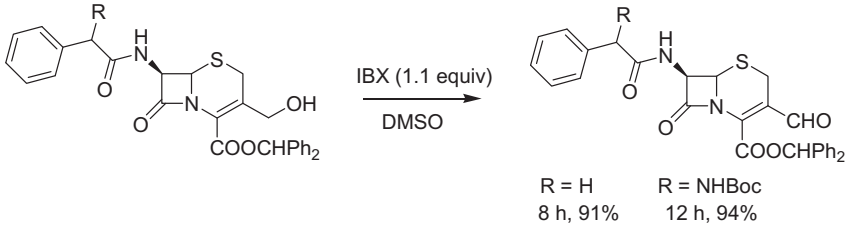
Scheme 11. Mechanism for the oxidation of alcohols by IBX.

IBX in DMSO is a mild oxidant, and a variety of functional groups are compatible with its use. In particular, the chemoselective oxidation of alcohols in the presence of thioethers and amines is noteworthy. Frigerio et al.[20] reported that alcohols are cleanly oxidized by IBX in the presence of thioethers and 1,3-dithiolane (Scheme 12). In the case of thiochroman-4-ol (**3**), even if the oxidation conditions were forced using 10.0 equiv of IBX (ambient

temperature, 120 h), the only reaction product obtained was thiochroman-4-one (**4**), with no evidence of sulfoxide or sulfone by-products. The 3-hydroxymethyl group of cephem derivatives can also be easily oxidized to aldehyde without overoxidation and/or double-bond isomerization (Scheme 13).[20]

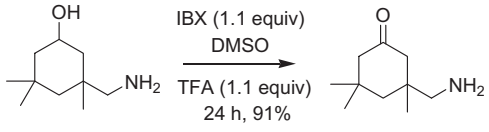


Scheme 12.

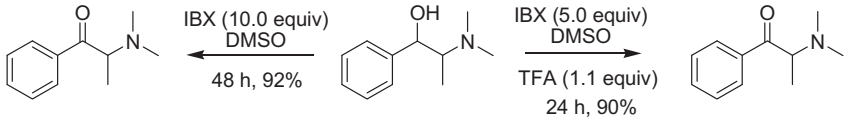


Scheme 13.

IBX can be successfully used to oxidize amino alcohols to amino carbonyl compounds. The oxidation of amino alcohols is a general synthetic problem that usually requires protection of the amine as a nonbasic derivative.[21] The most widely used methodology for the oxidation of amino alcohols is the Swern oxidation that requires anhydrous conditions and low temperatures. Frigerio et al.[20] showed that IBX oxidizes alcohols selectively in the presence of primary, secondary, and tertiary amines in good yields. Primary and secondary amines must be temporarily protected in situ with acid (e.g., TFA, 1–1.5 equiv), otherwise low yields of the desired amino carbonyl compounds are obtained (Scheme 14). Tertiary amines do not require protection during the oxidation reaction, although the presence of TFA helps to speed up the oxidation (Scheme 15).

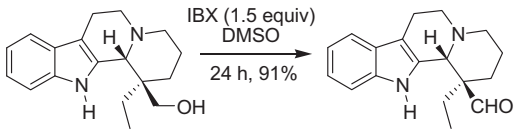


Scheme 14.

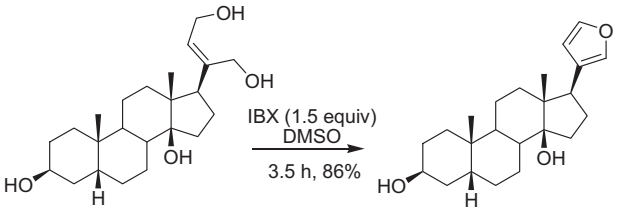


Scheme 15.

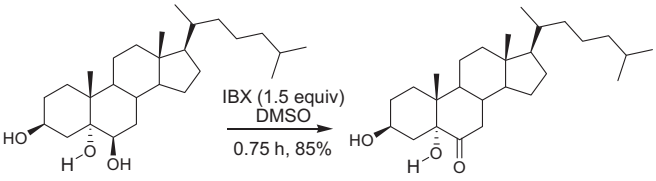
Indoles, in particular those with an unsubstituted –NH group, are known to be unstable in the presence of oxidizing agents, but oxidation of indolyl alcohols with IBX requires no protection of the indol-NH group (Scheme 16). IBX also shows selectivity in the oxidation of polyalcohols [primary allylic vs secondary alcohol (Scheme 17); *trans*-1,2-diol vs secondary alcohol (Scheme 18)].[20]



Scheme 16.



Scheme 17.

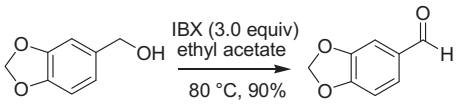


Scheme 18.

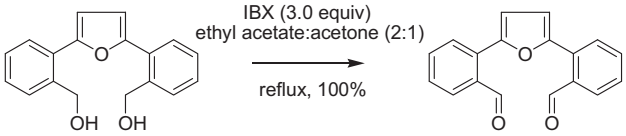
Although many functional groups like carboxylic acids, esters, carboxamides and both conjugated and isolated double bonds are compatible with IBX, phenols and anilines do not withstand the presence of IBX (complex and dark-colored reaction mixtures are obtained).

Finney and More[22] found that, at elevated temperatures, IBX is sufficiently soluble in most organic solvents to permit the clean oxidation of alcohols to the corresponding aldehydes and ketones. They proposed ethyl acetate and dichloroethane as the solvents of choice because they are inert and all by-products are insoluble at room temperature, such that no purification is required beyond simple filtration. Reactions in several other solvents like chloroform, acetone, acetonitrile, and benzene provided higher yields and shorter reaction times, but required chromatographic purification (Schemes 19–22).

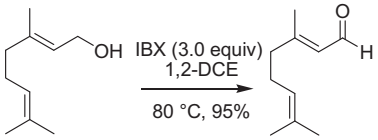
IBX in THF, however, leads to solvent oxidation as the primary reaction, affording only small amounts of the desired aldehyde



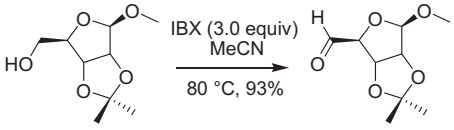
Scheme 19.



Scheme 20.



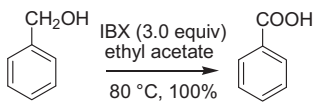
Scheme 21.



Scheme 22.

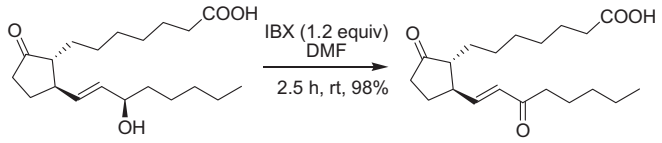
(Nicolau et al.[56] suggested that IBX forms a co-ordination complex with THF, which induces a single-electron-transfer (SET) mechanism to furnish complex oxidative transformations). Toluene is also not a suitable solvent, as it leads to intractable dark-colored reactions (probably because IBX brings about oxidation of the benzylic positions[61,63]). The important feature of oxidation reactions using IBX is that the by-products isolated by filtration contain iodosylbenzoic acid (IBA) as a primary component, which can be re-oxidized to the active IBX using aqueous oxone. Finney and More[22] reported that the regenerated IBX was indistinguishable from IBX prepared freshly from *o*-iodobenzoic acid. Thus, the insolubility of IBX, previously regarded as problematic, was exploited to provide all of the advantages of resin-bound IBX equivalents without requiring sophisticated reagent preparation.

It should be noted that virtually every alcohol investigated by Finney and More[22] in their study was oxidized to the corresponding carbonyl compound in >90% yield, except benzyl alcohol, which was quantitatively oxidized to benzoic acid when treated with IBX in ethyl acetate under reflux conditions (Scheme 23).



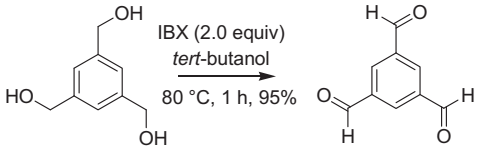
Scheme 23.

Pivnitsky et al.[13] investigated IBX-mediated oxidations in DMF, as they found that IBX dissolves slowly in DMF at room temperature. The reactions in DMF as a solvent proceeded practically identically to those in DMSO (Scheme 24). DMF possesses a significant advantage, due to its much greater volatility (bp 153 °C/760 Torr, 50 °C/18 Torr, 25 °C/3.7 Torr) than DMSO. Therefore, the isolation of high-boiling products of the oxidations in DMF can be performed without aqueous treatment, extraction, and chromatography and, merely by filtration (to remove IBA) and filtrate evaporation at <50 °C under vacuum, analytically pure products can be obtained in nearly quantitative yields. At the same time, without additional manipulations, more than 90% of the formed IBA, which could be used in an economic synthesis of IBX, can be isolated.



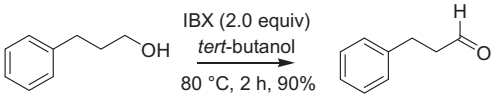
Scheme 24.

Very recently, Arman[14] reported that 2-methyl-2-propanol (*tert*-butanol) can be used as an effective solvent for IBX oxidation of primary alcohols to the corresponding aldehydes. A mixture of 1,3,5-tris-(hydroxymethyl)benzene and IBX (2.0 equiv) in *tert*-butanol, when stirred and heated to reflux for about 1 h, gave the desired trialdehyde in 95% yield (Scheme 25). The same reaction required more than 10 h for completion when performed at room temperature.



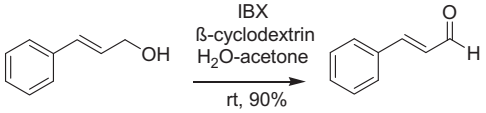
Scheme 25.

Arman[14] carried out the oxidation of various aliphatic, allylic, and benzylic alcohols including 2-phenylethanol (Scheme 26) to the corresponding aldehydes by using IBX in *tert*-butanol.



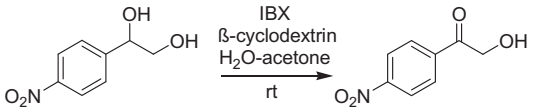
Scheme 26.

An elegant and simple methodology for the IBX-mediated oxidation of a variety of alcohols to the corresponding carbonyl compounds catalyzed by β-cyclodextrin was presented by Rama Rao et al.[23] They showed that when the alcohol dissolved in acetone is added to an aqueous solution of β-cyclodextrin followed by IBX, at room temperature, then, after 12 h, the corresponding carbonyl compound is obtained in impressive yields ranging from 85 to 98% without overoxidation to the acids (Scheme 27). The alcohol is smoothly oxidized, even in the presence of other functionalities such as methoxy, methylenedioxy, nitro, hydroxyl, and alkene double bonds, using this methodology. The protocol is highly selective for vicinal diols and oxidizes only the secondary hydroxy group α to the benzene ring (Scheme 28).



Scheme 27.

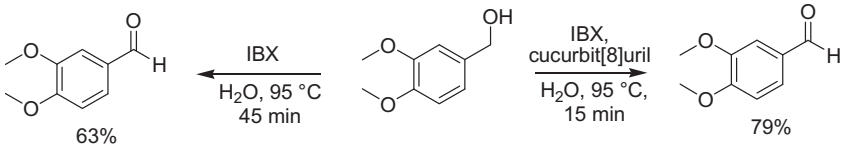
Rama Rao et al.[23] reported that arylcarbinols gave comparatively better yields than the aliphatic alcohols. β-Cyclodextrin was used only in catalytic amounts (0.1 mmol/mmol alcohol) and was recovered and re-used. The reactions did not take place in the absence of cyclodextrin. Cyclodextrins (CDs), which are cyclic oligosaccharides, exert



Scheme 28.

micro-environmental effects, leading to selective reactions. They catalyze reactions by supramolecular catalysis through noncovalent bonding, as seen in enzymes.

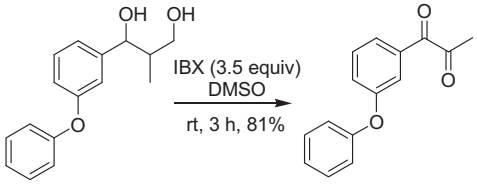
Another example of IBX-mediated oxidation of alcohols to the corresponding aldehydes or ketones under supramolecular catalysis was reported by Hang et al.,[24] who investigated the heterogeneous catalytic oxidation of veratryl alcohol to veratraldehyde with IBX in the presence of cucurbit[8]uril (Q[8]). The rapid transformation of veratryl alcohol to the corresponding aldehyde in high yield was observed under the catalytic effect of cucurbit[8]uril (Scheme 29). The optimized molar ratio of Q[8], substrate, and IBX was found to be 0.1:1:1.



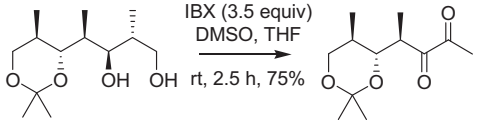
Scheme 29.

Hang et al.[24] also reported that other benzylic alcohols such as benzyl alcohol and 3-methoxybenzyl alcohol exhibited a similar enhanced transformation to the corresponding aldehyde under IBX-mediated supramolecular oxidation by cucurbit[8]uril.

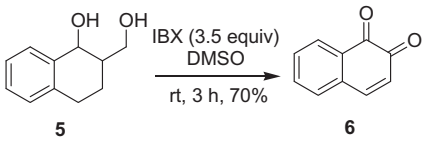
1,3-Diols undergo direct conversion into 1,2-diketones by oxidative cleavage of the C–C bond when treated with 3.5 equiv of IBX in DMSO at ambient temperature. Yadav et al.[25] showed that 1,3-diol systems with aliphatic as well as aromatic substituents can be oxidized with 3.5 equiv of IBX to obtain the respective 1,2-diketones in good yields with a reasonably short reaction time (Scheme 30). A variety of substrates such as simple aliphatic 1,3-diols, sterically hindered 1,3-diols, and 1,3-diols substituted with aryl groups containing electron-withdrawing or -donating substituents were oxidized to the corresponding 1,2-diketones using this mild and efficient protocol. The protocol is especially useful in obtaining 1,2-diketones in the presence of acid- and base-sensitive protecting groups (Scheme 31). A cyclic 1,3-diol (**5**), however, underwent dehydrogenation to afford the unsaturated diketone (**6**) in 70% yield under similar reaction conditions (Scheme 32).[25]



Scheme 30.



Scheme 31.



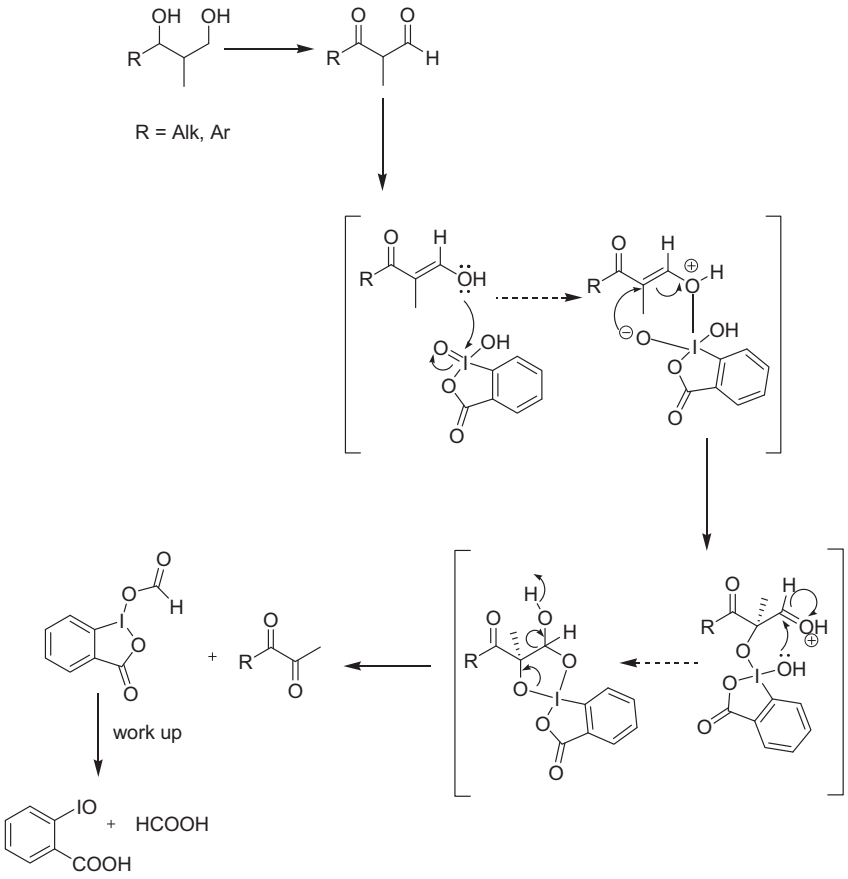
Scheme 32.

The reaction proceeds via the formation of an α-formyl ketone, as shown in the plausible mechanism suggested by Yadav et al.[25] (Scheme 33).

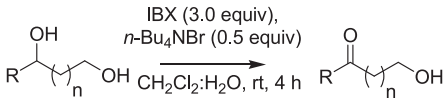
Kuhakarn et al.[26] reported the application of IBX for the selective oxidation of a secondary hydroxyl group in the presence of a primary hydroxyl within the same molecule. They showed that diols containing both the primary and the secondary hydroxyl functional groups undergo chemoselective oxidation to the hydroxyl ketones when treated with 3.0 equiv of IBX and 0.5 equiv of tetrabutylammonium bromide (n-Bu_4NBr) in the H_2O–CH_2Cl_2 (1:1 v/v) solvent system at room temperature. The reaction provides ketones with the primary alcohol untouched in moderate-to-good yields (Scheme 34). A variety of diols undergo smooth oxidation under similar reaction conditions. However, in some cases, the dicarbonyl compounds as well as five- or six-membered ring lactones are also formed as minor products (Table 1).

This type of selective transformation of secondary hydroxyl groups to ketones has been a challenging target for synthetic chemists, since it offers an alternative to synthesis via selective protection and deprotection. Although many oxidizing reagents are known to promote selective oxidation of secondary alcohols in the presence of primary alcohols, this IBX-mediated oxidation protocol is superior, as it does not involve moisture-sensitive and environmentally unfriendly agents. Kuhakarn et al.[26] reported that the phase-transfer catalyst (PTC) plays a very important role in this chemoselective oxidation. For example, the oxidation of 2,2,4-trimethyl-1,3-pentanediol in the absence of n-Bu_4NBr gave all of the possible products, i.e., hydroxyketone (31%), hydroxyaldehyde (4%), dicarbonyl (2%), and recovered starting material (37%) (Scheme 35). The oxidation under standard IBX reaction conditions in DMSO and ethyl acetate gave the corresponding dicarbonyl compound in 77 and 86% yields, respectively (Scheme 35). The chemoselective transformation of 2,2,4-trimethyl-1,3-pentanediol to the corresponding hydroxyketone exclusively took place only in the presence of PTC in the bi-phasic solvent system H_2O–CH_2Cl_2 (1:1 v/v) (Scheme 35).

Kuhakarn et al.[26] evaluated a variety of phase-transfer catalysts like n-Bu_4NBr, Et_4NCl, Et_4NBr, Et_4NI, $BnMe_3NBr$, and $BnEt_3NCl$ in order to select an effective phase-transfer catalyst (PTC). They observed that the type of halide anion of the catalyst had a considerable effect on the oxidation reaction. Tetrabutylammonium bromide (n-Bu_4NBr) and tetraethylammonium bromide (Et_4NBr) catalyzed the reaction more effectively than the corresponding iodide and chloride, respectively. n-Bu_4NBr was found to be the most effective PTC and was therefore chosen as the catalyst of choice. The role of the bromide anion in this reaction is to accelerate the reaction rate by causing polarization of the 'I=O' bond in IBX.



Scheme 33. Mechanistic rationale for direct conversion of 1,3-diols into 1,2-diketones by IBX.



Scheme 34.

Recently, Knight et al.[27] found that IBX is very useful reagent for the oxidation of 2-furylethanols. They found that, rather than giving the corresponding aldehyde or carboxylic acid, Jones oxidation of 5-substituted-2-furylethanols gives rise to high yields of the corresponding dihydro-2-(2-oxoethyl)furan-3(2*H*)-ones, following Achmatowicz-type oxidative ring opening and subsequent reclosure by a 5-*exo* Michael addition of the pendant hydroxy group to the enedione function. Other oxidation methods such as Swern oxidation give lower yields of the same products, while magnesium monoperphthalate (MMPP) tends to yield the intermediate enediones. IBX, on the other hand, converts 2-furylethanols into the corresponding furyl aldehydes in high yields at room temperature in 2 h (Scheme 36).

5.2. Oxidation of 1,4-diols to γ-lactols using IBX

Corey et al.[28] showed that 1,4-diols can be easily oxidized to γ-lactols using IBX in DMSO at ambient temperature. Thus, the chiral lactol (**8**) can be prepared in good yields using IBX from the primary-secondary 1,4-diol (**7**) as a precursor (Scheme 37). Oxidation does not proceed further to give the lactone to an appreciable degree. This successful conversion of the primary-secondary diol into the γ-lactol implies that oxidation of the primary hydroxyl group in **7** is considerably faster than that of the secondary hydroxyl function of either **7** or **8**. This result is especially noteworthy, since, as a rule, secondary lactols are readily oxidized to lactones, even by mild reagents, which do not affect primary or secondary alcohols.

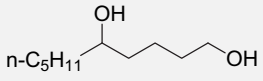
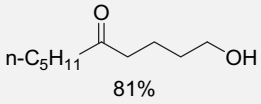
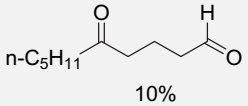
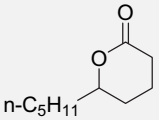
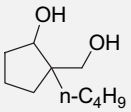
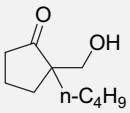
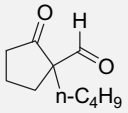
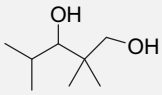
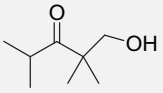
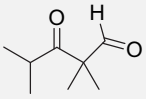
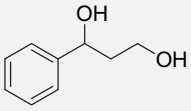
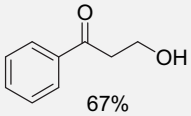
Benzylic primary alcohols are oxidized preferentially, relative to 1-alkanols. Thus, δ-lactols are formed from 1,5-diols in good yields (Scheme 38).[28]

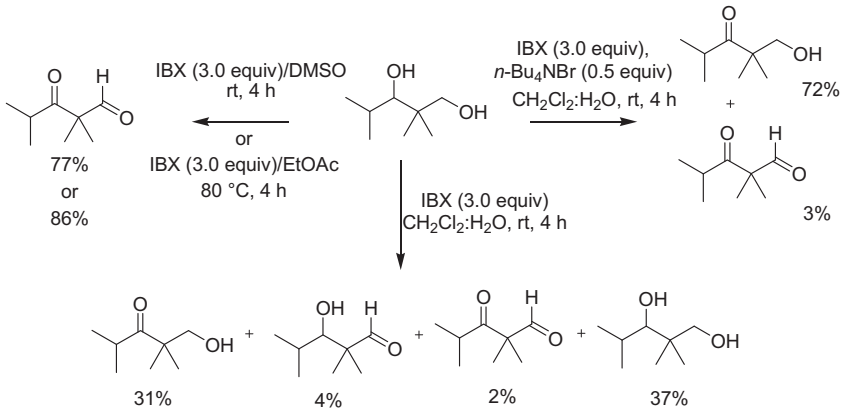
Corey and Palani[28] also found that, at room temperature, the lactols thus formed undergo oxidation with IBX in neat DMSO only sluggishly, despite their clear solubility. Narasimha-Moorthy and co-workers[29] corroborated this observation and presented a method to convert lactols into lactones using IBX in a facile manner in good-to-excellent isolated yields. They reported that the lactol-to-the lactone conversion takes place with 1.2 equiv of IBX in a mixed solvent system consisting of ethyl acetate–DMSO in a 9:1 ratio at reflux temperature (Scheme 39). In this solvent system, the lactols dissolved at the ethyl acetate reflux temperature, although IBX remained as a suspended material. The same oxidation in a heterogeneous phase in chloroform, ethyl acetate or benzene at reflux temperature yielded lactone in respectable isolated yields, albeit in longer reaction times.[29]

5.3. Oxidation of alcohols to carboxylic acids using IBX

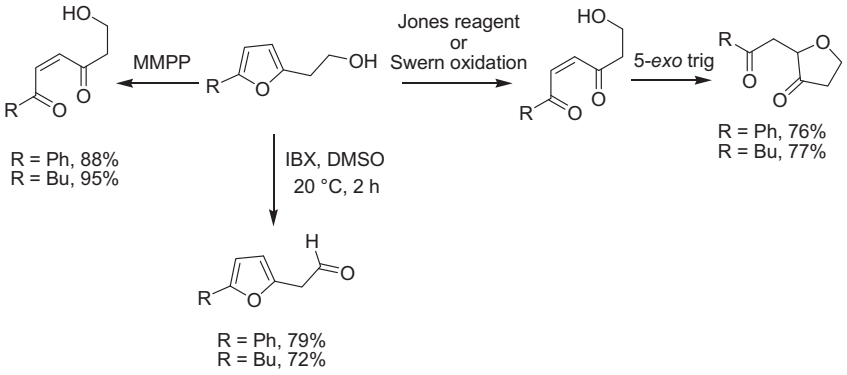
IBX was not known to transform primary alcohols into carboxylic acids. For the first time, Giannis et al.[30] reported that primary alcohols could be oxidized easily in the presence of IBX and certain O nucleophiles to give carboxylic acids at ambient temperature in high yields. 2-Hydroxypyridine was used as an O nucleophile. In the presence of 2.0 equiv of IBX and 4.0 equiv of 2-hydroxypyridine, 1-decanol was oxidized to form decanoic acid in 48 h in 92% yield (Scheme 40).

Table 1
Selective oxidation of secondary hydroxyl group in the presence of primary hydroxyl within the same molecule using IBX (3.0 equiv) and *n*-Bu_4NBr (0.5 equiv) in H_2O–CH_2Cl_2 (1:1)

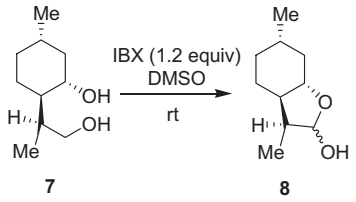
Substrate	Product		
	Hydroxy ketone	Dicarbonyl compound	Lactone
	 81%	 10%	 3%
	 84%	 8%	—
	 72%	 3%	—
	 67%	—	—



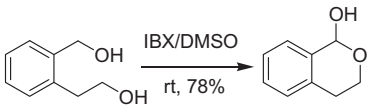
Scheme 35.



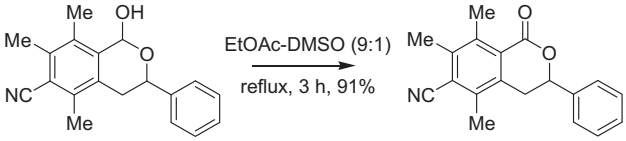
Scheme 36.



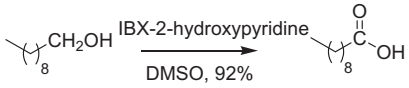
Scheme 37.



Scheme 38.

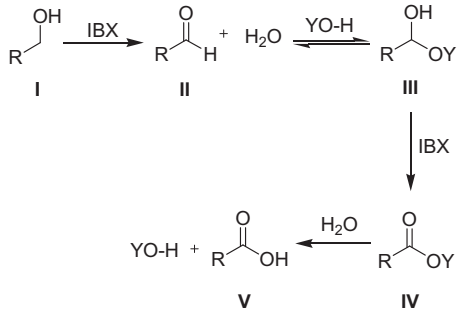


Scheme 39.



Scheme 40.

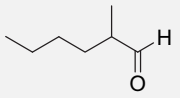
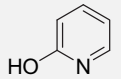
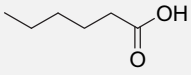
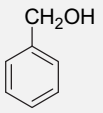
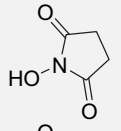
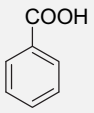
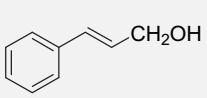
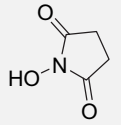
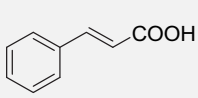
As per the postulated mechanism depicted in Scheme 41 the aldehyde **II**, generated from a primary alcohol **I** and an excess of IBX, reacts with O nucleophiles (YO–H) to form the intermediate **III**. This intermediate is then oxidized to the corresponding active ester **IV**, which in turn is hydrolyzed to give the desired carboxylic acid **V**.

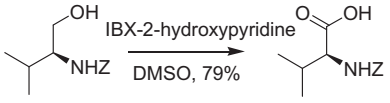


Scheme 41. Mechanism of the IBX-mediated oxidation of primary alcohols to carboxylic acids.

In cases where 2-hydroxypyridine is insufficiently nucleophilic to form semiacetals of the type **III**, 1-hydroxybenzotriazole (HOBT) or *N*-hydroxysuccinimide (NHS) can be used, as their hydroxy groups show an increased nucleophilic character, caused by the α-effect. *N*-Hydroxysuccinimide is especially preferred, as it is stable to IBX. A series of other alcohols and aldehydes can be oxidized by using the appropriate O nucleophile under the same reaction conditions in high yields to obtain the carboxylic acid analogues (Table 2).[30] This remarkable method of oxidation of alcohols to carboxylic acids using IBX tolerates a wide variety of functional groups, such as isolated and conjugated double bonds, alkyl halogenides, urethanes, and electron-rich and -poor aromatic compounds. In addition, starting from the chiral *N*-protected α-amino alcohol, the corresponding amino acids can be generated without racemization (Scheme 42).[30]

Table 2
Oxidation of primary alcohols to corresponding carboxylic acids with IBX in presence of O nucleophiles

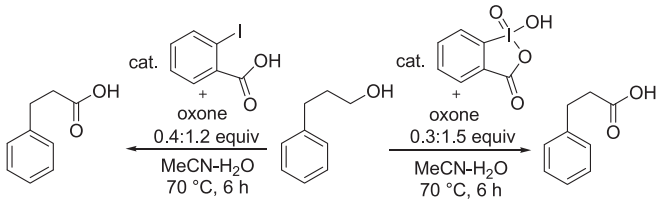
Substrate	O nucleophile	Product	Yield (%)
			74
			79
			64



Z = protecting group

Scheme 42.

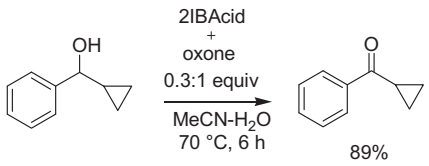
In all of the reactions with IBX, at least a molar equivalent of IBX is necessary to accomplish the oxidation. Thottumkara et al.[31] demonstrated that IBX can be used in catalytic amounts in the presence of oxone as a co-oxidant to carry out the oxidation of primary and secondary alcohols in user- and eco-friendly solvent mixtures. This strategy depends on the in situ re-oxidation of the reduced form of IBX, namely, iodosobenzoic acid (IBA), back to the active I(V) state, using oxone. However, using this method, the primary alcohols undergo oxidation to the corresponding carboxylic acids and not to the aldehydes. Interestingly, secondary alcohols undergo oxidation to provide ketones without the undesired accompaniment of the Baeyer–Villiger oxidation of ketones, due to the presence of oxone in the reaction. The non-explosive IBA, a precursor to IBX, or commercially available 2-iodobenzoic acid (2IBAcid), the ultimate precursor for IBX and IBA, can also be potentially used as a catalytic reagent in place of IBX. Thus, oxidation of 3-phenyl-1-propanol gave 3-phenylpropanoic acid in more than 90% yield (Scheme 43).



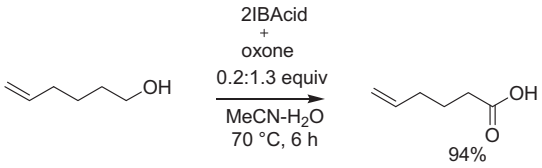
Scheme 43.

This protocol by Thottumkara et al.[31] is widely applicable and tolerates presence of a wide range of substituents on substrates. Oxidation of vicinal alcohol does not result in the cleavage of C–C bond, and a sensitive group such as a cyclopropyl moiety survives the reaction conditions (Scheme 44). Also noteworthy is the fact

that the oxidation of 5-hexene-1-ol cleanly provides the corresponding acid without affecting and/or oxidatively transforming the double bond (Scheme 45).



Scheme 44.

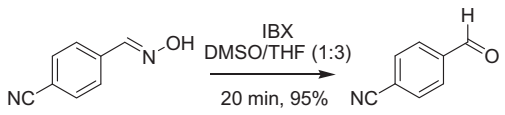


Scheme 45.

It must be noted that oxone alone does not oxidize alcohols efficiently. The oxidation reactions carried out by Thottumkara et al.[31] using oxone (in the absence of IBX) gave the carboxylic acid only in 30% yield.

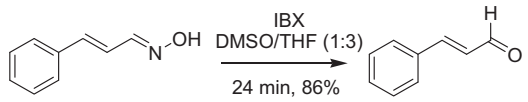
5.4. De-oximation of oximes to carbonyl compounds using IBX

Oximes are important precursors in organic synthesis because of their use in the protection and deprotection of carbonyl compounds. Many valuable reactions such as the Barton reaction have been developed to prepare oximes from other than carbonyl compounds. Although several methods are available for oxime cleavage, only a few are suitable for aldoximes. Moreover, some of these methods invariably require higher temperatures, longer reaction times, use of toxic metal ions as catalysts, which are detrimental to the environment, and form overoxidation products leading to low yields. Hence, a mild and efficient de-oximation reaction assumes great importance, leading to new methods of preparing carbonyl compounds. A facile method, which uses inexpensive IBX as an oxidizing agent for the generation of carbonyl compounds from both oximes (aldoximes and ketoximes) and tosylhydrazones was developed by Bose and Srinivas.[32] They reported that the reaction of IBX with oxime in a DMSO–THF (1:3) solvent system at ambient temperature yields the corresponding carbonyl compound in high yield (Scheme 46).

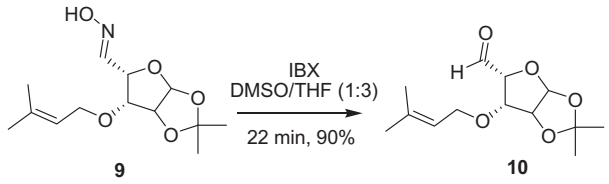


Scheme 46.

This mild and efficient protocol overcomes many of the disadvantages associated with other de-oximation methods. It is noteworthy that, unlike other oxidative hydrolytic methods, the major drawback of overoxidation of the resulting aldehydes is not encountered under the IBX reaction conditions. The α,β-unsaturated oximes undergo de-oximation very efficiently without affecting the C=C bond (Scheme 47). Acid- and base-sensitive protecting groups, esters, and other linkages can survive under these reaction conditions. In addition, IBX-mediated de-oximation of chiral substrates proceeds without racemization. For example, the stereochemical integrity of the chiral aldehyde (**10**), obtained from the chiral oxime (**9**), was found to be retained under the reaction conditions (Scheme 48).[32]

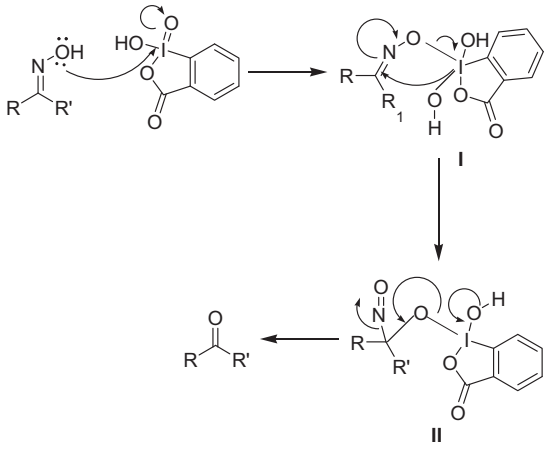


Scheme 47.



Scheme 48.

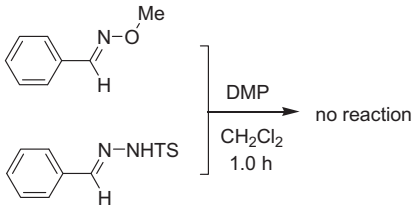
According to the proposed reaction mechanism for this oxidative de-oximation (Scheme 49), an intermediate **II** is formed through nucleophilic addition of the hydroxyl group of the oxime to IBX, followed by sigmatropic rearrangement of the intermediate **I**. The intermediate **II** thus formed undergoes decomposition to give the carbonyl compound.



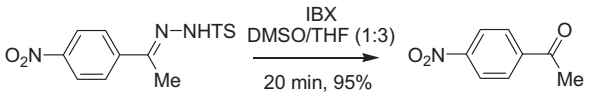
Scheme 49. Proposed reaction mechanism for oxidative de-oximation using IBX.

A similar protocol for the de-oximation reaction using Dess–Martin periodinane (DMP) was reported by Akamanchi et al.[33] However, in their method of de-oximation using DMP, some by-products were formed under the reaction conditions of room temperature, which necessitated conducting the reaction at low temperatures, preferably at 0–5 °C. DMP was also found to be unsuitable for the generation of carbonyl compounds from tosylhydrazones and *o*-methyloximes (Scheme 50). Indeed, the IBX-mediated protocol of Bose and Srinivas[32] elegantly transformed tosylhydrazones into the corresponding carbonyl compounds (Scheme 51).

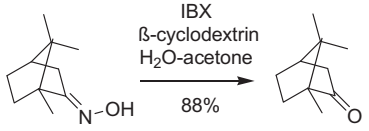
Rama Rao et al.[34] showed that the de-oximation of various oximes to carbonyl compounds can be carried out using IBX under supramolecular catalysis with β-cyclodextrin in water (Scheme 52). The reactions are carried out by dissolving β-cyclodextrin in water followed by the addition of oxime and IBX at room temperature. The carbonyl compound is obtained in high yields.



Scheme 50.



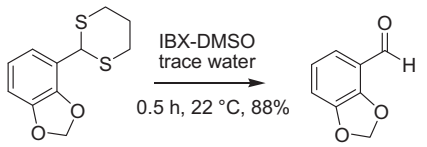
Scheme 51.



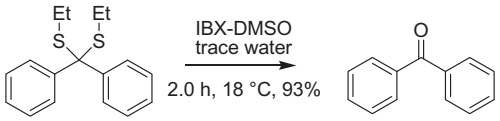
Scheme 52.

The reaction does not take place in the absence of cyclodextrin. The cyclodextrin not only activates the oxime, but also forms a cyclodextrin·IBX complex through hydrogen bonding, which then oxidizes the oxime to the corresponding carbonyl compound.

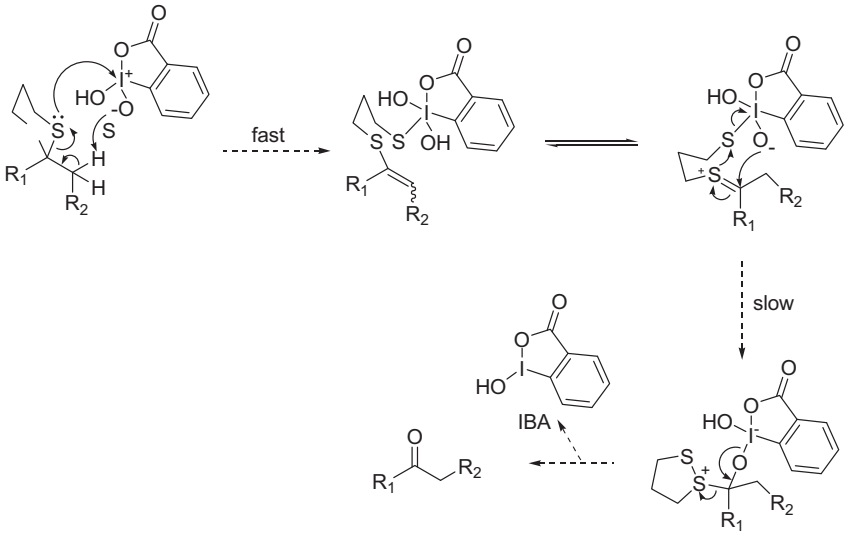
thioacetals/thioketals excellent protecting groups in synthesis. In addition, the 1,3-dithianes formed from aldehydes can form carbanions on treatment with a strong base, which easily react with various electrophiles to afford thioketals, representing a useful means of carbon–carbon bond formation. It is therefore evident that dithianes/dithiolanes are of great importance in synthesis. Wu et al.[35] have reported the application of IBX for deprotection of activated dithianes/dithiolanes (e.g., those at benzylic and allylic positions). Treatment of the substrate with IBX in DMSO containing traces of added water at ambient temperature affords the corresponding carbonyl compound. A variety of thioketals/thioacetals can be cleaved into the corresponding carbonyl compounds in high yields (Schemes 53 and 54), following the mechanism depicted in Scheme 55.



Scheme 53.



Scheme 54.



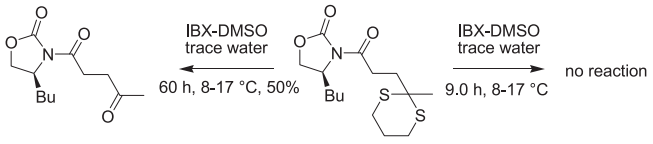
Scheme 55. Mechanistic rationale for deprotection of dithianes by IBX.

The catalytic amount of β-cyclodextrin used in the reaction can be recovered and re-used. In addition, the 2-iodosobenzoic acid obtained as by-product can be recycled by oxidation to IBX.[34]

5.5. Deprotection of thioacetals/thioketals using IBX

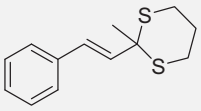
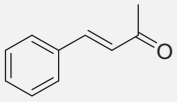
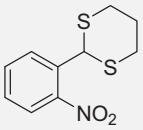
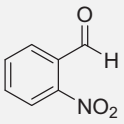
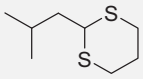
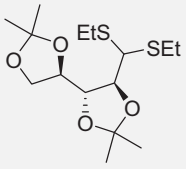
Compared with their oxygen counterparts, thioacetals/thioketals, especially dithianes/dithiolanes, are much easier to form and are remarkably more stable under acidic as well as basic conditions. They can be cleaved cleanly to release free carbonyl groups under essentially neutral conditions by using the proper oxidant. It is possible to cleave thioacetals/thioketals selectively in the presence of acetals/ketals and vice versa. These properties make

Wu et al.[35] reported that the dithianes/dithiolanes at benzylic or allylic positions are easily cleaved, whereas those at non-activated positions remain intact, unless subjected to prolonged exposure to the cleaving conditions for many hours, and even days (Scheme 56) (Table 3).

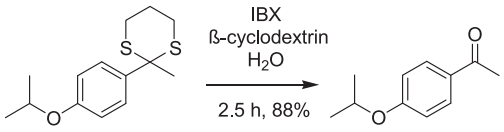


Scheme 56.

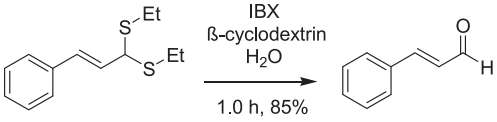
Table 3
IBX-mediated cleavage of thioketals/thioacetals into corresponding carbonyl compounds

Substrate	Conditions	Product	Yield (%)
	16 h/22–32 °C		74
	0.5 h/15 °C		92
	1 h/11–18 °C 5 h/11–18 °C	No reaction Starting material of 89% recovered	— —
	10 h/15–25 °C 22 h/25 °C	No reaction Starting material of 89% recovered	— —

Rama Rao et al.[36] reported that the hydrolysis of various thioacetals/thioketals to carbonyl compounds can be carried out under supramolecular catalysis in water with β-cyclodextrin and IBX (Schemes 57 and 58). The β-cyclodextrin is used only in catalytic amounts, without which the reactions do not proceed. Phenyl-substituted thiol groups are hydrolyzed faster. Although these reactions under supramolecular catalysis do take place with thioacetals of aliphatic aldehydes, the yields are less than satisfactory. For example, the yields with 2-heptyl-1,3-dithiolane and nonyl-1,3-dithiolane are 18 and 20%, respectively, with the recovery of starting materials.



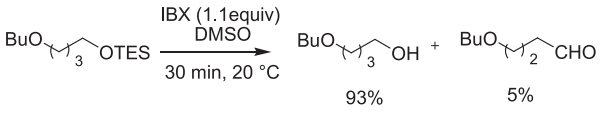
Scheme 57.



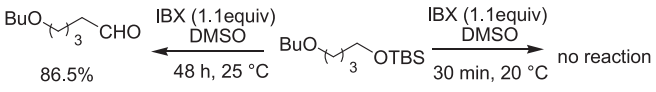
Scheme 58.

5.6. Deprotection of silyl ethers using IBX

Silyl ethers, which are used as protecting groups for alcohol functionalities have played an increasingly important role in the synthesis of complicated molecules. Among silyl protecting groups, triethylsilyl (TES) ethers hold a special position. Compared with trimethylsilyl (TMS) ethers, TES ethers are remarkably more stable and thus can survive many more synthetic transformations and chromatographic purifications. At the same time, TES ethers do not introduce as much steric bulkiness as *tert*-butyldimethylsilyl (TBS) or *tert*-butyldiphenylsilyl (TBDPS) ethers. Selective removal of TES protecting groups in the presence of TBS ethers or other, even more stable, silyl protecting groups has been a challenging task. Reagents like mesoporous silica MCM-41[37] have been reported to be used for their deprotection. IBX can be used as a highly effective and selective desilylation agent, which allows for the facile cleavage of triethylsilyl ethers. Wu et al.[38] reported that IBX cleaves a TES protecting group giving an alcohol (rather than a carbonyl compound) as the main product. The resulting alcohols could be further oxidized into the corresponding carbonyl compounds in high yields only if excess IBX is used and the reaction time is prolonged. The rates at which the alcohols are oxidized are much lower than those for the silicon–oxygen bond cleavage. The unhindered primary TES ethers are cleaved in high yields within less than 1 h (Scheme 59). It is important to note that the closely related TBS ethers remain untouched under the same conditions and undergo cleavage when the reaction time is prolonged (Scheme 60).[38]



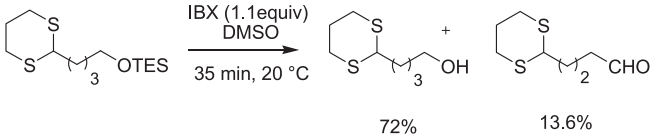
Scheme 59.



Scheme 60.

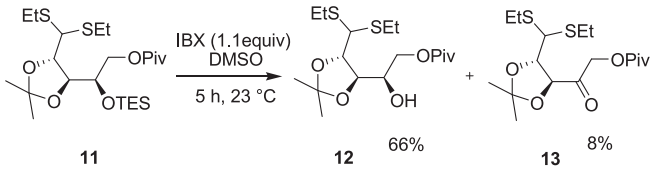
Some commonly employed protecting groups such as ketal, thioacetal, pivolyl, benzyl, and benzoyl groups remain unaffected under the reaction conditions to a detectable degree. It is a very interesting fact that IBX, which elegantly deprotects thioacetals/thioketals to the corresponding carbonyl compounds, selectively cleaves TES ethers in high yields in the presence of thioacetals/thioketals (Scheme 61).[38]

Wu et al.[38] have also reported that cleavage of sterically hindered TES ethers requires longer reaction times. For example, in the case of deprotection of (**11**), full consumption of the starting TES ether took 5 h at 23 °C. Workup and chromatographic separation



Scheme 61.

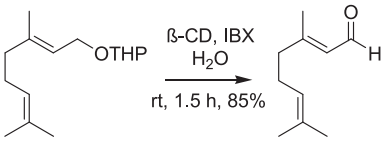
gave the corresponding alcohol (**12**) in 66% yield, along with a small amount of ketone (**13**) (8%) (Scheme 62).



Scheme 62.

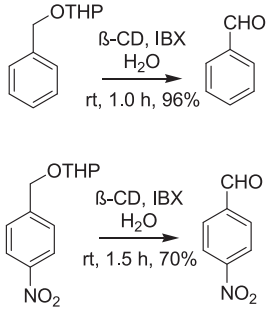
5.7. Deprotection of THP ethers using IBX

The tetrahydropyranylation of alcohols and the cleavage of tetrahydropyranyl ethers to their parent alcohols is an important protection/deprotection protocol in synthetic organic chemistry. In view of the importance of oxidative deprotection of THP ethers, a number of reagents have been studied, but the direct synthesis of carbonyl compounds from tetrahydropyranyl ethers is not widespread in the literature.[39] Rama Rao et al.[40] explored the oxidative deprotection of tetrahydropyranyl ethers with IBX and β-cyclodextrin in water. They showed that THP-protected alcohols when treated with IBX and catalytic amounts of β-cyclodextrin (β-CD) in water undergo direct conversion into the corresponding carbonyl compounds in impressive yields (up to 96%). No overoxidation products were detected in the case of aldehydes (Scheme 63).



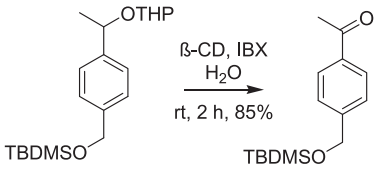
Scheme 63.

Rama Rao et al.[40] also reported that the yields from THP ethers with an aromatic moiety were found to be comparatively better than those from saturated THP ethers. However, the yields were diminished when $-NO_2$ group was present on the aromatic ring, due to a decrease in the nucleophilicity of the alcoholic oxygen, since the reaction proceeds via nucleophilic attack of the alcoholic oxygen on IBX (Scheme 64).

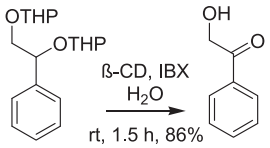


Scheme 64.

Interestingly, when both −OTBDMS and −OTHP groups were present in the same substrate, the −OTHP group was found to be cleaved selectively (Scheme 65). In the case of substrates having both benzylic and aliphatic −OTHP groups, keto-alcohols were the only products formed resulting from oxidation of the benzyl alcohol, due to the ease with which the α-hydrogen can be abstracted (Scheme 66).[40]



Scheme 65.

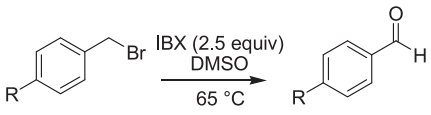


Scheme 66.

These reactions can be efficiently carried out using catalytic amounts of β-cyclodextrin (0.1 mmol), which is inexpensive and can be recovered and re-used. It is assumed that the cyclodextrin activates the tetrahydropyranyl ethers by hydrogen bonding and thereby facilitates the hydrolysis. Since the β-cyclodextrin cavity is hydrophobic in nature, it may also be forming reversible complexes with the THP ethers. In the absence of β-cyclodextrin, no deprotection took place and, hence, no oxidation occurred. When the reaction was performed without IBX, only deprotection occurred and no oxidized product was noticed.[40]

5.8. Conversion of benzylic halides into the corresponding aldehydes/ketones using IBX

Narasimha-Moorthy et al.[41] reported that IBX in DMSO can be conveniently utilized to accomplish the conversion of benzylic halides into the corresponding aldehydes/ketones in respectable yields under mild reaction conditions. A variety of benzyl halides were found to undergo conversion into their corresponding aldehydes/ketones when the reactions were run in DMSO in the presence of 1.5–3.0 equiv of IBX at 60–70 °C (Scheme 67).

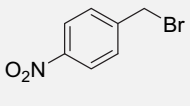
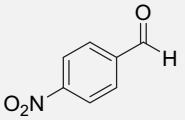
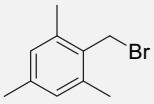
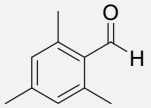
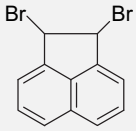
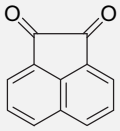
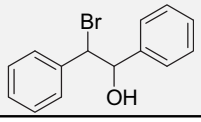
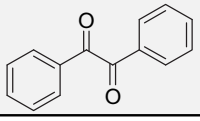


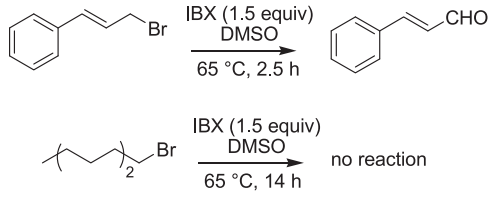
Scheme 67.

4-Nitrobenzyl bromide (Table 4, entry 1) and sterically hindered mesityl bromide (Table 4, entry 2) undergo smooth conversion into the corresponding aldehyde in good yields. Even dibromides such as acenaphthylene dibromide (Table 4, entry 3) could be readily converted into the corresponding diketone. In a similar manner, bromohydrin (Table 4, entry 4) was conveniently converted into the diketone.[41]

An allylic bromide such as cinnamyl bromide gives cinnamaldehyde in 62% isolated yield, whereas aliphatic bromides, such as octyl bromide, were found to be unreactive, even after 14 h at 65 °C (Scheme 68).[41]

Table 4
Conversion of benzylic halides into corresponding carbonyl compounds in DMSO using IBX at 60–70 °C

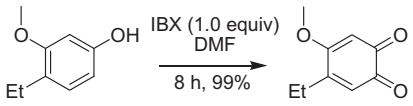
Entry	Bromo compound	Carbonyl compound	IBX (equiv)	Time (h)	Yield (%)
1			2.5	8.0	73
2			1.6	2.5	80
3			2.5	4.0	50
4			3.0	4.0	83



Scheme 68.

The reaction depends on the nature of halogen. The reaction is quite fast when the halide is iodide, whereas the reaction of the chloro derivative is sluggish. Benzyl bromide reacts with a reasonable rate. Narasimha-Moorthy et al.[41] conveniently adapted this transformation for the one-pot conversion of diaryl-substituted olefins into 1,2-diketones via the formation of bromohydrins using NBS–H_2O. Thus, 1,2-diphenylethene was converted into the corresponding bromohydrin with NBS–H_2O in DMSO, which was subjected to oxidation by introducing IBX into the same pot to afford benzil in 50% isolated yield (Scheme 69).

temperature in excellent yields (Scheme 70). The starting phenol, however, must contain at least one electron-donating group. Phenols without electron-donating substituents and those containing electron-withdrawing groups such as –C(O)R, –CHO, and $-NO_2$ fail to undergo oxidation. Phenol itself does not get oxidized with IBX under these reaction conditions.

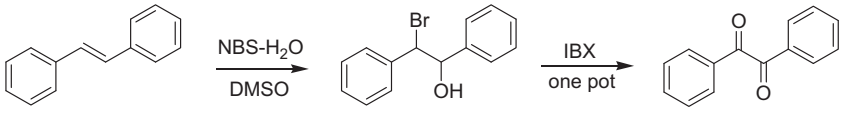


Scheme 70.

DMF is the superior solvent for this transformation. Pettus et al.[42] also reported that the oxidation of 4-methoxyphenol to 4-methoxy-*o*-quinone required 14 h for completion in $CDCl_3$ and proceeded in 85% yield. Use of DMF speeded up the same conversion in 1.5 h in 99% yield (Scheme 71).

The process most likely follows the pathway shown in Scheme 72. The starting material combines with IBX to extrude H_2O, producing the I(V) intermediate **I**, which serves to intramolecularly deliver the oxygen to the most nucleophilic and least congested *ortho*-site on the starting phenol. During this delivery process, the I(V) atom in intermediate **I** is concurrently reduced to I(III), giving the intermediate **II**, which in turn undergoes tautomerization to produce the intermediate **III**. Intermediate **III** then oxidatively collapses with concurrent reduction of the iodine atom to produce *o*-quinone and an I(I) reagent. This highly regioselective oxidation of phenols to *o*-quinones with IBX is remarkable, because it represents a double oxidation: a hydroxy residue is regioselectively installed and the resulting catechol intermediate is oxidized.

The *o*-quinones so obtained, when subjected to hydrogenation with a Pd/C catalyst or exposed to sodium dithionite ($Na_2S_2O_4$), afford substituted catechols. Thus, after an oxidation conducted in DMF was complete, potassium carbonate (2.5 equiv), acetic anhydride (2.1 equiv), and Pd/C (5 mol%), when added to the crude product mixture and the resulting suspension stirred under a hydrogen atmosphere for 24 h, produced the bis-acetylated catechol (Scheme 73).[42] Since oxidation, reduction, and acylation occur successively in the same pot, this procedure embodies a high-yielding, one-pot conversion of an electron-rich phenol into a catechol. The method proves to be useful for the construction of a variety of catechols using mild, non-toxic conditions.

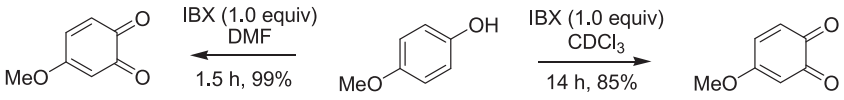


Scheme 69.

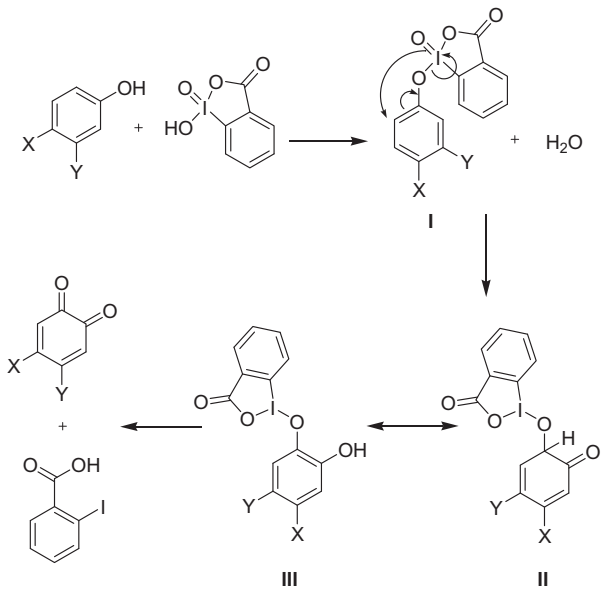
5.9. Conversion of phenols into *o*-quinones using IBX

Regioselective procedures for the direct conversion of a phenol into an *o*-quinone are rare. Pettus et al.[42] have reported an efficient regioselective method for the oxidation of phenols to *o*-quinones. The oxidation of an array of phenols in DMF with a suspension of IBX (1.0 equiv) affords the corresponding *o*-quinones at room

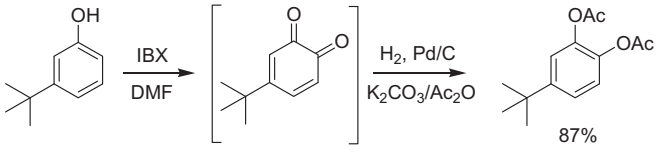
Pettus et al.[43] successfully used this IBX-mediated protocol for the direct conversion of a phenol into an *o*-quinone in the total synthesis of (±)-brazilin (**14**) (Fig. 2), a natural product found in the alcoholic extracts of Brazil wood trees located in the equator regions. In the synthetic sequence of brazilin, the phenolic intermediate (**15**) was oxidized to the *o*-quinone derivative (**16**) in DMF at room temperature with IBX (1.05 equiv). The *o*-quinone



Scheme 71.



Scheme 72. Mechanistic rationale for IBX-mediated conversion of phenols into *o*-quinones.



Scheme 73.

derivative (**16**) on in situ reduction with 3.0 equiv of sodium hydrosulfite afforded the benzylated catechol (**17**) in 58% isolated yield without contamination by the corresponding regioisomeric catechol (Scheme 74).

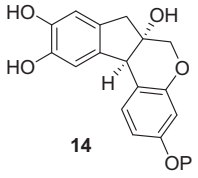


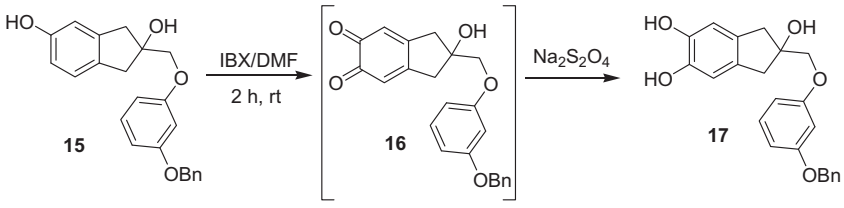
Figure 2. Structure of brazilin.

They reacted the Boc–tyrosine–OMe derivative with IBX (1.2 equiv) in THF at room temperature to obtain the *o*-quinone derivative, which on in situ reduction with sodium dithionite in water afforded the Boc–DOPA–OMe derivative in 95% yield (Scheme 76). It is noteworthy that the stereochemical integrity of the final product was not compromised during the oxidative/reductive step. The procedure was extended to various tyrosine derivatives containing dipeptides and tripeptides bearing amino acids with different aliphatic or aromatic side-chain residues to obtain DOPA derivatives in good conversion and yield.

Bernini et al.[46] also described the application of this protocol to devise a short, efficient, and low-cost synthetic procedure to obtain hydroxytyrosol as well as its lipophilic derivatives, starting from commercially available and natural compounds such as tyrosol (Scheme 77).

The protocol to convert phenols into *o*-quinones and then into catechols using IBX was modified by Pezzella et al.[47] In their modified procedure, IBX was treated with phenol in $CHCl_3$–MeOH (3:2 v/v) under cold conditions to prevent quinone conversion into possible intractable materials and the critical reductive treatment was efficiently carried out with methanolic $NaBH_4$ under homogeneous-phase conditions. In a typical procedure, solid IBX (2.5 equiv) was added to a solution of the appropriate phenol in $CHCl_3$–MeOH (3:2 v/v) at −25 °C and the mixture was stirred for 24 h. Methanolic $NaBH_4$ was then added at −25 °C under vigorous stirring. After mild acidification with acetic acid to remove excess $NaBH_4$, the mixture was washed with saturated NaCl solution containing 10% sodium dithionite buffered at pH 7.0 with sodium phosphate. Evaporation of the organic layer furnished the desired catechols in good-to-excellent yields. Use of cold methanolic $NaBH_4$ after oxidation of the phenols proved to be critical for efficient quinone reduction since, with a $CHCl_3$/MeOH mixture as the solvent, a simple reductive workup with sodium dithionite at room temperature was found to be tedious and was not entirely satisfactory leading, in some cases, to a poor recovery of the catechol products. Thus, α- and β-naphthols were easily converted into naphthalene-1,2-diol and 8-hydroxyquinoline was converted into quinoline-7,8-diol (Scheme 78).

The catecholestrogens, which are the starting materials for novel steroidal derivatives with antiestrogenic properties can be easily prepared by IBX-promoted *o*-hydroxylation of estrogens (Schemes 79 and 80). Two *ortho* regioisomers are produced in comparable yields. Chemoselective reduction of the quinone moiety, sparing the carbonyl function in estrone substrates

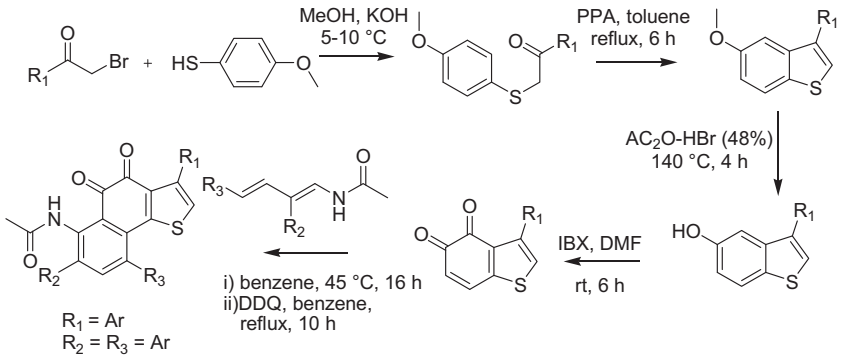


Scheme 74.

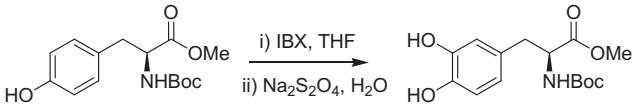
Bu et al.[44] successfully utilized this regioselective protocol for the direct conversion of a phenol into an *o*-quinone using IBX for the synthesis of heteropolycyclic *o*-quinones such as substituted *o*-naphthothiophenequinones (Scheme 75), when most of the reactions failed in transforming a single phenolic hydroxyl group into an *o*-quinone group in satisfactory yield.

Bernini et al.[45] used this IBX-mediated protocol for the *ortho*-hydroxylation of phenol derivatives to devise an efficient synthetic route to 3,4-dihydroxyphenylalanine (DOPA) and DOPA peptides. (Scheme 80), was made possible by the low temperature maintained during $NaBH_4$ treatment and the cold acid-quenching of the mixture; partial reduction occurred when the treatment was performed at room temperature and/or the cold acid-quenching step was omitted prior to solvent evaporation.[47]

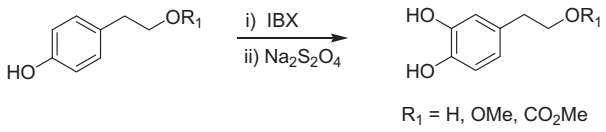
A particularly important feature of this modified protocol is the conversion of phenol itself into catechol in good yield, for which the IBX-mediated hydroxylation reported by Pettus et al.[42] was unsuccessful.



Scheme 75. Synthesis of substituted *o*-naphthothiophenequinones using IBX.

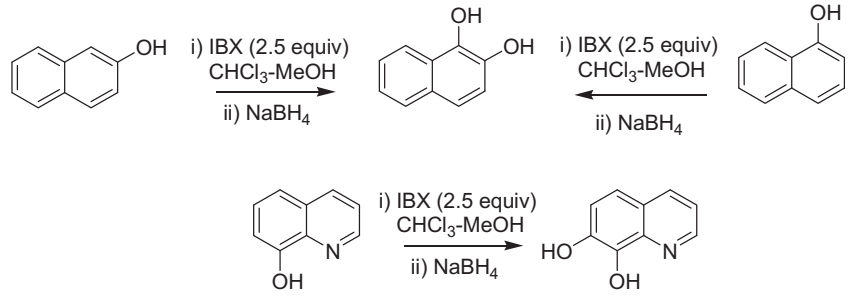


Scheme 76.



Scheme 77.

which can be efficiently carried out with IBX in aqueous ammonia.[48] Addition of the appropriate aldehyde to a solution of IBX in aqueous ammonia results in oxidation to the corresponding nitrile. The reaction is usually complete within 2.0 h at room temperature and the nitrile is obtained in high yield and excellent purity. A variety of aldehydes including aromatic, heteroaromatic, and α, β-unsaturated aldehydes can be transformed into nitriles smoothly using this protocol. In some cases, acetonitrile can be used as a co-solvent to dissolve the aldehyde. The methodology is chemoselective and tolerates functionalities such as phenol, tertiary amine, allyl ether, and alkene (Scheme 81). Aliphatic aldehydes also undergo this transformation smoothly, although the reactions take longer for completion (Scheme 82).

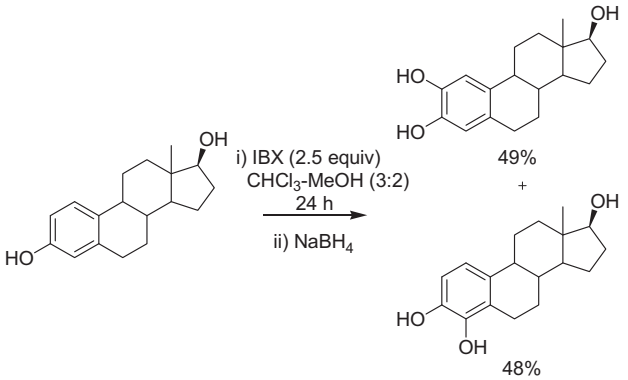


Scheme 78.

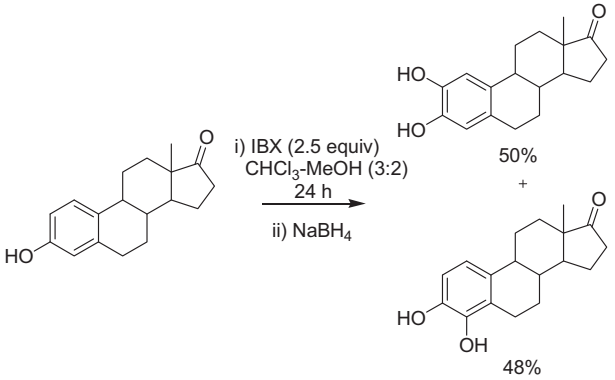
5.10. Conversion of aldehyde group into cyano using IBX/ aqueous NH_3

The preparation of nitriles from the corresponding aldehydes is an important functional-group transformation in organic synthesis,

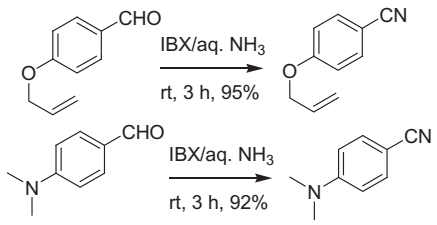
This unique oxidation protocol was used by Hansen and Anwar[49] to develop a one-pot procedure for the synthesis of substituted salicylnitriles. Thus, phenols were converted into salicylaldehydes with paraformaldehyde and $MgCl_2$–Et_3N in THF, which on subsequent treatment with aqueous ammonia gave the



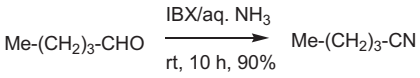
Scheme 79.



Scheme 80.

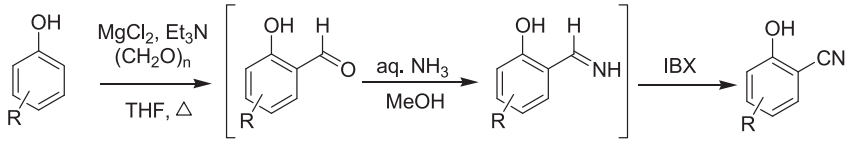


Scheme 81.



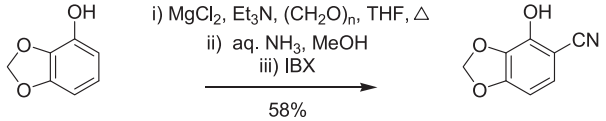
Scheme 82.

corresponding imines. The imines were oxidized with IBX to the desired salicylnitriles. The sequence of reactions was conveniently carried out as a one-pot procedure under mild conditions (Scheme 83).

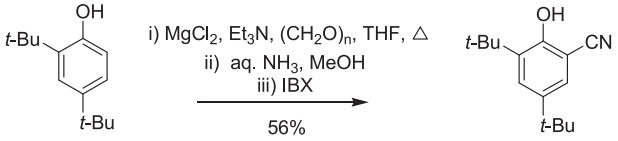


Scheme 83.

Several 2-substituted phenols were subjected to this one-pot procedure to afford the corresponding salicylnitriles in good yields. 2,3-(Methylenedioxy)phenol, a structural entity found in some highly oxygenated natural products, such as narciclasine and pancratistatin, cleanly gives the desired nitrile in 58% overall yield (Scheme 84). 2,4-Disubstituted phenols like (**18**) afford the 3,5-disubstituted salicylnitriles (**19**) (Scheme 85). This one-pot process offers time-cost benefits gained by avoiding the isolation, handling, and chromatography of intermediates. The Dess–Martin reagent can also be used under these conditions, but affords lower yields, compared to IBX.[49]



Scheme 84.



18 **19**

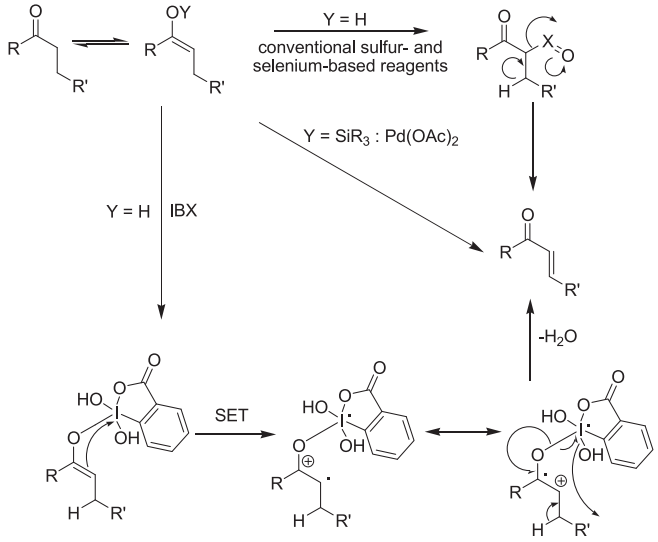
Scheme 85.

5.11. Conversion of alcohols, ketones, and aldehydes into the corresponding α,β-unsaturated carbonyl compounds using IBX

Nicolaou et al.[50] discovered a general synthetic method for the mild, swift, and highly efficient conversion of a range of alcohols, ketones, and aldehydes into the corresponding α,β-unsaturated carbonyl compounds in one pot using the non-toxic IBX reagent. The keto–enol equilibrium inherent in carbonyl systems was exploited in new way to selectively furnish the desired α,β-unsaturated carbonyl systems. Despite the ubiquity and utility in organic chemistry of α,β-unsaturated carbonyl compounds, their synthesis is often tedious and sometimes a challenging transformation. Most of the protocols rely on highly toxic selenium reagents in one- or two-step procedures.[51] Another regularly employed tactic involves the palladium-catalyzed oxidation of enol-ethers derived from carbonyl compounds.[52] However, the new protocol to obtain α,β-unsaturated carbonyl compounds developed by Nicolaou et al.,[50] using IBX, is extremely easy, tolerant of a range of functionalities and high-yielding. Scheme 86 depicts the mechanistically inspired design of a process for oxidation adjacent to a –C=O bond.

Following the mechanistic rationale presented in Scheme 87, cyclooctanol is smoothly oxidized to 2-cycloocten-1-one when treated with 2.0 equiv of IBX at 55 °C in a fluorobenzene–DMSO (2:1) solvent system for 3 h. If cyclooctanol is treated with 4.0 equiv of IBX at 80 °C, cyclooctadienone is obtained (Scheme 87).

This methodology works elegantly on dehydrogenated steroidal systems to obtain unsaturated derivatives (Scheme 88), and is faster at six-membered ring sites in preference to five-membered

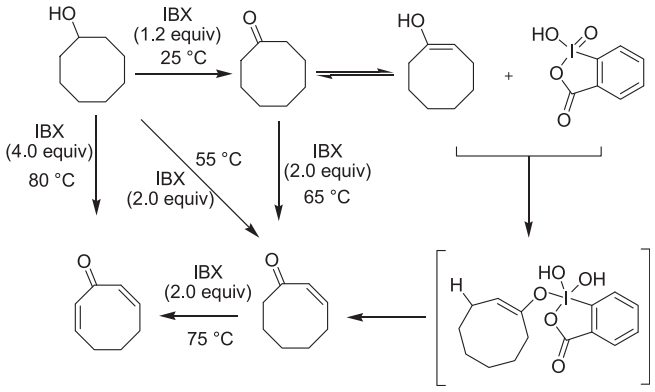


Scheme 86. Mechanistically inspired design of process for oxidation adjacent to –C=O bond using IBX.

ring systems (Scheme 89) when both are present within the same molecule. It oxidizes primary alcohols conveniently into the corresponding α,β-unsaturated aldehydes in a controlled fashion (Scheme 90).[50]

Nicolaou et al.[50] observed that the addition of a catalytic amount of *p*-toluenesulfonyl chloride (0.3 equiv) as an additive accelerates the reaction, as it increases the population of the enol form of the carbonyl group. Addition of pyridine decreases the rate of reaction, although the isolated yields are not affected after extended reaction times.

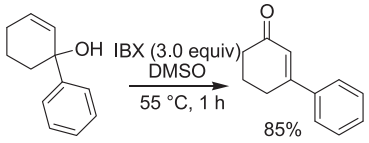
Iwabuchi et al.[53] reported that cyclic tertiary allylic alcohols undergo oxidative rearrangement to β-disubstituted cyclic α,β-unsaturated ketones when heated with IBX in DMSO at 55 °C



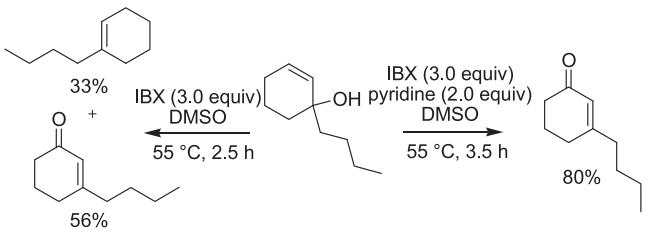
Scheme 87.

(Scheme 91). This method enabling the transposition of a functional group from one carbon to another can be performed on various five- and six-membered cyclic tertiary allylic alcohols in an ecologically and user-friendly manner, avoiding the use of hazardous oxochromium(VI)-based oxidants such as PCC and PDC.

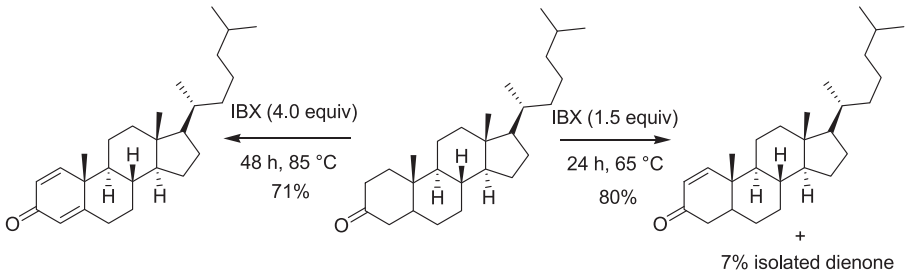
addition of 2.0 equiv of pyridine was found to suppress this undesired side reaction, giving 3-butyl-2-cyclohexenone in 80% yield (Scheme 93).[53]



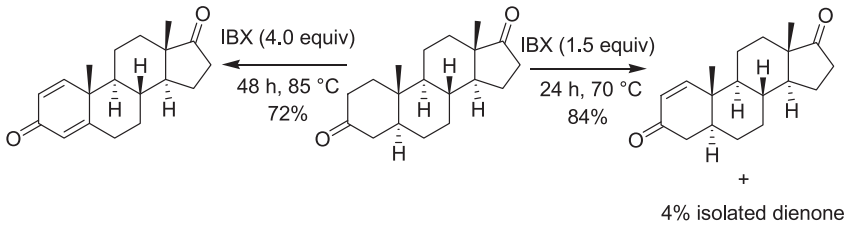
Scheme 92.



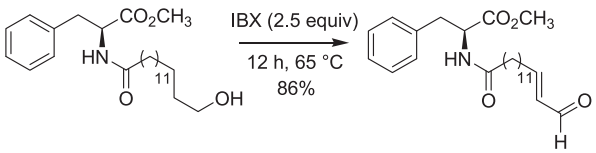
Scheme 93.



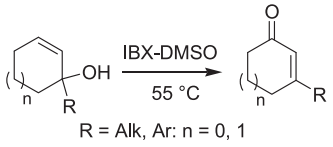
Scheme 88.



Scheme 89.



Scheme 90.

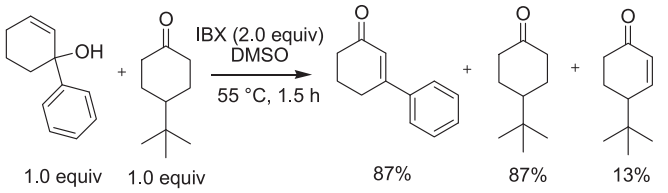


Scheme 91.

Phenyl-substituted 2-cyclohexenol, under these reaction conditions, affords 3-phenyl-2-cyclohexenone (Scheme 92). Alkyl-substituted substrates such as 1-butylcyclohex-2-enol under similar reaction conditions underwent dehydration. However, the

This reaction tolerates conventional protecting groups such as acetyl, MOM, and TBDPS. A TBS group attached to the primary alcohol, however, was found to be partially deprotected and oxidized to the corresponding aldehyde. Iwabuchi et al.[53] reported that an intermolecular competition reaction, in which 1-phenyl-2-cyclohexen-1-ol was treated with IBX in DMSO at 55 °C in the presence of 1.0 equiv of 4-*tert*-butylcyclohexanone, preferentially gave 3-phenyl-2-cyclohexenone, suggesting chemoselectivity of this oxidation protocol (Scheme 94).

Among other hypervalent iodine reagents, $PhIO_2$ in DMSO at high temperature (90 °C) effects this oxidative rearrangement with almost the same efficacy as IBX, while Dess–Martin periodinane suffers a significant side reaction to yield the 3-acetoxy-1-substituted-2-cycloalkene as a major product. HIO_3 and I_2O_5, which seem to be more atom efficient, bring about this oxidative rearrangement in moderate yield of about 40%, presumably due to the decomposition caused by their considerable acidic properties. The iodine(III)-based oxidant PhIO and the recently developed

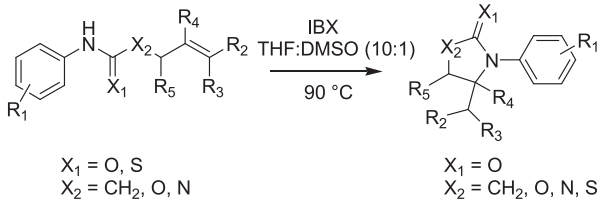


Scheme 94.

oxidation reagent PhIO/KBr/H_2O fail to undergo the desired oxidative transposition.[53]

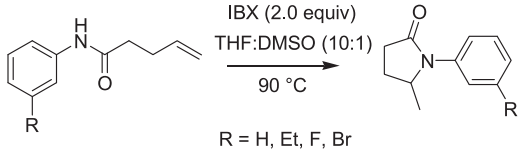
5.12. Construction of heterocycles from functionalized anilide systems using IBX

Nicolaou et al.[54] developed a fundamentally innovative strategy for the construction of heterocycles by treatment of unsaturated aryl amides, carbamates, thiocarbamates, and ureas with IBX. This straightforward protocol gives access to a plethora of oxazolidinones, thiazolidinones and cyclic ureas from the corresponding carbamates, thiocarbamates, and open-chain ureas, respectively (Scheme 95).



Scheme 95.

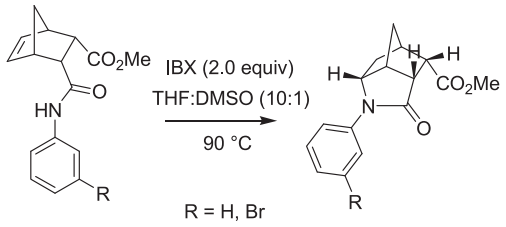
The reaction of very simple anilides bearing a terminal alkene with IBX (2.0 equiv) in a mixed solvent system of THF–DMSO (10:1) at 90 °C for 8–12 h in a pressure tube leads to γ-lactams in high yields (Scheme 96).



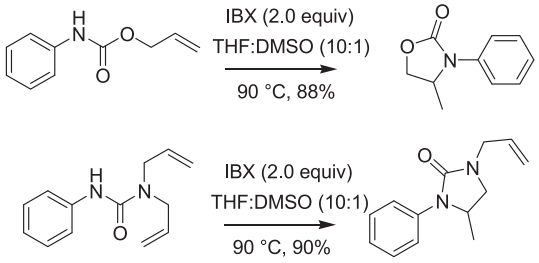
Scheme 96.

Using the same conditions, a diverse series of γ-lactams can be prepared (Scheme 97). Significantly, the reaction is unbiased toward substitution on the aryl moiety. Reactions with substrates, which harbor electron-donating groups, electron-withdrawing groups, halides, and sterically encumbered groups situated at *ortho*, *meta*, or *para* positions all proceed smoothly and in excellent yields. The reaction is impervious to air or water, foregoing the requirement of an inert environment or scrupulously dried solvents.

The reaction of carbamates and ureas with 2.0 equiv of IBX in THF–DMSO (10:1) at 90 °C affords the corresponding oxazolidinones and cyclic ureas (Scheme 98). It should be noted that only ureas prepared from secondary allylic amines readily cyclize. Ureas prepared from primary allylic amines slowly decompose under the reaction conditions without providing any cyclized product.[54]

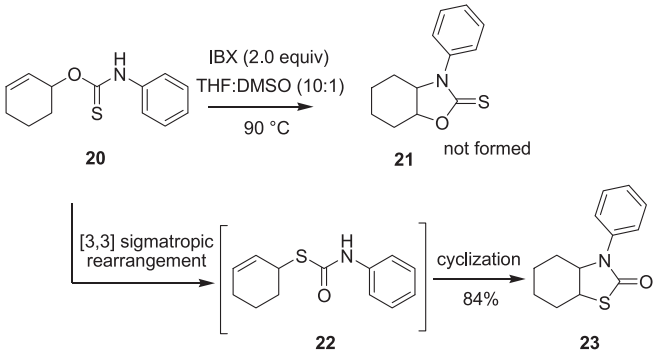


Scheme 97.



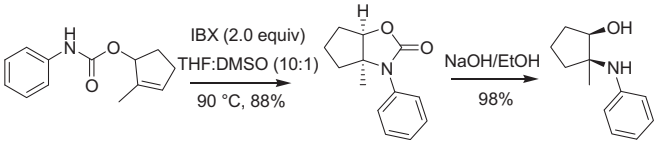
Scheme 98.

In contrast to aryl carbamates and ureas, aryl thionocarbamates do not directly cyclize to provide thionooxazolidines. When thionocarbamate (**20**) (Scheme 99) is subjected to the standard reaction conditions [IBX, THF–DMSO (10:1), 90 °C] for 12 h, thiazolidinone (**23**) is isolated (84% yield) instead of cyclic thione (**21**). Nicolaou et al.[55] suggested that the thionocarbamate (**20**) first undergoes a [3,3]-sigmatropic rearrangement to the corresponding allylic carbamothioate (**22**), which then undergoes IBX-mediated cyclization to provide the thiazolidinone (**23**).

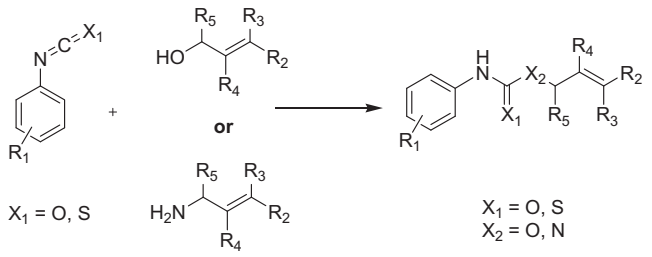


Scheme 99.

A remarkable application of this protocol is the efficient synthesis of *N*-phenyl-1,2-aminoalcohols, which are important precursors for many natural products. Hydrolysis of oxazolidinones in alcoholic sodium hydroxide gives access to *cis*-*N*-phenyl-1,2-aminoalcohols, which are otherwise difficult to synthesize (Scheme 100).[54] The staring materials such as aryl carbamoyl alkenes, carbamates and thiocarbamates can be easily synthesized from a plethora of readily available phenyl isocyanates or phenyl *iso*(thio)cyanates, allylic alcohols or allylic amines (Scheme 101). Thus, a diverse array of building blocks could potentially be funneled into this unique protocol.



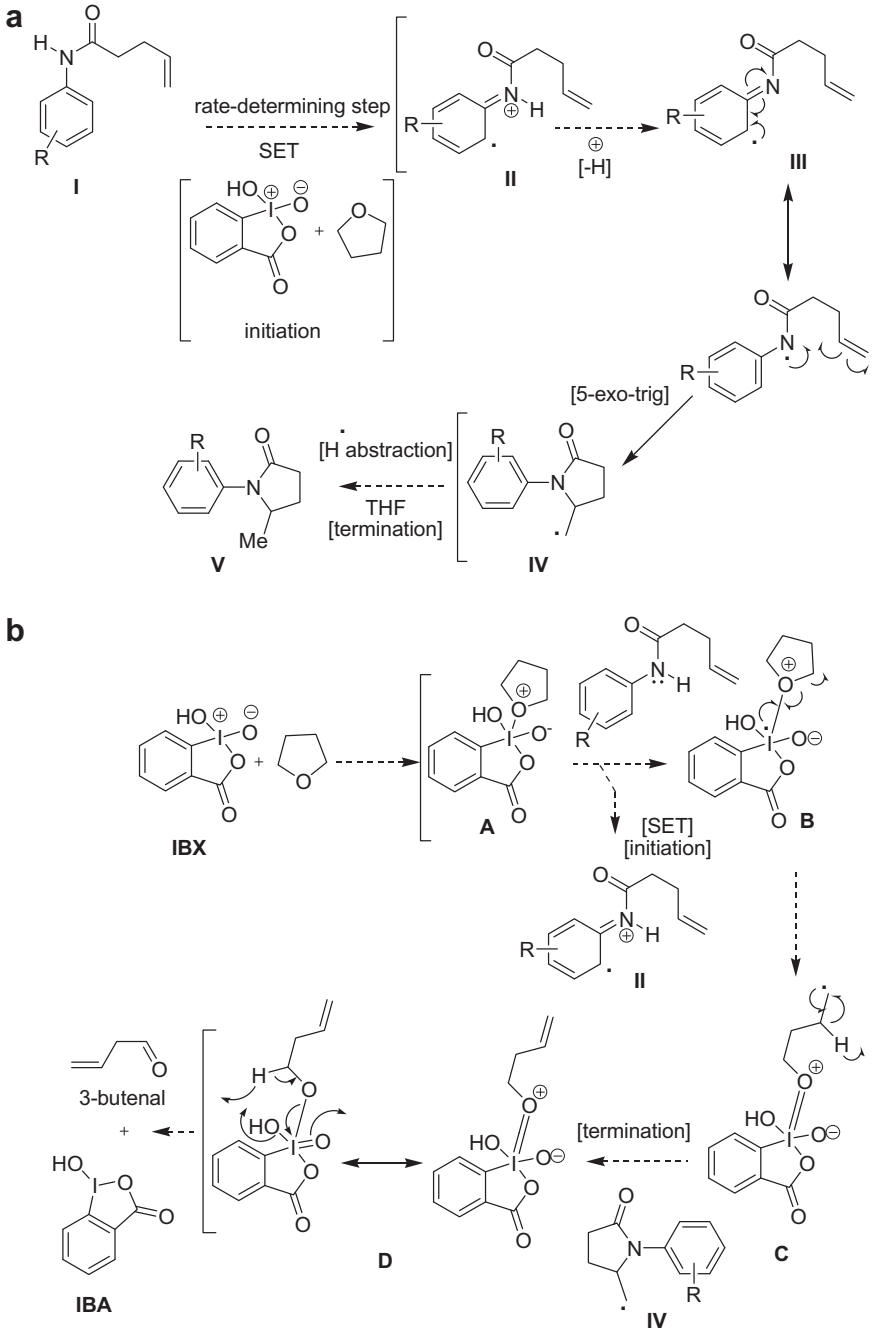
Scheme 100.



Scheme 101.

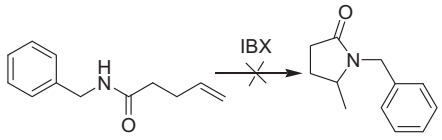
Nicolaou et al.[56] proposed a single-electron-transfer (SET)-based mechanism for the IBX-mediated ring closures of anilides and related systems to *N*-heterocycles (Scheme 102a and b). Supporting evidence for the mechanistic rationale of the unique interactions of IBX with anilides and related substrates was provided, based on isotope labeling, kinetic studies, cyclic voltammetry measurements, NMR spectroscopic analysis, and designed cascade reactions.

According to this mechanistic protocol, a viable scenario might involve the co-ordination of THF to IBX, which would lead to intermediate **A** (Scheme 102b). This intermediate would act as an extraordinary oxidant, which would then initiate the cyclization of **I** (Scheme 102a) by SET to furnish intermediates **II** (Scheme 102a) and **B** (Scheme 102b). Rearrangement of **B** to **C** followed by hydrogen abstraction by **IV** would lead to the product **V** in addition to **D**, which should rapidly lead to IBA and 3-butenal. The solvent plays an integral role in this transformation, besides being a source of hydrogen. The reaction does not proceed if a hydrogen-donating solvent such as THF or dioxane is absent.

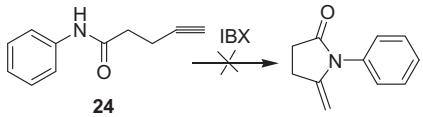


Scheme 102. (a and b) Proposed mechanism of IBX-mediated ring closure of anilides and related systems to *N*-heterocycles (I→V) (SET=single-electron-transfer).

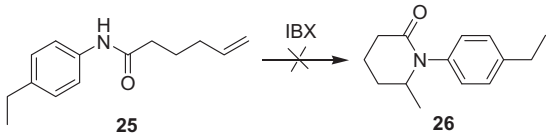
Substrates lacking the *N*-aryl moiety do not undergo this IBX-mediated cyclization (Scheme 103). Alkynes such as (**24**) are also unsuitable substrates for reaction (Scheme 104). It should also be noted that the reaction cannot be entrusted to produce δ-lactams, as the anilide (**25**) failed to furnish δ-lactam (**26**) under the usual conditions (Scheme 105).



Scheme 103.

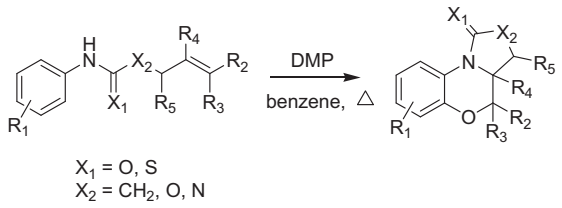


Scheme 104.



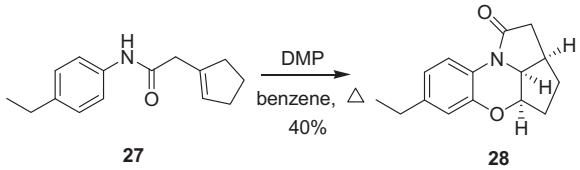
Scheme 105.

Dess–Martin periodinane (DMP) reacts with anilides, carbamates, thiocarbamates, and ureas on refluxing in benzene to afford different heterocycles based on benzomorpholines (Scheme 106).[57]



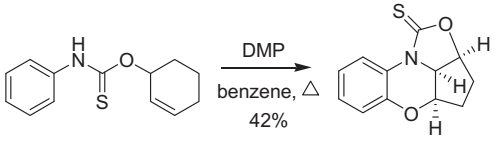
Scheme 106.

Anilides with an olefinic segment like (**27**) on treatment with DMP in refluxing benzene furnish benzomorpholine-based heterocycles (e.g., **28**) in moderate yield (Scheme 107).

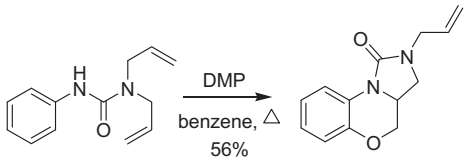


Scheme 107.

Thiocarbamates and ureas afford the corresponding polycycles in moderate-to-good yields (Schemes 108 and 109). Given that hypervalent iodine reagents readily interact with sulfur-containing molecules, the ease with which the reaction occurs with thiocarbamates is admirable. In the case of carbamates as starting materials, the formed products can be easily hydrolyzed with ethanolic sodium hydroxide to provide the corresponding benzomorpholines in excellent yields (Scheme 110).



Scheme 108.

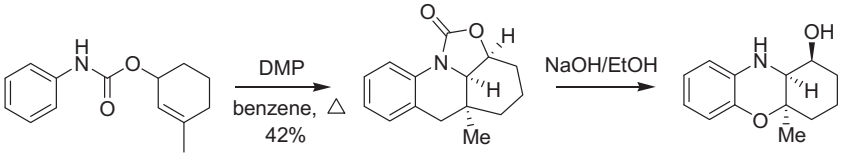


Scheme 109.

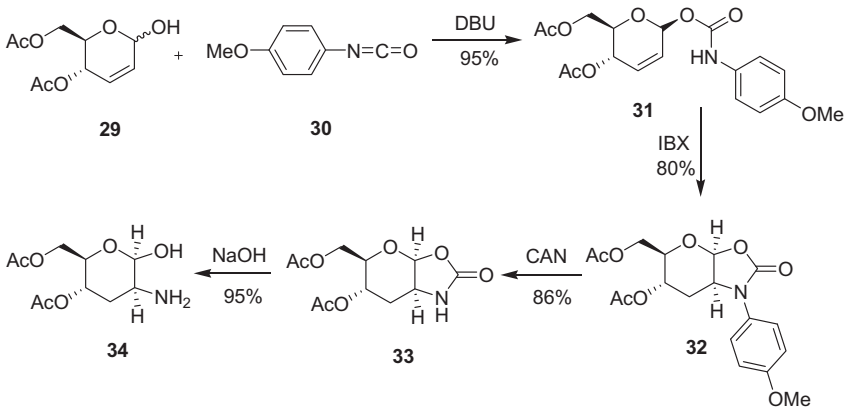
Operationally, the reactions are as simple as the DMP-mediated oxidation of alcohols and are performed in benzene or benzotrifluoride (BTF) at 80 °C under an aerobic atmosphere and are usually complete within 1 h. Standard workup followed by chromatography furnishes the products in generally moderate-to-good yields, which are satisfying, due to the high level of complexity attained rapidly in a single step.[57]

The efficacy of the IBX-mediated protocol for forming carbon–nitrogen bonds was extended to the preparation of amino sugars.[58] Amino sugars constitute integral components of a plethora of natural products and medicinally relevant compounds.[59] Several refined methods for the construction of this class of compounds have been reported and extensively reviewed.[60] However, a general method that is highly stereoselective, relies upon inexpensive materials, and does not introduce unwanted carbon functionality, remains a challenging goal in this area. The protocol developed by Nicolaou et al.[58] using IBX as a facile reaction mediator carries a distinct advantage over other methods. Thus, reaction of (**29**) with *p*-methoxyphenyl isocyanate (**30**) in the presence of a catalytic amount of DBU followed by reaction with IBX furnishes the bicyclic compound (**32**), through urethane (**31**). *p*-Methoxyphenyl cleavage using ceric ammonium nitrate (CAN) affords the protected amino sugar (**33**), which on treatment with 2 N NaOH leads cleanly to the *cis*-1,2-aminoalcohol (**34**) (Scheme 111). Base-labile, acid-sensitive, and sterically bulky functionalities have no effect on the efficiency or stereoselectivity of the reaction.

Nicolaou et al.[58] reported that presence of water in this reaction presents an interesting and unique potential of IBX in organic synthesis. D-Glucal-derived substrate (**35**) provides 1-deoxyamino sugar (**36**) in excellent yield under standard reaction conditions in the absence of water. The reaction of (**35**) in the presence of water leads to crystalline (**37**) with complete control of the two newly

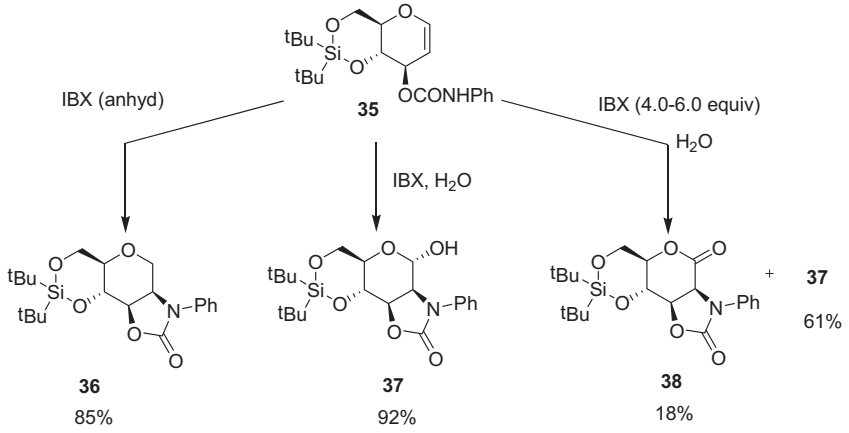


Scheme 110.



Scheme 111.

formed stereocentres and in 92% yield. Reaction of (**35**) in the presence of water with an excess of IBX furnishes the lactone (**38**) in 18% yield accompanied by 61% of (**37**) (Scheme 112).

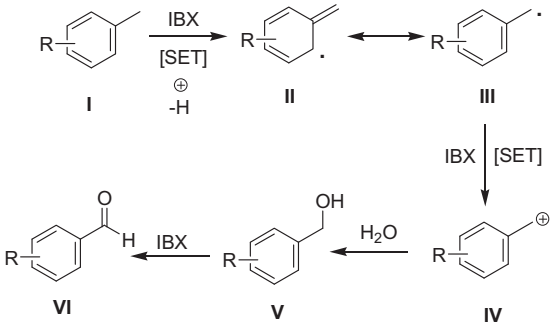


Scheme 112.

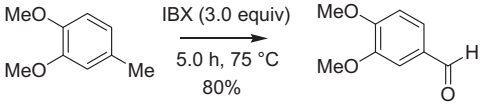
5.13. Oxidation of benzylic positions using IBX

The selective oxidation reaction of electron-rich sites, such as the benzylic position of an aromatic ring, with IBX follows a SET mechanism, as described in Scheme 113, to yield the corresponding benzylic alcohols, which are rapidly oxidized with an additional equivalent of IBX to afford the corresponding aldehydes.[61] Single-electron-transfer (SET) from the aromatic ring of compound **I** to IBX followed by loss of a proton leads to the radical intermediate **II**. Depiction of the canonical form **III** of this species illustrates how this could then undergo a second, IBX-facilitated, oxidation to give the benzylic carbocation **IV**. The trace amount of water present intercepts intermediate **IV** to furnish the benzylic alcohol **V**, which is rapidly oxidized with an additional equivalent of IBX to afford the product, aldehyde **VI**.

This IBX-induced oxidation of benzylic positions is quite general and proceeds efficiently in a mixed solvent system of fluorobenzene–DMSO (2:1) or in neat DMSO at 80–90 °C (Scheme 114). The oxidation of a variety of substituted toluenes and related systems proceeds in good-to-excellent yields. Over-oxidation to the corresponding carboxylic acid, a common feature of transition-metal-based benzylic oxidants, is not observed, even in electron-rich substrates. The presence of halogens and steric hindrance of *ortho*-substituents does not harm the desired oxidation. The reaction is not affected by the presence of water.[61]



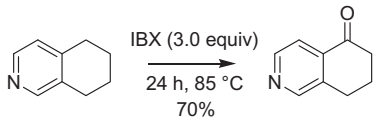
Scheme 113. Mechanistic blueprints for IBX-mediated SET oxidation adjacent to aromatic system.



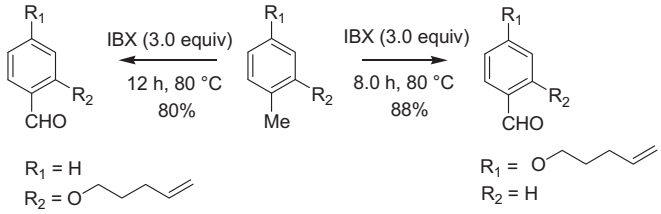
Scheme 114.

The oxidation of unsaturated substituted toluenes proceeds smoothly with IBX, as compared to the use of DDQ, PDC or CAN, all of which give low conversion or decomposition[62] (Scheme 116).[61]

For the oxidation of *N*-containing aromatic systems, slightly longer times or higher temperatures are necessary. It is noteworthy that no N-oxidation is observed in such cases (Scheme 115).

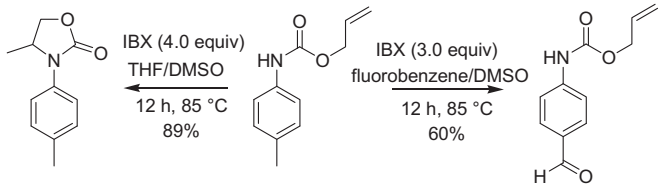


Scheme 115.



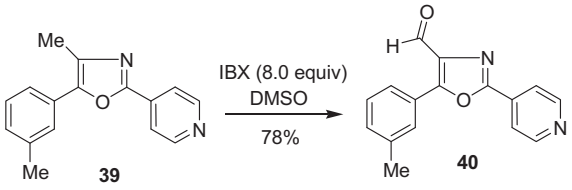
Scheme 116.

The amide functionality does not hamper the oxidation reaction, but, remarkably, the reaction could be turned toward the oxazolidinone pathway by modulating the reactivity of the reagent simply by switching from a fluorobenzene–DMSO solvent system to a THF–DMSO solvent system (Scheme 117).[61]



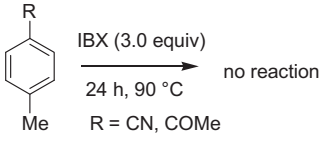
Scheme 117.

Complex structures, such as bis-methyl-substituted pyridyloxazole (**39**), in which more than one benzylic position is available for oxidation, could be oxidized at 110 °C by employing 8.0 equiv of IBX in DMSO to furnish the aldehyde (**40**) in 78% yield. It is interesting to note that the position of oxidation is the oxazole-bearing methyl group and not the benzylic methyl group (Scheme 118).[61]



Scheme 118.

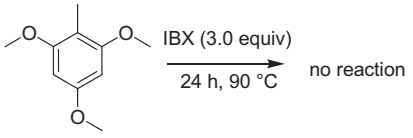
Electron-poor substituted toluenes do not undergo this reaction (Scheme 119). 2,4,6-Trimethoxytoluene fails to yield the corresponding aldehyde because of lack of a free *o*-position, which is the requirement for this oxidation protocol, as explained by the SET mechanistic rationale (Scheme 120).



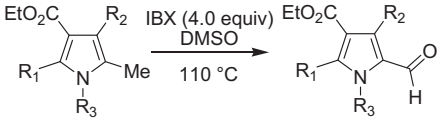
Scheme 119.

A full account of the scope, generality and usefulness of this general synthetic reaction for the selective oxidation of benzylic and other similarly activated positions is presented by Nicolaou et al.[63]

Kirsch and Binder[64] efficiently extended the application of this method for heteroaromatic systems. For example, oxidation of 5-methylpyrroles with 4.0 equiv of IBX in DMSO at 110 °C afforded the corresponding valuable 5-formylpyrroles in good yields (Scheme 121).



Scheme 120.

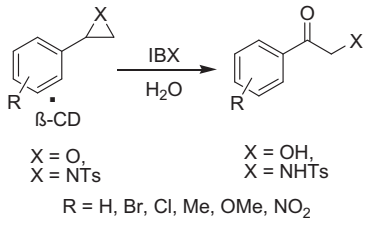


R_1 = Ph, R_2 = Ph, R_3 = Ph; 60%
R_1 = Ph, R_2 = Me, R_3 = *m*-Cl(C_6H_4); 76%

Scheme 121.

5.14. Synthesis of α-substituted carbonyl compounds using IBX

5.14.1. Synthesis of α-hydroxyketones and α-aminoketones from epoxides and aziridines using IBX/β-cyclodextrin. Rama Rao et al.[65] described the utility of IBX in an aqueous medium for the synthesis of α-hydroxyketones and α-aminoketones from the easily accessible epoxides and aziridines using β-cyclodextrin. The β-cyclodextrin (β-CD) inclusion complexes of the epoxide or aziridine, prepared in water, were reacted in situ with IBX at room temperature to obtain the α-hydroxyketones or α-aminoketones, respectively, in impressive yields (Scheme 122).



Scheme 122.

This reaction protocol is unique, as these reactions do not take place in the absence of cyclodextrin (CD). The reaction of epoxide/aziridine and IBX, when carried out in the absence of CD in DMSO, gave a mixture of products, i.e., epoxide yielded keto-alcohol and diol, whereas aziridine gave keto-amine and amino alcohol in an almost equal ratio. Cyclodextrin plays a crucial role in these reactions. In addition, the fact that IBX is insoluble in water shows the essential role of cyclodextrin. It appears that the cyclodextrin not only activates the epoxide/aziridine, but also forms a CD–IBX complex through H-bonding (Fig. 3). This complex first oxidizes the epoxide to 1,2-diol and aziridine to α-amino alcohol, and these first oxidation products are further oxidized at the secondary position to give the respective ketones. Cyclodextrins, which are cyclic oligosaccharides with hydrophobic cavities, mimic enzymes in their capability to bind substrates selectively and catalyze chemical reactions. They catalyze reactions by reversible formation of host–guest complexes having noncovalent bonding. Complexation depends on the size, shape, and hydrophobicity of the guest molecule.[65]

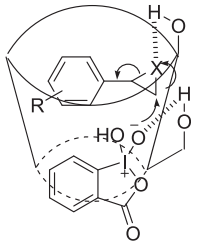
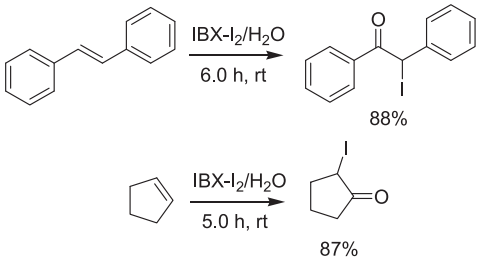
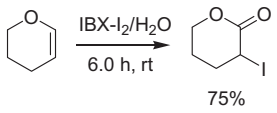


Figure 3.

5.14.2. Synthesis of α-iodoketones by oxidation of alkenes and alkynes using IBX/I_2 or IBX/N-iodosuccinimide. The direct and metal-catalyst-free oxidation of alkenes and alkynes using the IBX/I_2 reagent system to produce α-iodoketones under mild conditions was described by Yadav et al.[66] The method works well with both cyclic and acyclic olefins to give the desired α-iodoketones in good yields (Scheme 123). This oxidative iodination protocol was successful, even with 3,4-dihydro-2*H*-pyran (Scheme 124).

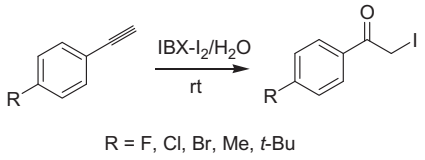


Scheme 123.



Scheme 124.

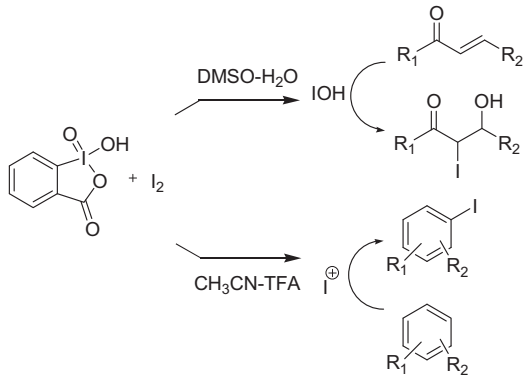
The reaction of aromatic alkynes such as 4-substituted-phenylacetylenes with the IBX/I_2 system proceeds smoothly at room temperature to obtain 2-iodo-1-(4-substituted-phenyl)ethanones (Scheme 125).



Scheme 125.

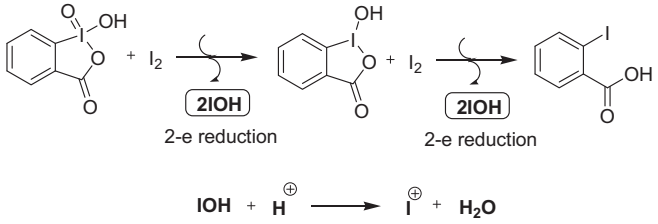
Yadav et al.[66] reported that other oxidants such as oxone/I_2, *N*-iodosuccinimide/I_2, ceric ammonium nitrate/I_2, and Selectfluor™/I_2 were not as effective for this transformation. Of the various hypervalent iodine reagents examined for this reaction, including iodosobenzene (PhIO), iodobenzenediacetate (PhI(OAc)$_2$), and Dess–Martin periodinane (DMP), 2-iodoxybenzoic acid (IBX) was found to be the most effective in terms of conversion. The combination of IBX and water, less expensive and readily available reagents, makes this method a simple, convenient, user-friendly, and attractive strategy for the preparation of α-iodoketones in a single-step operation.

Moorthy et al.[67] systematically studied the redox chemistry of IBX with molecular iodine. They showed that IBX is readily reduced to IBA in the presence of molecular iodine in DMSO to generate hypoiodous acid (IOH), which reacts with a variety of olefins as well as α,β-unsaturated ketones leading to their respective iodohydrins with *anti* stereochemistry. They also reported that the same redox chemistry in acetonitrile containing TFA produces iodonium ions and permits the facile iodination of a variety of aromatic compounds in excellent isolated yields (Scheme 126).



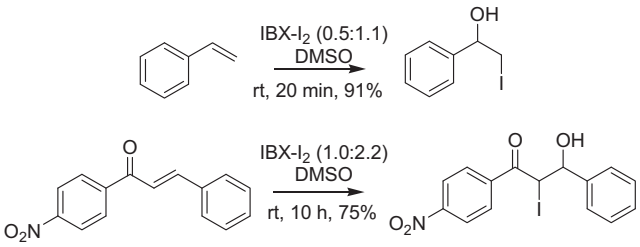
Scheme 126.

Based on meticulous reaction monitoring by ^{1}H NMR, Moorthy et al.[67] concluded that IBX undergoes facile two-electron reduction in the presence of I_2 in DMSO, leading to IOH and an I(III) species (IBA), which undergoes further two-electron reduction to generate an I(I) species, 2-iodobenzoic acid. In the presence of TFA, however, IOH captures a proton to form reactive iodonium ions (Scheme 127).



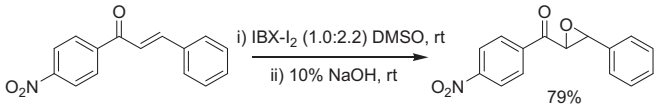
Scheme 127.

Electron-rich olefins react readily with IBX and I_2 in DMSO to afford the corresponding iodohydrins in near-quantitative yields, while electron-deficient olefins like α,β-unsaturated ketones react rather slowly and require the employment of a slight excess of the reagent (Scheme 128).



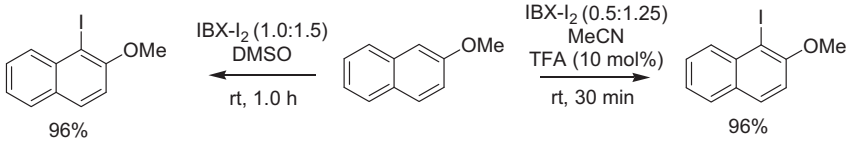
Scheme 128.

It is also possible to convert α-iodo-β-hydroxyketones into the corresponding α,β-epoxyketones in one pot by treatment with a base. Addition of 10% NaOH solution to the reaction mixture after the disappearance of the α,β-unsaturated ketone affords the desired epoxide in high yield (Scheme 129).[67]



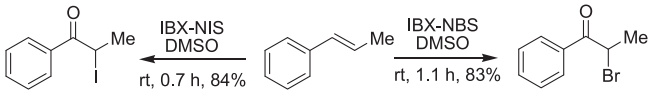
Scheme 129.

Moorthy et al.[67] also reported that this protocol works well for the iodination of a variety of aromatic compounds. The reaction can be carried out with IBX–I_2 in DMSO as well as MeCN–TFA (Scheme 130). While the iodination was found to be more efficient with activated aromatics, excess reagent was needed for less activated aromatics.



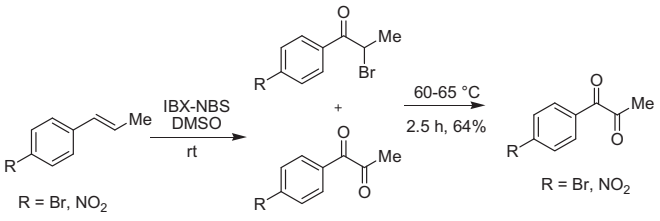
Scheme 130.

Using a similar approach, Moorthy et al.[68] described the utility of IBX and NBS/NIS to obtain α-bromo/iodoketones. They showed that a variety of olefins undergo conversion into the corresponding α-bromo/iodoketones when reacted with NBS/NIS and IBX (2.0 equiv) in DMSO at room temperature (Scheme 131).



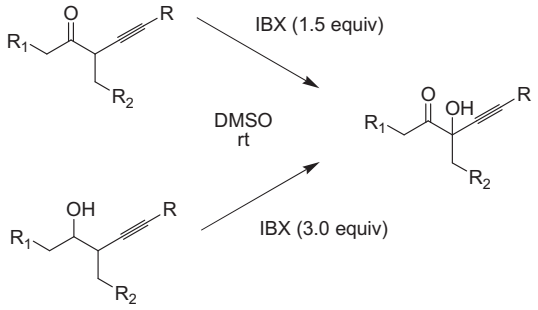
Scheme 131.

While the reaction occurs rapidly with electron-rich arylolefins, leading to the corresponding haloketones in excellent yields, those containing electron-withdrawing groups are found to yield diketones concomitantly, such that the latter are the exclusive products over extended duration of the reactions. For instance, *p*-bromo- and *p*-nitro-2-methylstyrenes react with NBS/NIS and IBX at room temperature to yield the diketone concomitantly with the formation of α-haloketones. On raising the temperature to 60–65 °C, however, this initially formed α-haloketone can be converted completely into the diketone (Scheme 132).



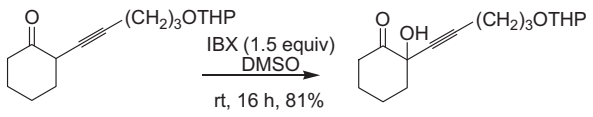
Scheme 132.

5.14.3. α-Hydroxylation of α-alkynyl carbonyl compounds using IBX. IBX is an excellent reagent for the α-hydroxylation of α-alkynyl carbonyl compounds without giving dehydrogenation products.[69] α-Alkynyl carbonyl compounds undergo selective α-hydroxylation when treated with 1.5 equiv of IBX in DMSO at room temperature. The same protocol can be efficiently extended to 2-alkynyl alcohols, which on treatment with 3.0 equiv of IBX furnish α-hydroxy-α-alkynyl carbonyl compounds (Scheme 133). The formation of α,β-unsaturated carbonyl compounds through dehydrogenation is not observed under these conditions.



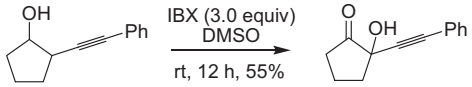
Scheme 133.

The conversion of various ketones into the corresponding tertiary alcohols can be accomplished at ambient temperature without the formation of enolates and silyl enol ethers. 2-Hydroxy carbonyl compounds having aryl and heteroaryl substituents at the alkyne terminus can be prepared in good yields. Functional groups such as ether, silyl ether, and acetal are well tolerated. Ketones with alkyl substituents at the alkyne terminus can also be effectively converted into the tertiary alcohols (Scheme 134).[69]



Scheme 134.

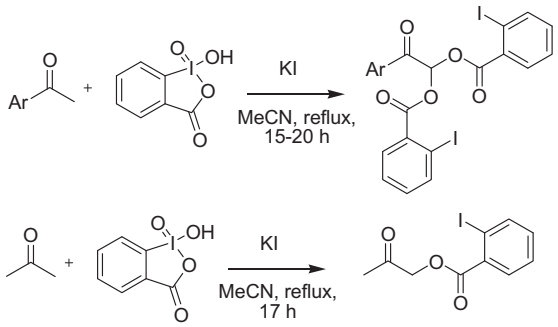
It is also possible to obtain tertiary alcohols starting from 2-alkynyl alcohols. 2-Hydroxy-2-(2-phenylethynyl)cyclopentanone, which is difficult to synthesize can be formed in moderate yield from 2-(2-phenylethynyl)cyclopentanol using 3.0 equiv of IBX in DMSO (Scheme 135).[69]



Scheme 135.

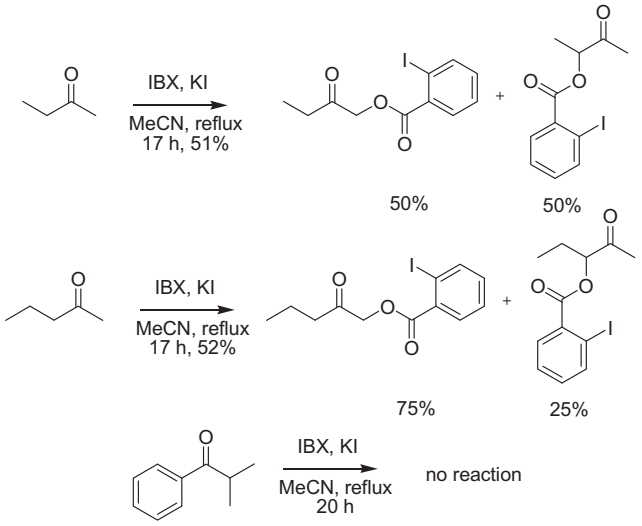
This convenient procedure is useful for the construction of a variety of tertiary alcohols under mildly acidic conditions. However, this method is limited to the conversion of ketones and secondary alcohols; aldehydes and primary alcohols are not transformed at room temperature or at elevated temperatures. Additionally, the presence of an alkynyl moiety is essential, as the reaction of carbonyl compounds containing alkyl substituents at C2 rather than alkynyl does not take place under these conditions. Even at elevated temperatures, these substrates form product mixtures, which mainly contain dehydrogenation products.[69]

5.14.4. Synthesis of α-(2-iodobenzoyloxy)ketones using IBX/KI. Liang et al.[70] reported that a 2-iodobenzoyloxy group derived from IBX can be installed at the α-position of ketones possessing α-methene when they are refluxed with IBX in acetonitrile in the presence of potassium iodide. Methyl aryl ketones produce bi-substituted products, whereas aliphatic ketones produce only mono-substituted products, even with an increased amount of IBX (Scheme 136).



Scheme 136.

Various structures of ketones give products having different regioselectivity. The results mainly depend on the activity of α-hydrogen atoms and steric hindrance of α-carbon atoms. In the case of 2-butanone and 2-pentanone, the reaction gave two isomers in a ratio of 1:1 and 3:1, respectively, whereas 2-methyl-1-phenylpropanone did not react under standard reaction conditions (Scheme 137). The substrates did not afford any α,β-unsaturated ketones. Liang et al.[70] tested a variety of solvents such as toluene, DMSO, CH_2Cl_2, MeCN, and THF, but found that MeCN was highly favorable for the reaction.

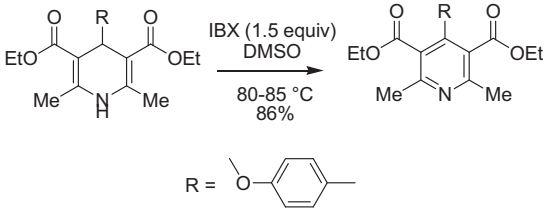


Scheme 137.

It is worth noting that, under the same conditions, the reactions of ketones with trivalent iodinanes such as 1-hydroxy-1,2-benziodoxol-3-(1*H*)-one (IBA) and iodobenzenediacetate [PhI(OAc)$_2$] did not give α-oxygenated products. This protocol by Liang et al.[70] provides a new approach for the synthetic application of IBX, as α-functionalized ketones are versatile intermediates for the synthesis of a variety of heterocyclic compounds, as well as natural products and related compounds.

5.15. Dehydrogenation using IBX to introduce unsaturation

The oxidation of Hantzsch 1,4-dihydropyridines is one of the challenging issues in organic chemistry. Generally, strong oxidants such as CrO_3, HNO_3, $KMnO_4$, cupric nitrate, ferric nitrate, and pyridinium chromate are used to accomplish this oxidation.[71] However, many of these methods necessitate the use of strongly acidic conditions and require extended reaction times or the need for excess oxidant. The yields using these reagents are also far from satisfactory. Yadav et al.[72] have reported an efficient protocol for the aromatization of Hantzsch 1,4-dihydropyridines using IBX as an oxidation agent. They treated diethyl-2,6-dimethyl-4-(*p*-methoxyphenyl)pyridine-3,5-dicaboxylate with IBX (1.5 equiv) in DMSO at 80–85 °C for 2.5 h to afford the corresponding pyridine derivative in 86% yield (Scheme 138).



Scheme 138.

In a similar manner, Hantzsch 1,4-dihydropyridines having various alkyl, aryl, and heterocyclic substituents present on the 4-position can be aromatized without any problem. Yadav et al.[72] proposed a possible mechanism for this oxidation, which proceeds via an ionic, concerted pathway or by an ensuing single-electron-transfer (SET) from the 1,4-dihydropyridine to the IBX to afford a nitrogen radical cation, followed by fragmentation. Both of these processes consequently supply the desired pyridine derivatives along with *o*-iodosobenzoic acid (IBA) (Scheme 139).

This method is very mild. Under the reaction conditions, no debenzylation or dealkylation, which is normally observed in aromatization of dihydropyridines by other oxidants was found to occur. In the aromatization of dihydropyridines with metallic nitrates, nitrated side products are generally observed, but these were absent during the aromatization by IBX.[72]

Coleman et al.[73] reported a remarkable and high-yielding double dehydrogenation to introduce unsaturation in the imidazo[4,5-*d*]azepine ring system using IBX. They successfully accomplished the total synthesis of ceratamines A and B using this novel application of IBX. The 7,8-dihydroimidazo[4,5-d]azepin-5(1*H*,4*H*,6*H*)-one ring was cleanly dehydrogenated upon treatment with IBX in DMSO at 35 °C to obtain the fully oxidized imidazo[4,5-*d*]azepine ring system (Scheme 140).

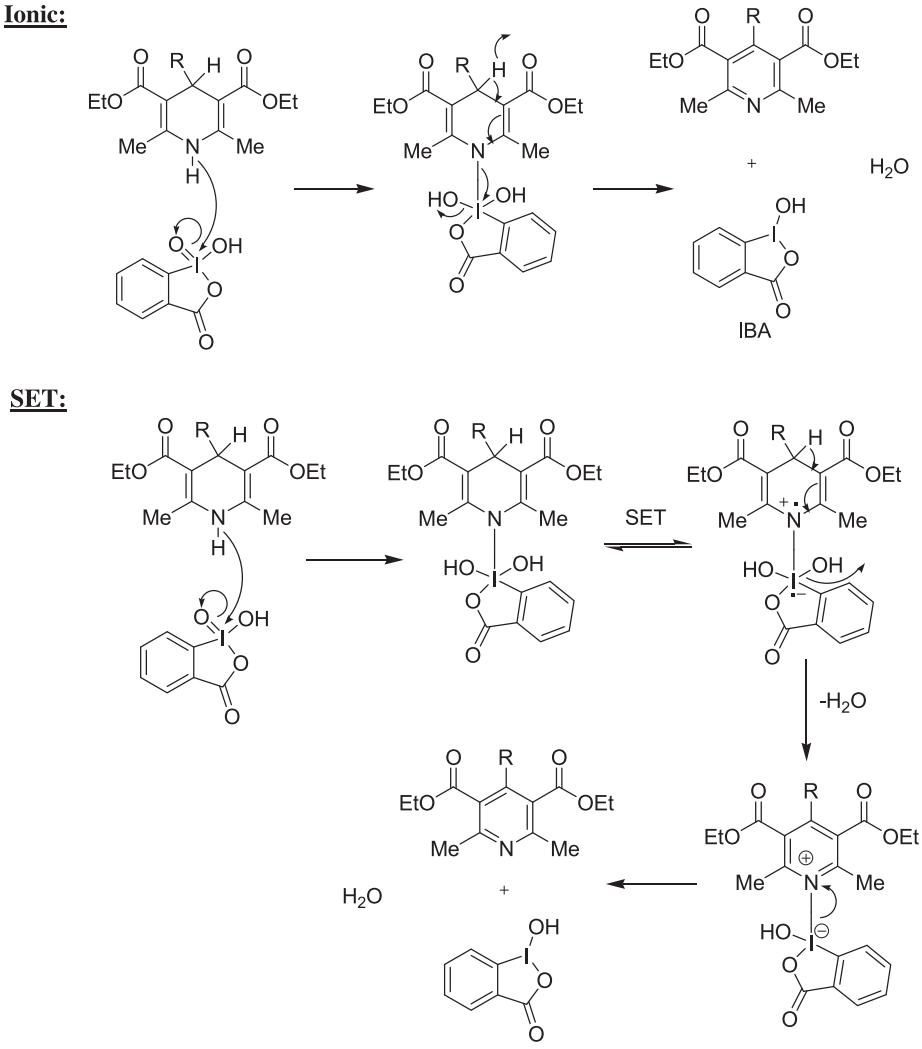
Martin et al.[74] employed IBX to oxidize dihydronaphthols to the corresponding naphthols in ethyl acetate at reflux temperature. The naphthols were obtained in excellent yields with no or little dehydration (Scheme 141).

Acetone and THF were also found to be suitable solvents for this protocol. DMSO, which is frequently used as a solvent in IBX oxidations, was found to be unsatisfactory for the oxidation of dihydronaphthols, because the naphthol products underwent rapid decomposition. For example, when a homogeneous solution of the dihydronaphthol (**41**) in DMSO containing IBX was stirred at room temperature for 2 h, less than 10% of naphthol (**42**) was recovered, while oxidation of the same dihydronaphthol (**41**) with IBX (3.0 equiv) in ethyl acetate at 80 °C for 3.0 h afforded the naphthol (**43**) in 94% yield (Scheme 142).[74]

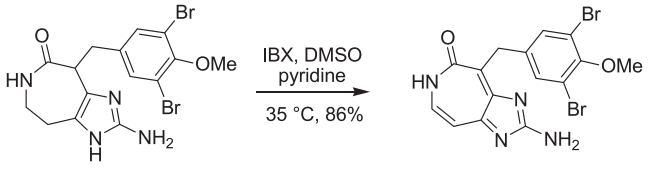
Nicolaou et al.[75] reported a remarkable IBX-mediated dehydrogenation protocol for the oxidation of secondary amines to the corresponding imines in excellent yield, under mild conditions and with short reaction times (Scheme 143).

This dehydrogenation protocol tolerates a wide range of substrate functionality and was found to be regioselective when unsymmetrical secondary amines were employed. Generally, the reaction proceeded to form the conjugated *N*-benzylidene preferentially, rather than occurring at the alternative unactivated site to furnish the imine (Scheme 144).[75]

Nicolaou et al.[75] also reported the IBX-mediated oxidative aromatization of functionalized nitrogen heterocycles from simple substrates, including those with no activating groups. Ttreatment of



Scheme 139. Mechanistic pathway (ionic and SET) for aromatization of Hantzsch 1,4-dihydropyridines using IBX.



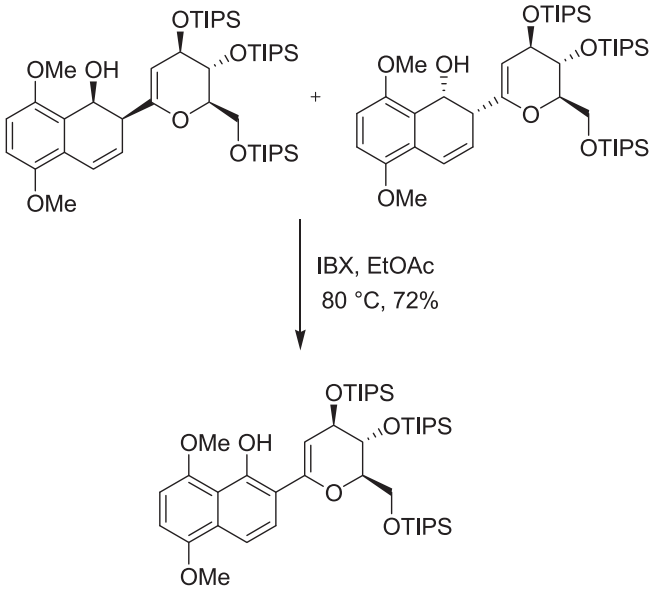
Scheme 140.

2-phenyl-4,5-dihydro-1*H*-imidazole with IBX (1.5 equiv) in DMSO for 14 h at 45 °C gave 2-phenylimidazole (Scheme 145). Despite requiring oxidation at an unactivated α-methylene group with respect to the nitrogen atom (i.e., not a benzylic methylene), the reaction proceeded smoothly to furnish the corresponding imidazole in high yield.

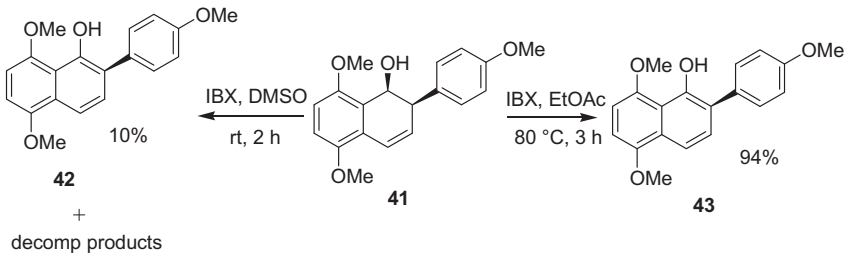
4-(4-Chlorophenyl)pyridine could also be obtained in high yield from the corresponding tetrahydropyridyl compound using this remarkable application of IBX (Scheme 146).[75]

5.16. Synthesis of quinoxalines using IBX

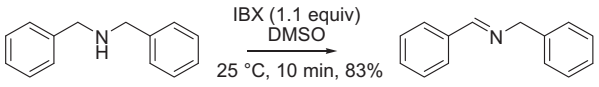
Quinoxalines are a very important class of heterocyclic compounds as their derivatives find applications in various fields of science and technology, such as dyes, pharmaceuticals, electrical/photochemical materials, etc. Generally, quinoxaline derivatives are synthesized by the condensation of 1,2-dicarbonyl compounds with substituted 1,2-diaminobenzenes at elevated temperatures for several hours. Heravi et al.[76] have reported the synthesis of quinoxaline derivatives by the condensation of *o*-phenylenediamines with 1,2-dicarbonyl compounds in acetic acid in the presence of



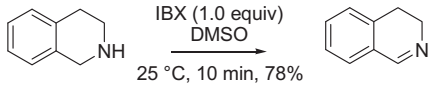
Scheme 141.



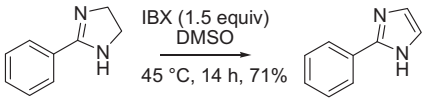
Scheme 142.



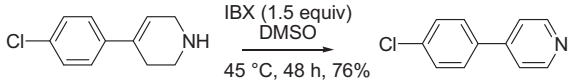
Scheme 143.



Scheme 144.

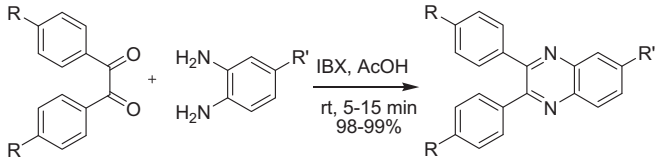


Scheme 145.



Scheme 146.

catalytic amounts of IBX at room temperature (Scheme 147). The reaction proceeds very smoothly and free from side products in 5 to 15 min. The products are obtained in quantitative yields. Just 1 mol% of IBX is sufficient to effect the reaction, in the absence of which the reaction does not complete, even after 24 h.



Scheme 147.

Although the role of IBX is not clearly known, Heravi et al.[76] suggested that it activates the carbonyl compound and facilitates attack of the amino group on the carbonyl compound, as illustrated in Scheme 148.

If the reaction is performed in water, only moderate yields of products (30%) are obtained, even after 24 h. Various *o*-phenylenediamines and 1,2-dicarbonyl compounds with electron-donating or -withdrawing groups can be used without any effect on the time of reaction and yields of products.[76]

5.17. Cyclization of acylated alkoxyamines into isoxazolidines using IBX

Studer and Janza[77] showed that acylated alkoxyamines can be cyclized to isoxazolidines using IBX as an oxidant. The cyclization proceeds via IBX-generated *N*-alkoxyamidyl radicals. The reaction of *N*-(1-phenyl-3-butenyloxy)acetamide with IBX (2.0 equiv; added in two portions) in dioxane–DMSO (5:1; 0.01 M) at 110 °C provided the cyclization product, *N*-acetyl-3-methyl-5-phenylisoxazolidine, in 20 min (Scheme 149).

This IBX-mediated alkoxyamidyl radical cyclization works only with *N*-acylated alkoxyamines. While Boc-protected and sulfonylated alkoxyamines do not react under the standard cyclization conditions, the unprotected alkoxyamines give decomposition products. 4-Methoxybenzoylated alkoxyamines deliver the desired cyclization product only in trace amounts giving the ester, e.g., 1-phenyl-3-butenyl-4-methoxybenzoate, as a major product (Scheme 150).[77]

Since the O–N bond in isoxazolidines can be readily cleaved, this oxidative cyclization protocol has opened up a new entry to obtain 1,3-amino alcohols. Studer and Janza[77] reported that isoxazolidines when treated with SmI_2 in THF undergo reductive cleavage to provide the *N*-acetylated amino alcohols in 53% yield (Scheme 151).

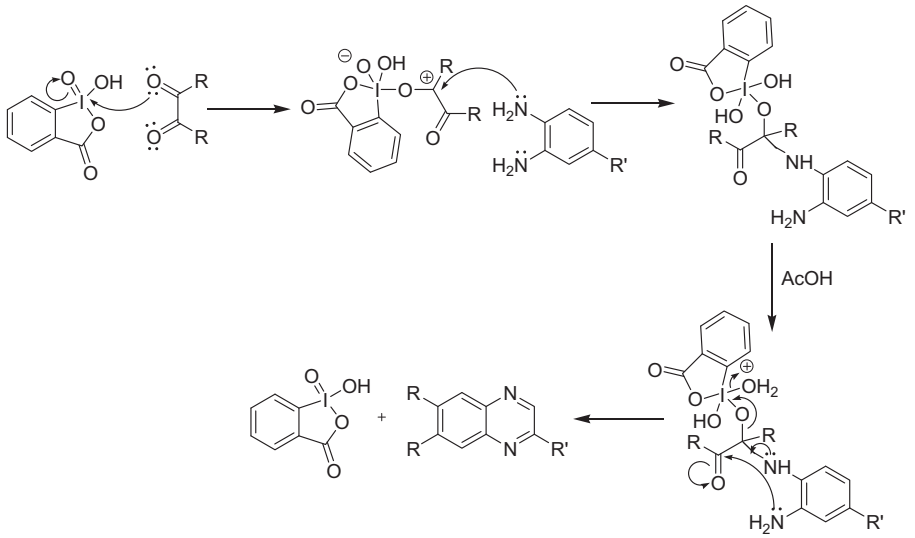
5.18. Dual acylation of the nitrogen and α-carbon centers of tetrahydroisoquinoline by carboxylic acid and isocyanide using IBX

Zhu and Ngouansavanh[78] described a highly efficient IBX-mediated oxidative three-component Ugi-type reaction that allows a dual acylation of the nitrogen and α-carbon centers of tetrahydroisoquinoline by a carboxylic acid and an isocyanide (Scheme 152). In a typical procedure, carboxylic acid (1.5 equiv), tetrahydroisoquinoline (1.5 equiv), and isocyanide (1.0 equiv) were added successively to a suspension of IBX (2.0 equiv) in dry THF and the mixture was heated at 60 °C to afford the desired functionalized tetrahydroisoquinolines in good yields. Thus, the three-component condensation of tetrahydroisoquinoline, benzoic acid, and benzyl isocyanide gave the three-compound adduct, 2-benzoyl-*N*-benzyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide, in 87% yield (Scheme 152).

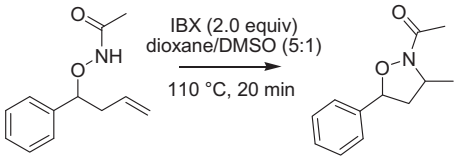
A variety of carboxylic acids including benzoic acid, acetic acid, and functionalized acids such as 2-iodobenzoic acid, cinnamic acid, (*E*)-4-ethoxy-4-oxobut-2-enoic acid, phenylpropiolate, and *N*-Cbz-glycine can be used as reaction partners to acylate the secondary amine. Isocyanides with different steric and electronic properties such as benzyl isocyanide, 2-iodobenzyl isocyanide, cyclohexyl isocyanide, *tert*-butyl isocyanide, and α-benzyl-α-isocyanoacetamide can be used to directly acylate the α-carbon atom of tetrahydroisoquinoline. Direct functionalization of an acyclic amine was also found to be feasible. Thus, the reaction of dibenzylamine with benzoic acid and benzyl isocyanide in DMSO afforded the α-acyloxy amide in 32% yield (Scheme 153).[78]

5.19. IBX/phase-transfer catalyst (PTC) combination for variety of oxidative transformations

5.19.1. Conversion of primary carboxamides into one-carbon dehomologated nitriles and α,α-disubstituted acetamides into one-carbon dehomologated ketones using IBX/TEAB. Akamanchi et al.[79] described

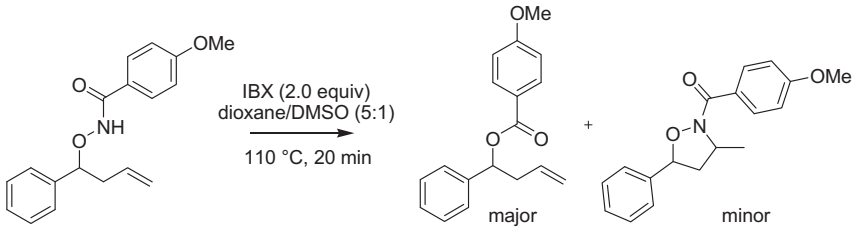


Scheme 148. Mechanistic approach for synthesis of quinoxalines using IBX.

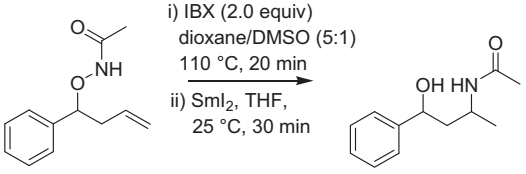


Scheme 149.

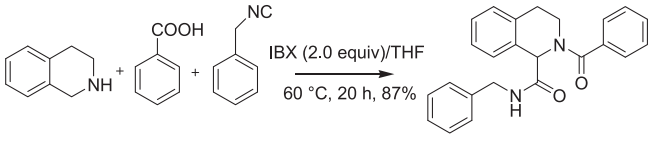
carboxamides were dehomologated to nitriles using a combination of IBX and TEAB (Table 5, entries 1–5). The reaction was carried out with 2.5 equiv of IBX/TEAB in acetonitrile at 60 °C. The reaction also proceeds at room temperature, although it requires a longer time. β-Keto amides can also be converted into the corresponding benzoyl cyanides in moderate yields under the same reaction conditions (Table 5, entry 5).[79]



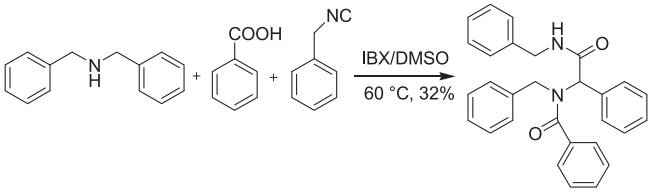
Scheme 150.



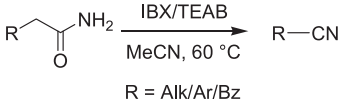
Scheme 151.



Scheme 152.



Scheme 153.

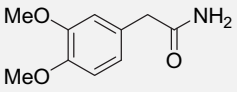
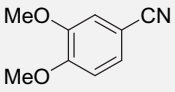
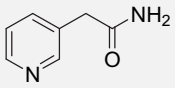
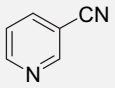
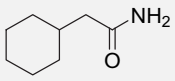
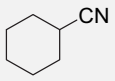
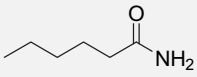
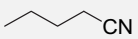
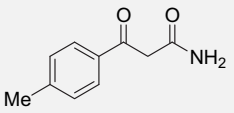
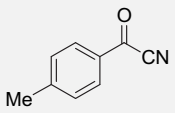


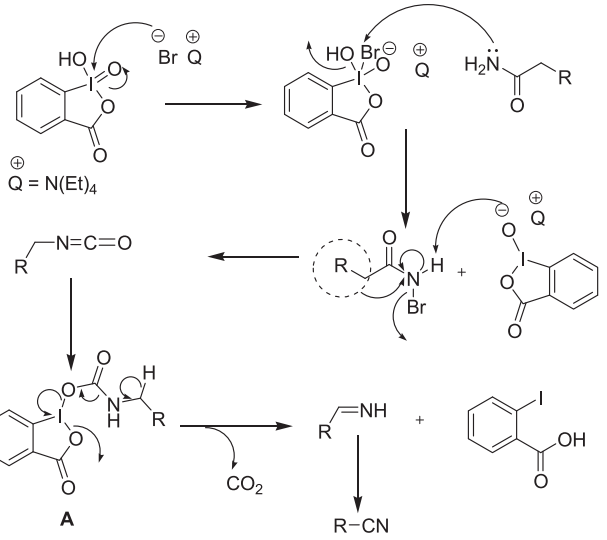
Scheme 154.

that IBX in combination with tetraethylammonium bromide (TEAB) induces a clean and efficient oxidative transformation of primary carboxamides to one-carbon dehomologated nitriles under neutral conditions (Scheme 154). This method possesses a high functional-group tolerance under the reaction conditions, affords clean products in moderate-to-high yields, and is of great utility in organic synthesis. A series of aromatic, heteroaromatic, and aliphatic

According to a plausible reaction pathway proposed by Akamanchi et al.,[79] TEAB plays a crucial role in the formation of the nitrile and in accelerating the reaction rate (Scheme 155). Addition of TEAB to IBX causes the oxidation of amide to *N*-bromoamide, which on subsequent rearrangement forms isocyanate. Nucleophilic attack by the oxygen of IBA on the isocyanate gives the intermediate **A**, which subsequently decomposes to give an imine, carbon dioxide, and *o*-iodobenzoic acid. The imine on further rapid oxidation gives the nitrile.

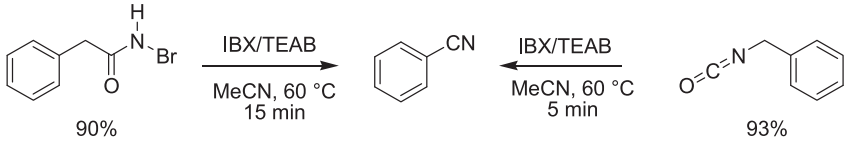
Table 5
IBX/TEAB-mediated oxidative transformations of primary amides to one-carbon dehomologated nitriles using 2.5 equiv of IBX and TEAB in acetonitrile at 60 °C

Entry	Amide	Nitrile	Time (h)	Yield (%)
1			0.3	95
2			0.5	83
3			2.5	72
4			3.5	60%+20% starting material
5			1.5	80



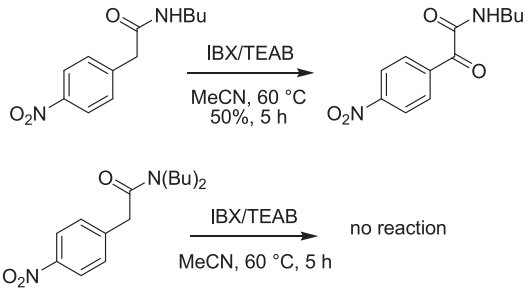
Scheme 155. Postulated mechanism for IBX/TEAB-mediated oxidative one-carbon dehomologation of primary carboxamides to nitriles.

In order to support this proposed mechanism and to justify the formation of isocyanate and *N*-bromo-α-substituted acetamide as possible intermediates in the mechanism, Akamanchi et al.[79] subjected the authentic *N*-bromobenzamide and benzyl isocyanate to established reaction conditions to obtain benzonitrile (Scheme 156).



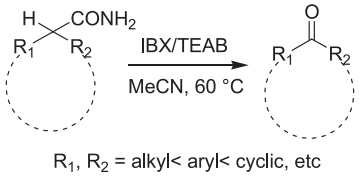
Scheme 156.

Secondary amides under the same reaction conditions underwent benzylic oxidation, whereas tertiary amides remained unaffected (Scheme 157).[79] Other hypervalent iodine compounds were also examined for this transformation. While the combination of DMP and TEAB was found to be viable for this transformation, no reaction was observed when HIO_3/TEAB and I_2O_5/TEAB combinations were used.



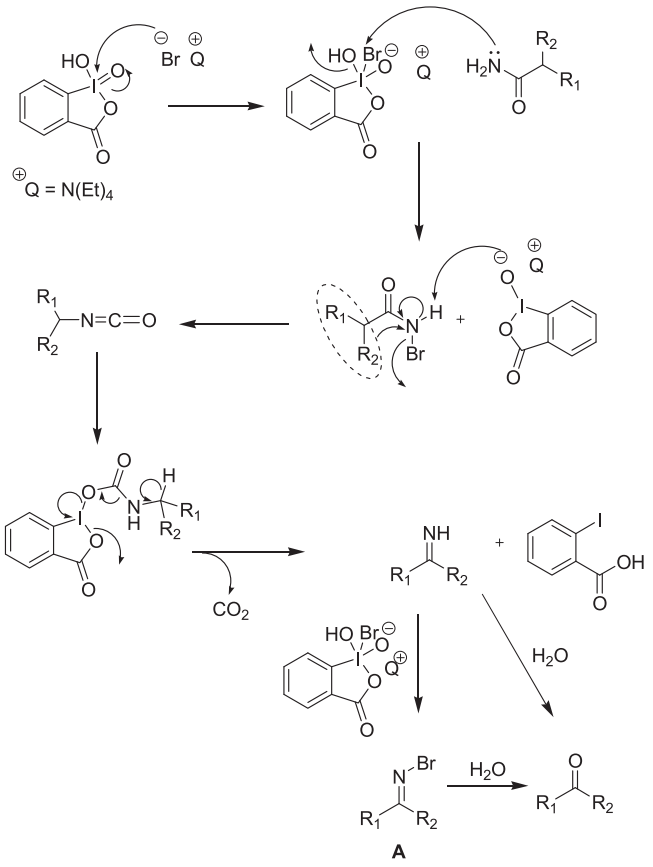
Scheme 157.

In another remarkable discovery, Akamanchi et al.[80] found that α,α-disubstituted (alkyl/aryl) acetamides on treatment with 2.0 equiv of IBX in combination with 1.0 equiv of TEAB in acetonitrile at 60 °C undergo oxidative dehomologation to the corresponding one-carbon-shorter ketones (Scheme 158). A variety of substrates were reacted to obtain the corresponding one-carbon-shorter ketones. Acetamides having at least one aromatic substituent at the α-position react comparatively faster and give relatively higher yields in comparison to the dialkyl and cycloalkyl acetamides.



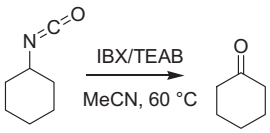
Scheme 158.

The proposed mechanism, as shown in Scheme 159, states that the reaction proceeds via the formation of an *N*-bromoimine intermediate **A**, which is less stable and hydrolyzes to give ketones. Akamanchi et al.[80] confirmed this fact by isolating the *N*-bromo-1,1-diphenylmethanimine formed during oxidative transformation of α,α-diphenylacetamide. The mechanism also explains why a molar equivalent of TEAB is required.

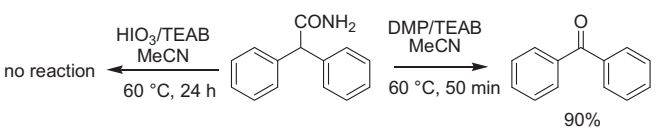


Scheme 159. Plausible mechanism for oxidative conversion of α,α-disubstituted acetamides into corresponding one-carbon-shorter ketones using IBX.

The inclusion of isocyanate as a possible intermediate in the mechanism was justified by converting cyclohexyl isocyanate into cyclohexanone under the same reaction conditions (Scheme 160). Other hypervalent iodine (λ^5) reagents like DMP and HIO_3 were screened under the same reaction conditions. DMP was found to carry out the desired transformation in good yield, while HIO_3 did not give any reaction (Scheme 161).[80]

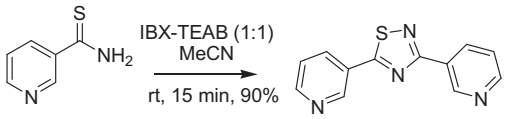


Scheme 160.



Scheme 161.

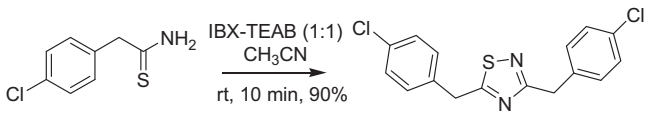
5.19.2. Oxidative dimerization of aromatic and heteroaromatic thioamides to obtain corresponding 3,5-disubstituted-1,2,4-thiadiazoles using IBX/TEAB. A reagent system consisting of a combination of IBX and TEAB has been utilized for the clean and efficient synthesis of 3,5-disubstituted-1,2,4-thiadiazoles from the corresponding thioamides. Akamanchi et al.[81] reported that a variety of aromatic and heteroaromatic thioamides undergo oxidative dimerization to form the corresponding 3,5-disubstituted-1,2,4-thiadiazoles when treated with 1.1 equiv of IBX–TEAB (1:1) in acetonitrile at room temperature (Scheme 162).



Scheme 162.

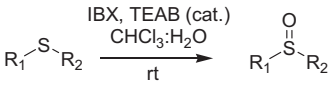
The reaction is facile and completes in only 5 min to afford the products in excellent yields. Dichloromethane and toluene can also be used as solvents for this transformation; however, the reactions in toluene were found to be slow and gave slightly lower yields. A noteworthy feature of this reaction is that benzylic positions, which are susceptible to IBX, remain unaffected. For instance, thioamides such as 4-chlorophenylthioacetamide undergo this oxidative dimerization to afford 3,5-bis(4-chlorobenzyl)-1,2,4-thiadiazole without any side products (Scheme 163).[81]

In the absence of TEAB, IBX alone brings about this reaction with a longer reaction time (1 h). Another hypervalent iodine reagent, DMP, in combination with TEAB also gives this oxidative dimerization product under similar reaction conditions.



Scheme 163.

5.19.3. Oxidation of sulfides to sulfoxides using IBX/TEAB. A large number of oxidants that convert sulfides into the corresponding sulfoxides have been reported in the literature. Most of these reagents require careful control of the reaction conditions to minimize the formation of the sulfone as a side product. Akamanchi et al.[82] reported a mild, selective, and high-yielding method for the oxidation of sulfides to sulfoxides using IBX in the presence of catalytic amounts of tetraethylammonium bromide (TEAB) (Scheme 164). A variety of sulfides carrying various functional groups such as acids, esters, alcohols, amides, nitriles, etc. were oxidized to the corresponding sulfoxides in almost quantitative yields (Table 6, entries 1–5). The reaction can be carried out in a biphasic solvent system of chloroform–water (100:1) at ambient temperature.



Scheme 164.

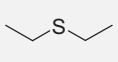
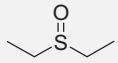
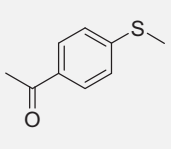
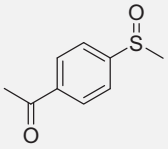
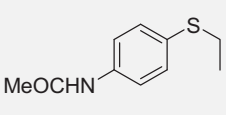
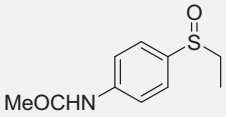
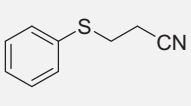
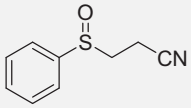
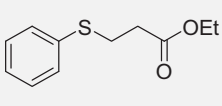
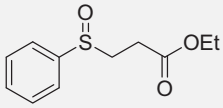
In the case of sterically hindered and less nucleophilic sulfides such as diphenyl sulfide and benzyl phenyl sulfide, longer reaction times are required (Scheme 165).[82]

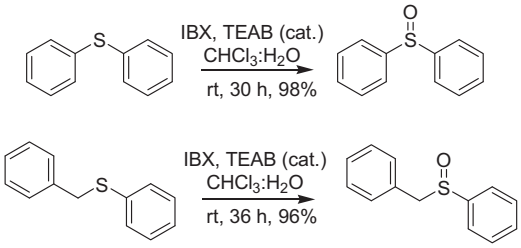
A significant feature of this oxidation protocol is the chemoselectivity of sulfide oxidation over alcohol. 3-(Phenylthio)butan-1-ol when subjected to oxidation in two different solvent systems and in the presence and absence of TEAB revealed that the selectivity can be shifted from sulfide to alcohol oxidation by changing the solvent system (Scheme 166).[82]

The main advantage of this method is that overoxidation to sulfones does not occur, even with an excess of IBX/TEAB over a long reaction period (24 h). This could be attributed to the low nucleophilicity of the sulfoxide. It is postulated that the oxidation involves an initial polarization of the I=O bond by TEAB and then a nucleophilic attack of sulfur on the hypervalent iodine(V) center, followed by a concerted oxygen transfer to give the sulfoxides (Scheme 167).[82]

5.19.4. Synthesis of α-iminonitriles using IBX/TBAB. Zhu et al.[83] described a one-pot synthesis of α-iminonitriles by the reaction of

Table 6
Oxidation of sulfides to sulfoxides at room temperature using 1.1 equiv of IBX and catalytic amount of TEAB in $CHCl_3$–H_2O (100:1)

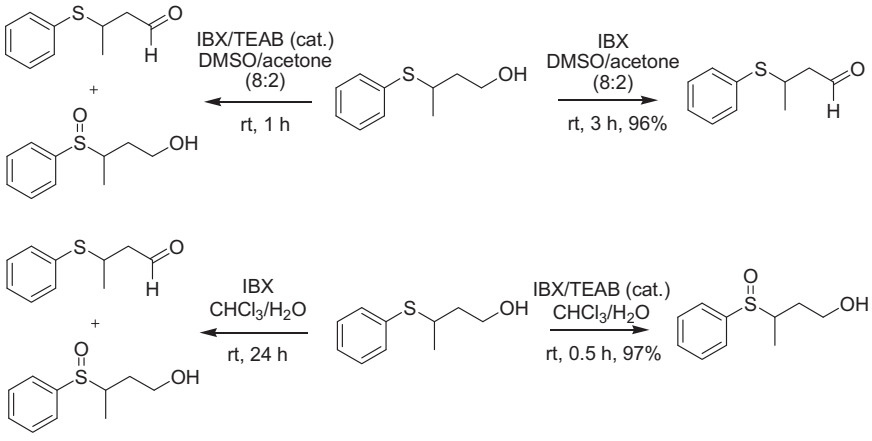
Entry	Sulfide	Sulfoxide	Time (min)	Yield (%)
1			20	98
2			30	97
3			30	98
4			210	98
5			240	97



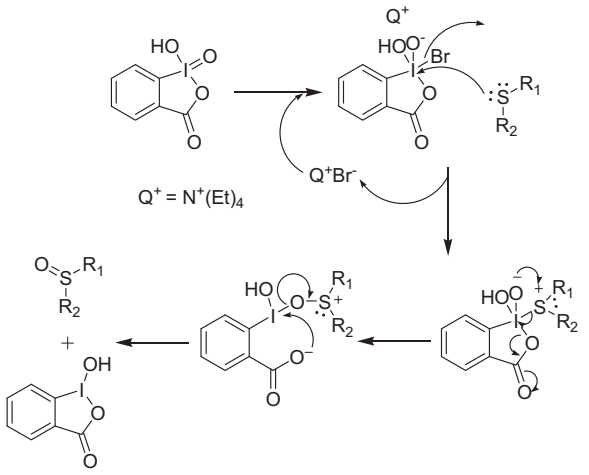
Scheme 165.

aldehydes, primary amines, and TMSCN using IBX as oxidant in conjunction with a catalytic amount of tetrabutylammonium bromide (TBAB) (Scheme 168). Either THF or acetonitrile can be used as a solvent.

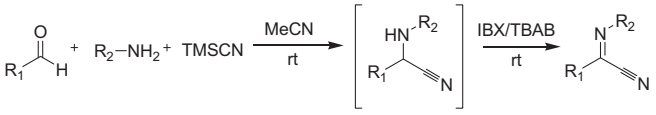
Electron-neutral, -rich, and -poor aromatic aldehydes, as well as α,β-unsaturated aldehydes are all compatible with the oxidative conditions, leading to the respective adducts in good-to-excellent



Scheme 166.

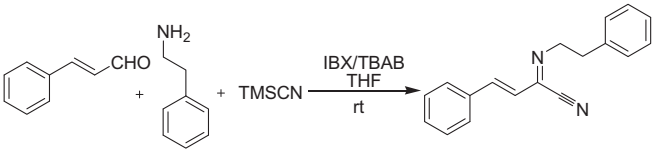


Scheme 167. Plausible mechanism of oxidation of sulfides to sulfoxides using IBX in presence of catalytic amount of TEAB.

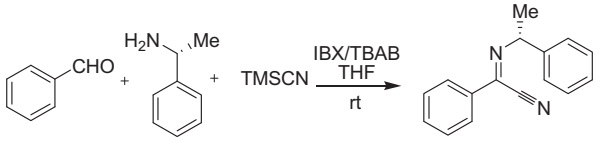


Scheme 168.

yields. Cinnamaldehyde when treated with 2-phenylethanamine under these reaction conditions gave 2-(phenylethylamino)-4-phenylbut-3-enenitrile in 97% yield (Scheme 169). (*S*)-1-Phenylethanamine on reaction with benzaldehyde afforded 2-phenyl-2-((*R*)-1-phenylethylamino)acetonitrile in almost quantitative yield without racemization (Scheme 170).[83]



Scheme 169.



Scheme 170.

When bulky amines such as *tert*-butylamine or aromatic amines like aniline were subjected to the same conditions, the reaction was found to be slowed down significantly. However, by adding a catalytic amount of iodine, which is known to catalyze the Strecker reaction, the desired iminonitrile could be isolated in excellent yields. This three-component reaction is also applicable to the synthesis of α-iminonitriles derived from aliphatic aldehydes whether linear or α-branched, which are far less accessible than their aromatic counterparts. However, in the case of aliphatic aldehydes, higher yields were generally obtained when IBX was introduced into the reaction mixture after the completion of the Strecker reaction (Scheme 171).[83]

Zhu et al.[83] successfully applied this methodology for the synthesis of indolizidines. The 2-cyano-1-aza-1,3-butadiene obtained by treating penten-1-amine with cinnamaldehyde and TMSCN in MeCN at room temperature in the presence of IBX/TBAB underwent a cycloaddition reaction under microwave irradiation conditions (300 W; 6 h; toluene) to afford the corresponding indolizidine in 99% yield as a mixture of two diastereomers (1:1) (Scheme 172).

Zhu et al.[84] also described the application of this protocol for an efficient synthesis of 2-amino-5-cyanopyrroles. α-Iminonitriles prepared using this protocol were subjected to a [4+1] cycloaddition reaction with isocyanides in the presence of a catalytic amount of $AlCl_3$ to afford the polysubstituted 2-amino-5-cyanopyrroles in good-to-excellent yields (Scheme 173).

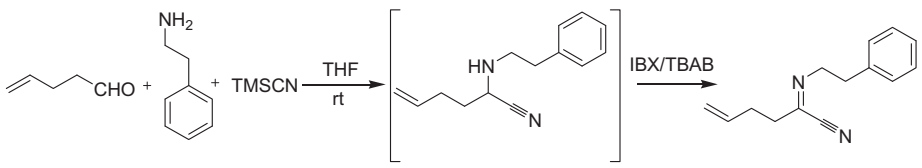
5.20. Catalytic system of IBX and rare earth metal salts or alkaline earth metal salts for various transformations

5.20.1. Synthesis of α,β-unsaturated δ-lactones from glycals using IBX/InCl₃. A simple and convenient method for the preparation of optically active α,β-unsaturated δ-lactones from glycals using $InCl_3$ in combination with IBX was reported by Yadav et al.[85] Treatment of a 3,4,6-tri-*O*-protected-D-glucal in water with 10 mol % $InCl_3$ and 2.5 equiv of IBX in refluxing acetonitrile resulted in the formation of the 4,6-di-*O*-protected-2,3-dideoxy-D-*erythro*-hex-2-enono-1,5-lactone in good yield (Scheme 174). Various D-glucals such as 3,4,6-tri-*O*-benzoyl-, 3,4,6-tri-*O*-allyl-, and 3,4,6-tri-*O*-benzyl-D-glucal derivatives can be converted into their corresponding 2,3-dideoxy-D-hex-2-enono-1,5-lactones using this procedure. Other glycals such as 3,4-di-*O*-acetyl-D-arabinal also afford the respective enelactones in fairly good yields under similar conditions (Scheme 175).

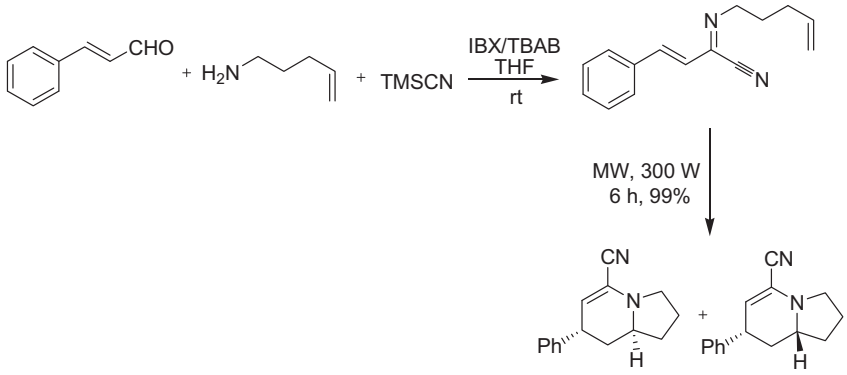
However, in the oxidation of disaccharides like hexa-*O*-acetyl-D-lactal under similar reaction conditions, cleavage of the glycosidic bond was observed to afford 3,6-dioxo-(2*R*)-3,6-dihydro-2*H*-2-pyranylmethyl acetate (Scheme 176).[85]

Mechanistically, the reaction is initiated by an $InCl_3$-induced allylic rearrangement of the glycal with water to form an intermediate 2,3-dideoxy-hex-2-enopyranoside, which on subsequent oxidation by IBX results in the formation of the corresponding enelactone (Scheme 177). Various catalysts such as scandium triflate, ytterbium triflate, cerium triflate, and indium triflate were also employed by Yadav et al.[85] for this transformation, but indium trichloride was found to be the most effective catalyst in terms of conversion and reaction rates. Furthermore, the combination of IBX with conventional Lewis acids such as $BF_3 \cdot OEt_2$, $TiCl_4$, and TMSOTf failed to give the desired enelactones.

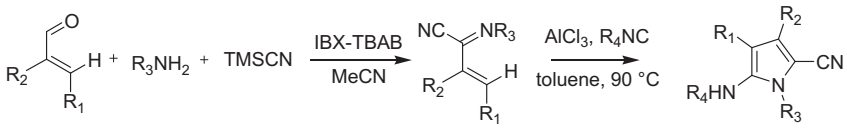
5.20.2. Oxidative conjugate addition of allyltrimethylsilane to Baylis–Hillman adducts using IBX/Sc(OTf)₃. Yadav et al. exploited combinations of IBX with different rare earth metal salts for various transformations. They described an efficient protocol for one-pot oxidative conjugate addition of allyltrimethylsilane to Baylis–Hillman adducts using IBX/$Sc(OTf)_3$ as a catalytic system.[86] The oxidative Michael reaction of ethyl 2-[hydroxyl(phenyl)methyl]



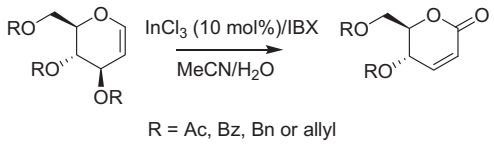
Scheme 171.



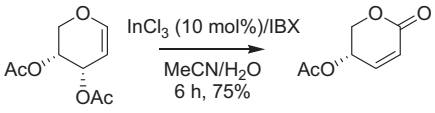
Scheme 172.



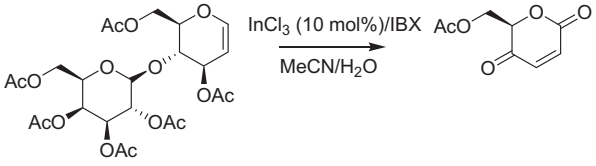
Scheme 173.



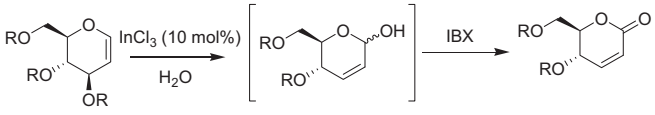
Scheme 174.



Scheme 175.



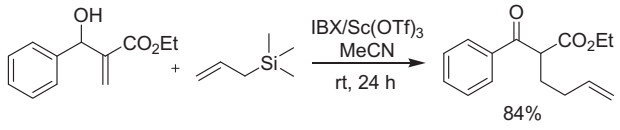
Scheme 176.



Scheme 177.

acrylate with allyltrimethylsilane in the presence of 1.2 equiv of IBX and 10 mol % $Sc(OTf)_3$ in acetonitrile at room temperature furnished ethyl 2-benzoylhex-5-enoate in 84% yield (Scheme 178). The method offers several advantages such as operational simplicity, mild reaction conditions, cleaner reaction profiles, and a simple workup procedure and is an attractive strategy for the preparation of homoallyl β-ketoesters in a single-step operation.

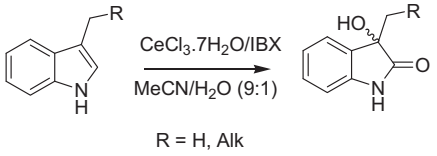
This method works well with substrates derived from both aliphatic and aromatic aldehydes and is compatible with various functionalities such as halides, aryl methyl ethers, esters, and alkenes. In the absence of $Sc(OTf)_3$, no allyl addition occurred, even



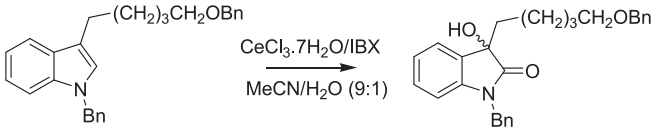
Scheme 178.

after long reaction times under reflux conditions. The use of other catalytic systems such as $IBX/InCl_3$, $IBX/InBr_3$, and $IBX/CeCl_3{\cdot}7H_2O$ did not give satisfactory yields of products.[86]

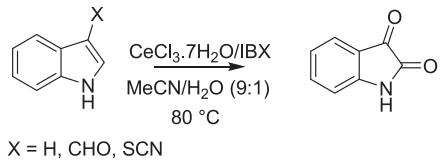
5.20.3. Synthesis of 3-hydroxyoxindoles from 3-alkylindoles using IBX/$CeCl_3{\cdot}7H_2O$. The catalytic system of $IBX/CeCl_3{\cdot}7H_2O$ was used by Yadav et al.[87] for the direct conversion of 3-alkylindoles into 3-hydroxyoxindoles in a single-step operation. Treatment of 3-methylindole with IBX (2.5 equiv) in the presence of $CeCl_3{\cdot}7H_2O$ (10 mol %) in MeCN–H_2O (9:1) at room temperature gave the corresponding 3-hydroxyoxindole in 82% yield (Scheme 179). Likewise, several 3-alkylindoles underwent smooth oxidation to produce 3-hydroxyindolin-2-ones in high yields. *N*-Alkyl or *N*-benzyl derivatives can also be efficiently converted into their corresponding 3-hydroxyindolin-2-ones (Scheme 180). Interestingly, using a similar reagent system, 3-formylindole, 3-thiocyanoindole, and unsubstituted indole underwent oxidation at a higher temperature (80 °C) to afford exclusively isatin, instead of 3-hydroxyoxindoles (Scheme 181).[87]



Scheme 179.



Scheme 180.



Scheme 181.

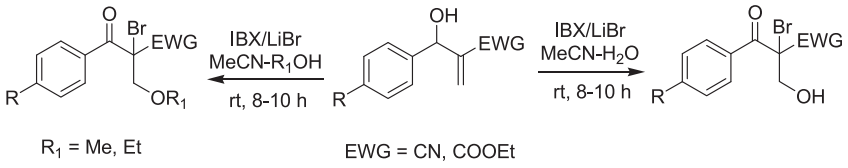
Yadav et al.[87] observed that, in the absence of $CeCl_3 \cdot 7H_2O$, this oxidation reaction was rather slow and afforded the corresponding 3-hydroxyoxindoles in lower yields (15–25%). Oxidation does not occur if the reaction is performed using 10 mol % of $CeCl_3 \cdot 7H_2O$ in the absence of IBX. Of the various cerium reagents such as $Ce(OTf)_3$ and ceric ammonium nitrate, which were tested, cerium(III) chloride was found to be the most effective Lewis acid for this conversion.

5.20.4. Oxidative bromohydroxylation and bromoalkoxylation of Baylis–Hillman adducts using IBX/LiBr. Yadav and Awasthi[88] reported the application of IBX/LiBr as a catalytic system for one-pot oxidative bromohydroxylation and bromoalkoxylation of Baylis–Hillman (BH) adducts. The reaction involves stirring a mixture of the BH adduct and IBX at room temperature for 2 h in MeCN followed by the addition of an aqueous solution of lithium bromide and stirring for a further 6–8 h at room temperature to afford the bromohydrin in good yield (Scheme 182). A MeCN–H_2O (2:1) mixture was found to be a better solvent system in terms of reaction time and yield. THF–H_2O can also be used as solvent system, but, because of the lower solubility of substrates in the THF–H_2O system, the reaction requires longer time and gives lower yields. Using MeOH or EtOH instead of H_2O affords the corresponding bromoethers in very good yields (Scheme 182). The important feature of this protocol is the complete regioselectivity in favor of the anti-Markownikov product, i.e., the hydroxy or alkoxy group is added to the β-position, exclusively, without traces of dibromides.

NaBr and KBr can also be used as a bromine source. However, LiBr and IBX give the best results as Li^+ ions appear to play a more efficient catalytic role than K^+ or Na^+ ions in the addition of bromine to the olefinic bond. The methodology avoids the use of heavy-metal halides or *N*-halosuccinimides as the halogen source to furnish α-halo-β-hydroxy derivatives (halohydrins), the versatile precursors, which can be readily transformed into epoxides, ketones and unusual β-hydroxy-α-amino acids.[88]

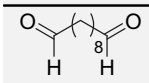
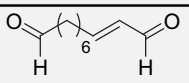
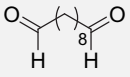
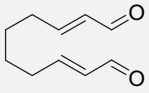
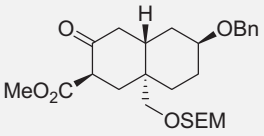
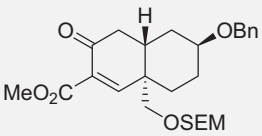
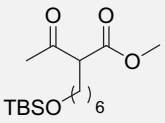
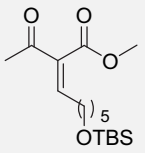
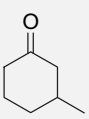
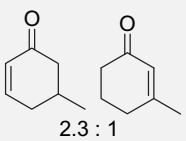
5.21. IBX·*N*-oxide complexes: a new class of oxidants

5.21.1. Dehydrogenation of carbonyl compounds to obtain α,β-unsaturated carbonyl compounds using IBX·MPO complex. The chemistry of IBX can be modulated by complexation with a variety of ligands, thus leading to dramatic changes in its reactivity profile. The ligand appended to IBX not only allows moderation of the



Scheme 182.

Table 7
Facile room temperature dehydrogenation of ketones and aldehydes using IBX·MPO complex

Substrate	Product	IBX·MPO (equiv)	Time (h)	Yield (%)
		2.2	22	84
		4.0	48	78+11% enone
		1.5	15	91
		1.8	20	77
		2.5	32	79

reagent's reactivity, but also differentiation between reaction pathways when a number of alternatives are available. Nicolaou et al.[89] introduced a new class of oxidants, the complexes of IBX with *N*-oxides (**44** and **45**) (Fig. 4), which often exhibit superior reactivity than that of the parent reagent.

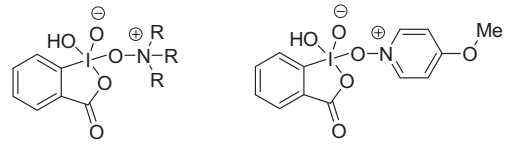
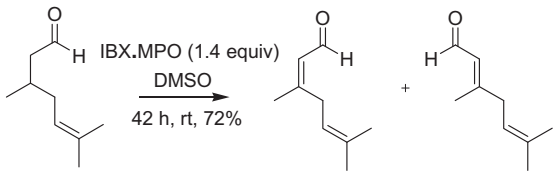


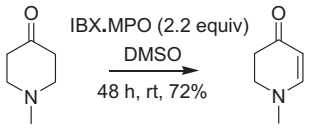
Figure 4.

Heteroatom oxide ligands when appended to IBX provide a unique electronic environment around the iodine center, which enhances the propensity of these reagents to serve as electron sinks. 4-Methoxypyridine-*N*-oxide (MPO) was examined as a potential ligand for complexation with IBX. This new oxidant, IBX·MPO complex (Fig. 4, **45**), when employed in the dehydrogenation reaction of carbonyl substrates was found to be general, mild, and highly efficient (Table 7). The IBX·MPO complex (**45**) is the reagent of choice for the dehydrogenation of reactive or volatile aldehydes (Scheme 183).



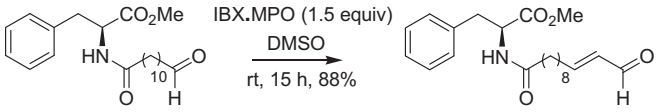
Scheme 183.

The substrates with an amine functionality often decompose readily when exposed to IBX at elevated temperatures. Such substrates can be easily dehydrogenated with IBX·MPO-mediated oxidations in DMSO (Scheme 184). The success of the reaction of these challenging substrates can be attributed directly to the lower temperature employed.



Scheme 184.

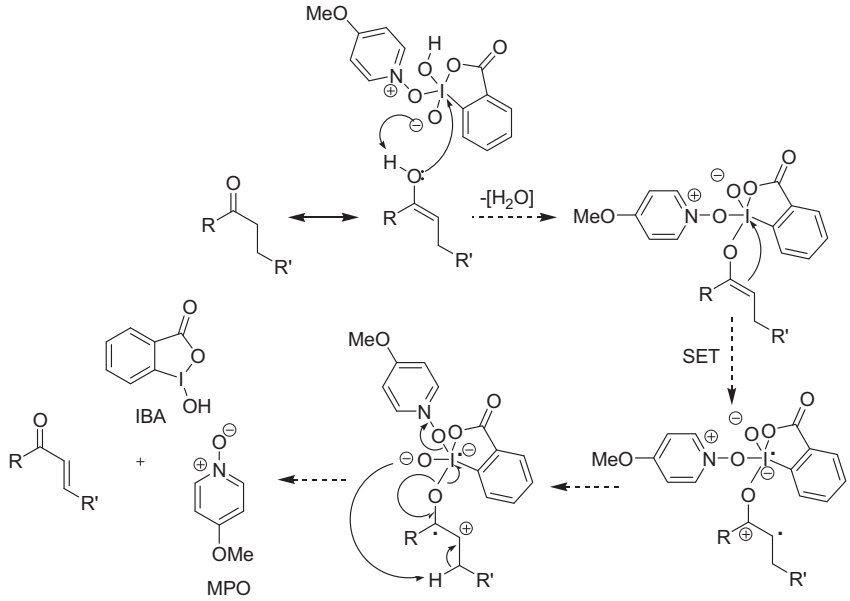
This method of oxidation is highly efficient and mild, and minimal purification is required. The other IBX-induced SET reactions such as benzylic oxidations do not compete with carbonyl dehydrogenation (Scheme 185).[89]



Scheme 185.

The IBX·MPO complex is readily prepared by mixing equivalent amounts of IBX and 4-methoxypyridine-*N*-oxide at ambient temperature. In addition to MPO, other potential ligands such as *n*-$Bu_3P{=}O$, *tert*-BuOH, 2-picoline-*N*-oxide, 4-phenylpyridine-*N*-oxide, and *N*-methylmorpholine-*N*-oxide can also furnish the desired dehydrogenation of carbonyl compounds, but the rate of reaction for these complexes was found to be lower than that of uncomplexed IBX under the same conditions. The success of 4-methoxypyridine-*N*-oxide relative to other *N*-oxides can be rationalized as resulting from two key features of MPO: mesomeric stabilization of the positive charge by the methoxy substituent, and the inclusion of the *N*-oxide moiety on the aromatic nucleus, thus preventing oxidative degradation of the ligand under the reaction conditions. For this oxidative protocol, Nicolaou et al.[89] proposed a single-electron-transfer (SET) mechanism, as described in Scheme 186.

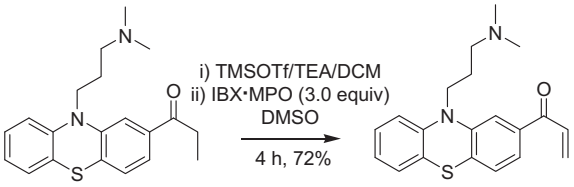
5.21.2. Oxidation of silyl enol ethers to enones using IBX·MPO complex. The IBX-mediated dehydrogenation reactions proceed through enolization (facilitated by the reagent) followed by single-electron-transfer (SET) to IBX and rearrangement of the resulting radical cation to give the α,β-unsaturated carbonyl compound. The silyl enol ethers also undergo a similar oxidation with IBX, giving



Scheme 186. Proposed mechanism for dehydrogenation of carbonyl compounds using IBX·MPO complex.

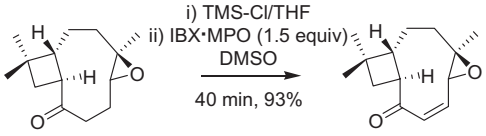
access to the synthesis of the much-coveted enone functionality. The oxidation of silyl enol ethers to enones has frequently been used in the construction of complex molecules. A number of procedures are reported in the literature for this transformation. Among them, the palladium-catalyzed protocol[52b,90] stands out, by virtue of its relative efficiency and mild nature. However, even this preferred method allows considerable room for improvement in the oxidation of silyl enol ethers because of the expense associated with the use of palladium and its incompatibility with various functional groups.

The IBX·MPO complex-mediated mild protocol converts TMS enol ethers into α,β-unsaturated carbonyl compounds with remarkable ease (Scheme 187). Nicolaou et al.[91] showed that a diverse set of ketones can be converted into their α,β-unsaturated counterparts by the fast oxidation of the corresponding TMS enol ethers induced by the IBX·MPO complex. The silyl enol ether formed has to be isolated and vacuum dried to minimize the amount of $(TMS)_2O$ present, as this is detrimental to the desired reaction. The substrates that contain reactive functionalities like amines, sulfides, mesylates, TBS ethers, dithianes or primary iodides all furnish the desired enones in high yield.



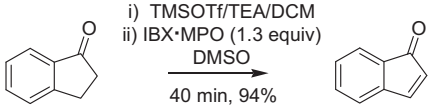
Scheme 187.

The reaction times are short and the yields are often high. This method performs admirably well in a number of situations where known methods have caused problems. For example, generation of a complex allylic epoxide proceeded in high yield using this unique protocol (Scheme 188).[91]



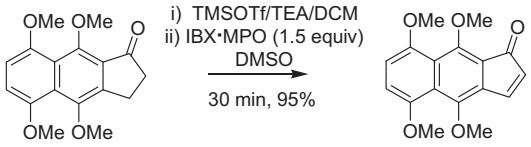
Scheme 188.

A survey of the literature revealed that the oxidation of indanones to form indenones is frequently cumbersome or can be plagued by low yields or multiple products.[92] The method involving the IBX·MPO complex outperforms other methods in this challenging situation and furnishes the corresponding enones in high yields that significantly exceed those obtained by the best published procedure[92c] (<75%), which involves the use of stoichiometric amount of $Pd(OAc)_2$ to oxidize the silyl enol ether (Schemes 189 and 190).



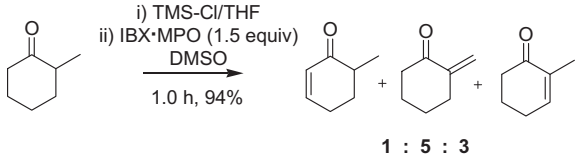
Scheme 189.

However, this method is not without its limitations. The oxidation reaction is essentially nonselective in the case of α-substituted ketones (Scheme 191). In some cases, the alternative reaction pathway, hydrolysis of the silyl enol ether back to the original starting

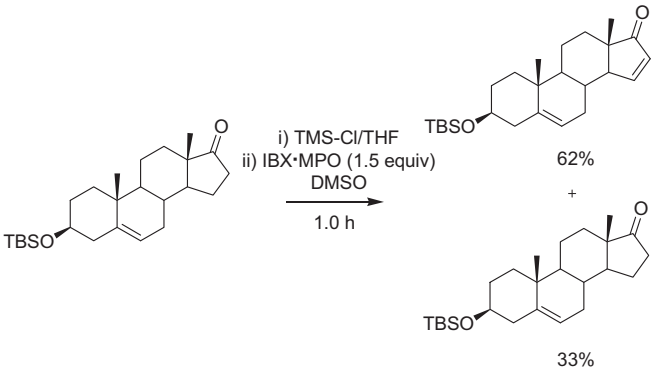


Scheme 190.

ketone, is of great significance (Scheme 192). This observed side reaction depends upon the solubility of the substrate in DMSO and also on the reactivity of the silyl enol ether.[91]

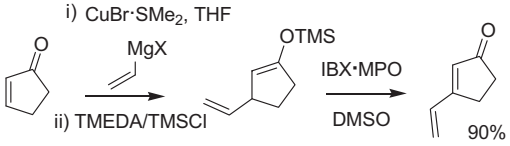


Scheme 191.

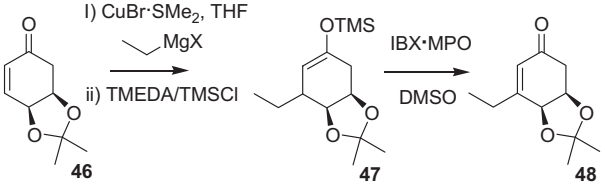


Scheme 192.

Nicolaou et al.[91] also observed that the incorporation of this oxidation method within a cascade reaction allowed a rapid increase in the molecular complexity. Particularly attractive is a sequence that involves conjugate addition to an enone followed by in situ silyl enol ether formation, and subsequent isolation and oxidation of the resulting product to regenerate a new enone functionality for further elaboration. Thus, addition of an appropriate nucleophile to enones followed by quenching with TMSCl and oxidation of the resulting silyl enol ethers with IBX or IBX·MPO furnished the elaborated enones in high overall yields (Scheme 193). The sensitive enone product (**48**), which is difficult to obtain from the corresponding saturated ketone (**46**) can be synthesized in excellent yield via **47** using this technique (Scheme 194).



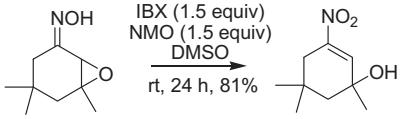
Scheme 193.



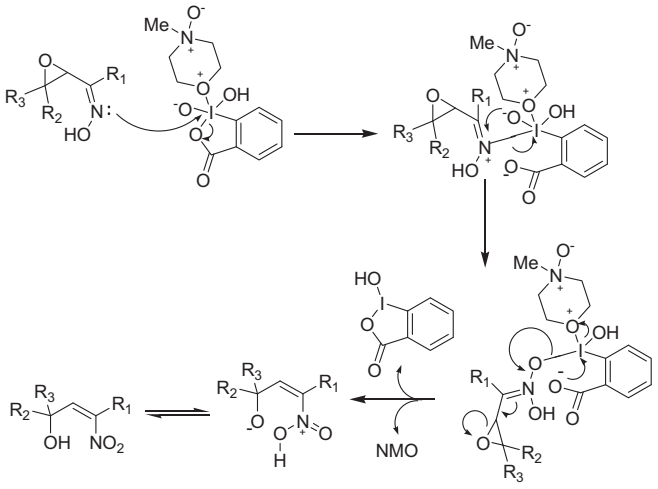
Scheme 194.

5.21.3. Preparation of γ-hydroxy-α-nitroolefins from α,β-epoxyketoximes using IBX·NMO complex. Jiménez et al.[93] developed a new oxidative method for the preparation of γ-hydroxy-α-nitroolefins from α,β-epoxyketoximes using IBX and *N*-methylmorpholine-*N*-oxide (NMO). The conjugated nitroolefins find numerous applications in organic synthesis. These compounds are powerful dienophiles or dipolarophiles in cycloaddition reactions to generate new carbon–carbon single or double bonds. A number of methods have been developed for the preparation of nitroolefins, but the IBX-mediated transformation of α,β-epoxyketoximes into γ-hydroxy-α-nitroolefins is remarkable because of the mild reaction conditions, lack of formation of overoxidation products, and easy workup procedure. The reaction proceeds with in situ generation of the IBX·*N*-methylmorpholine-*N*-oxide (NMO) complex in DMSO at room temperature (Scheme 195).

A plausible mechanism for this reaction is presented in Scheme 196. The reaction proceeds through the formation of the IBX·NMO complex in DMSO. The direct attack of the nitrogen atom of the oxime on iodine leads to the formation of the O=N double bond to originate the nitro functionality. Opening of the epoxy group generates a hydroxyl group at the γ-position and causes subsequent expulsion of iodosobenzoic acid (IBA).



Scheme 195.



Scheme 196. Plausible mechanism for formation of γ-hydroxy-α-nitroolefins from α,β-epoxyketoximes using IBX·NMO complex.

Interestingly, IBX is known to oxidatively de-oximate ketoximes smoothly to regenerate ketones,[32] but, in this case, the de-oximation of ketoximes with IBX is hampered by the presence of a good leaving group at the α-position, as this leads to the corresponding conjugated nitroolefins, instead of regeneration of the ketone.

6. IBX-promoted oxidations using ionic liquids as green solvents

In recent times, ionic liquids have gained recognition as possible environmentally benign alternatives to the more volatile organic solvents.[94] Ionic liquids possess many attractive properties, such as a wide liquid range, negligible vapor pressure, high thermal stability, and good solvating ability for a wide range of substrates and catalysts, which alleviate some of the environmental issues. Their nonvolatile nature can reduce the emission of toxic organic compounds and facilitate the separation of products and/or catalysts from the reaction mixtures. Their unprecedented ability to solvate a broad spectrum of substrates of an organic and inorganic nature has widened the horizon of their applicability. The wide popularity of ionic liquids has encouraged the scientists all over the world to explore newer reactions in these solvents. More recently, practical IBX oxidations have been studied in ionic liquids as recyclable polar reaction media.

Yadav et al.[95] demonstrated the utility of a hydrophilic 1-butyl-3-methylimidazolium tetrafluoroborate [(bmim)BF_4] ionic liquid (Fig. 5, **49**) as an efficient and polar alternative to conventional solvents for the IBX-promoted oxidations. This method avoids the use of polar organic solvents such as DMSO or DMF and high-temperature reaction conditions for IBX oxidations (Scheme 197). A variety of alcohols can be oxidized to the corresponding carbonyl compounds using this protocol (Table 8, entries 1–5).

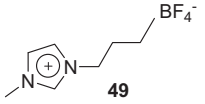
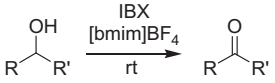
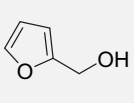
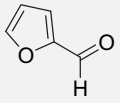
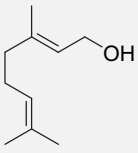
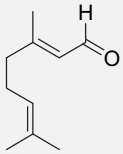
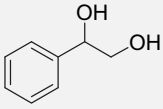
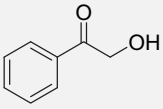
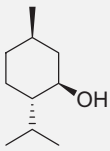
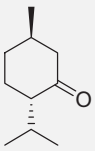
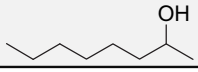
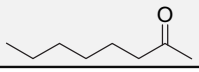


Figure 5. Structure of [bmim]BF_4 ionic liquid.



Scheme 197.

Table 8
Oxidation of various alcohols to corresponding carbonyl compounds using IBX in [bmim]BF_4 ionic liquid

Entry	Alcohol	Carbonyl compound	Time (h)	Yield (%)
1			3.5	95
2			4.5	94
3			5.5	92
4			6.0	86
5			7.5	89

Since the products are fairly soluble in the hydrophilic [bmim]BF_4 ionic liquid, they can be easily separated by simple extraction with diethyl ether. The rest of the ionic liquid can then be diluted with water and filtered to recover the by-product, iodosobenzoic acid (IBA). The recovered IBA can be re-oxidized to IBX and re-used in subsequent reactions. The aqueous phase can be lyophilized to

recover the ionic liquid. The recovered ionic liquid can be recycled in subsequent reactions with consistent activity. Yadav et al.[95] demonstrated that the products obtained had the same purity as those in the first run, and no decrease in yield was observed in runs carried out using the recycled ionic liquid. Yadav et al.[95] obtained similar results in the hydrophobic ionic liquid [bmim]PF_6 (Fig. 6, **50**). However, the recovery of IBA was especially simple in [bmim]BF_4, due to its hydrophilic nature. The use of an easily accessible and recyclable ionic liquid makes this protocol quite simple, more convenient, and environmentally benign.

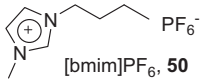
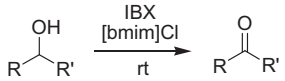


Figure 6. Structure of [bmim]PF_6 ionic liquid.

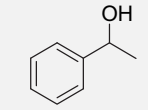
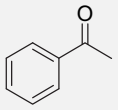
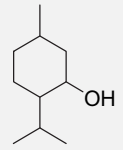
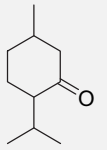
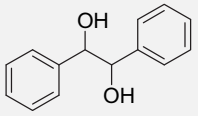
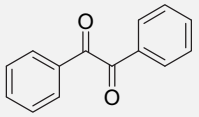
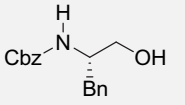
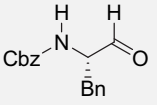
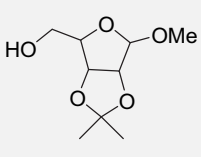
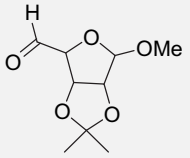
Two independent groups[96,97] have reported the IBX oxidation of alcohols using 1-butyl-3-methylimidazolium chloride ([bmim]Cl) as an ionic liquid. They described the oxidation of a variety of alcohols to the corresponding carbonyl compounds in high yields. Various ionic liquids like butylpyridinium tetrafluoroborate (bpyBF_4), butylpyridinium hexafluorophosphorate (bpyPF_6), butylpyridinium chloride (bpyCl), 1-butyl-3-methylimidazolium chloride ([bmim]Cl), 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]), and 1-butyl-3-methylimidazolium hexafluorophosphorate [bmim][PF_6] were examined for the IBX-mediated oxidation reaction. None of these ionic liquids, except [bmim]Cl, could dissolve IBX, even when heated to 80 °C. 1-Butyl-3-methylimidazolium chloride ([bmim]Cl) was found to readily dissolve IBX in the presence of a small amount of water at room temperature to form a homogeneous solution. Hence, the reactions were carried out by dissolving IBX in [bmim]Cl and water at room temperature followed by the addition of the corresponding alcohol (Scheme 198). All the alcohols investigated gave excellent yields, ranging from 88 to 99% in high purity (Table 9, entries 1–5).



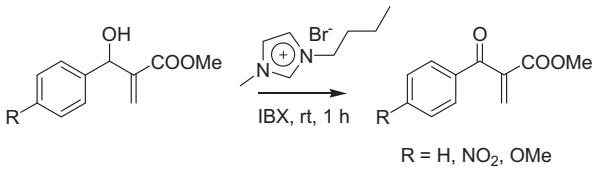
Scheme 198.

The ionic liquid [bmim]Cl can be recovered and re-used without decreasing the yields of products. Compared with the classical procedure in DMSO, the procedure involving the ionic liquid [bmim]Cl and water has the advantage of mild reaction conditions, homogeneous solution, facile recovery of the oxidant, and excellent yields of products. It is, to some extent, superior in terms of ready separation of products, small degree of consumption of the solvent, and recycling of the ionic liquid without decreasing the yields of products.

Table 9
Oxidation of various alcohols to corresponding carbonyl compounds using IBX in [bmim]Cl ionic liquid

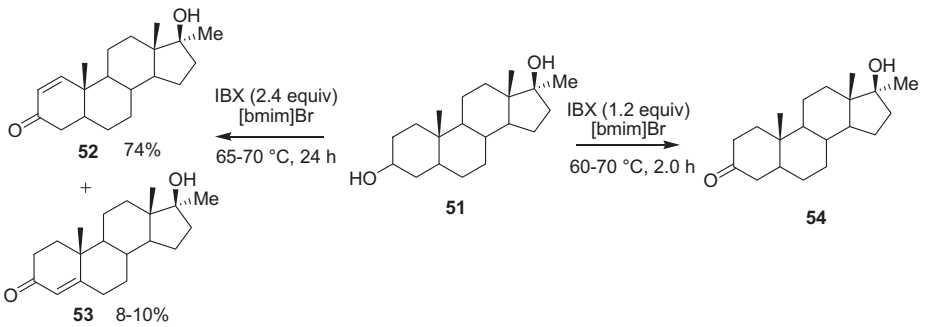
Entry	Alcohol	Carbonyl compound	Time (h)	Yield (%)
1			0.25	92
2			8.0	80
3			5	92
4			2.5	83
5			5	88

Yadav et al.[98,99] reported the ionic liquid-promoted IBX oxidation of Baylis–Hillman alcohols (BH alcohols) to the corresponding β-ketomethylene compounds (Scheme 199). They also examined this reaction in six different ionic liquids such as 1-butyl-3-methylimidazolium (bmim) tetrafluoroborate ([bmim]BF_4), [bmim]PF_6, [bmim]Br, butylpyridinium (bpy) tetrafluoroborate (bpyBF_4), bpyPF_6, and bpyBr. Among these ionic liquids, [bmim]Br dissolved IBX at room temperature and gave the best result. The other five ionic liquids did not dissolve IBX, even when heated to 80 °C in the presence of a small amount of water, and did not give satisfactory yields.



Scheme 199.

The same ionic liquid was used by Chhikara et al.[100] for synthesis of mestanolone (**54**) and 17β-hydroxy-17α-methyl-Δ^1-androsten-3-one (**52**), important intermediates in the synthesis of the



Scheme 200.

anabolic drug, oxandrolone, by the oxidation and dehydrogenation of 17α-methylandrostan-3β,17β-diol (**51**) with IBX (Scheme 200).

7. Polymer-supported IBX

Polymer-supported reagents and catalysts are currently undergoing a renaissance in synthetic chemistry. An attractive feature of polymer-bound reagents is that they can be easily isolated from the reaction mixture without workup using a simple filtration to yield a solution of the pure product. This technology is now being used to great effect in the parallel synthesis of libraries of compounds for use in drug-discovery programs. The use of polymer-bound reagents could be of interest to industry, as the spent reagent can be potentially re-used after recovery and regeneration. Many explosive reagents have been made safe by converting into a resin-bound version, e.g., a polymer-bound sulfonyl azide[101] reagent for diazo-transfer reactions and an azodicarboxylate[102] reagent for Mitsunobu reactions. Because of its proven synthetic importance, insolubility in common organic solvents and safety-related issues (IBX is potentially explosive at high temperature and on impact), IBX was thought to be an ideal candidate for the preparation of polymer-bound analogues. Various research groups have reported on the immobilization of IBX onto solid polymeric supports, which enable clean isolation of the product just by filtering the reaction mixture and recovery and regeneration of the separated polymer for efficient reuse for the next reaction (Fig. 7).

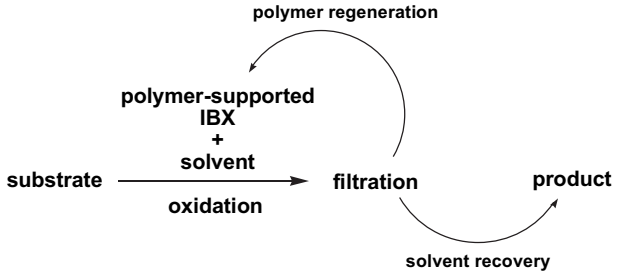
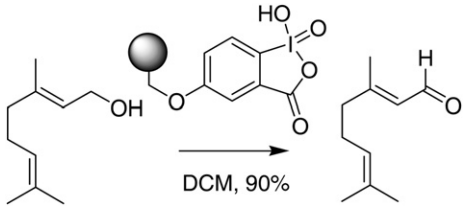


Figure 7.

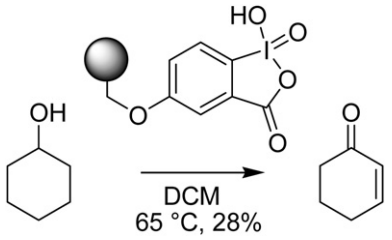
Janda et al.[103] investigated several polymers such as insoluble polystyrene gel-type *Janda*Jel resin, macroporous polystyrene ArgoPore resin, and soluble, non-crosslinked polystyrene resin as efficient supports for IBX. They synthesized polymer-supported IBX starting from 5-hydroxy-2-anthranilic acid, as described in Scheme 201. The efficiency of the support-bound oxidants was tested by stirring 2 equiv of oxidant with a solution of benzyl alcohol in dichloromethane to obtain benzaldehyde. Among the three polymer supports, the homogeneous non-crosslinked polystyrene-supported IBX reagent was found to be superior, as it gave 100% conversion of benzyl alcohol into benzaldehyde in only 1 h. The insoluble macroporous ArgoPore-supported reagent gave 93% conversion after 2.5 h and 100% after 4 h, while the gel-type polymer-supported reagent gave only 75% conversion after 2.5 h, which did not increase even after extended reaction times.

Using a similar approach, IBX was immobilized on chloromethylpolystyrene crosslinked with 1% divinylbenzene by Sorg et al.[104] An array of alcohols including the terpene alcohol shown in Scheme 202 were oxidized to the corresponding carbonyl compounds in high yields and purity using this polymer-bound IBX, which is stable toward air and moisture and can be stored without loss of activity.



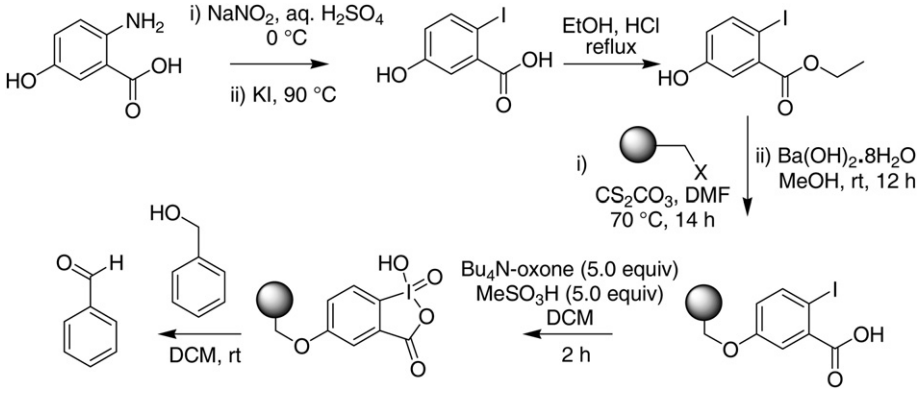
Scheme 202.

Sorg et al.[104] also reported that, at elevated temperatures, IBX can oxidize benzylic positions, which are abundant in the polystyrene backbone of resin-bound IBX and account for the competing reaction pathway. Thus, a comparatively lower yield (28%) of α,β-unsaturated cyclohexenone was obtained when cyclohexanol was reacted with resin-bound IBX in a closed vessel at 65 °C in DCM (Scheme 203). In addition, the polymer-supported IBX when used at high temperature cannot be recycled and re-used. However, if used at room temperature, or at lower temperatures, the resins can be recycled by repeated oxidation following extensive washings.

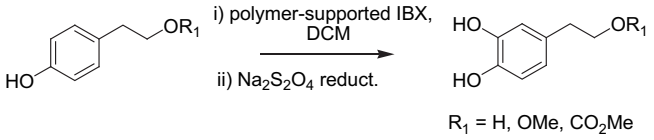


Scheme 203.

The other important transformations effected by IBX can also be carried out with polymer-bound IBX. Bernini et al.[105] described the application of polymer-supported IBX for the chemoselective and



Scheme 201.



Scheme 204.

regioselective hydroxylation of tyrosol derivatives (*o*-hydroxylation of phenolic compounds) in excellent yields (Scheme 204).

Giannis and Mülbaier[106,107] developed polymer-supported IBX (Fig. 8, **55**) based on aminopropyl silica gel and demonstrated its oxidizing potential on a variety of alcohols to afford the corresponding carbonyl compounds in high yields.

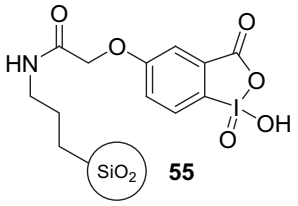
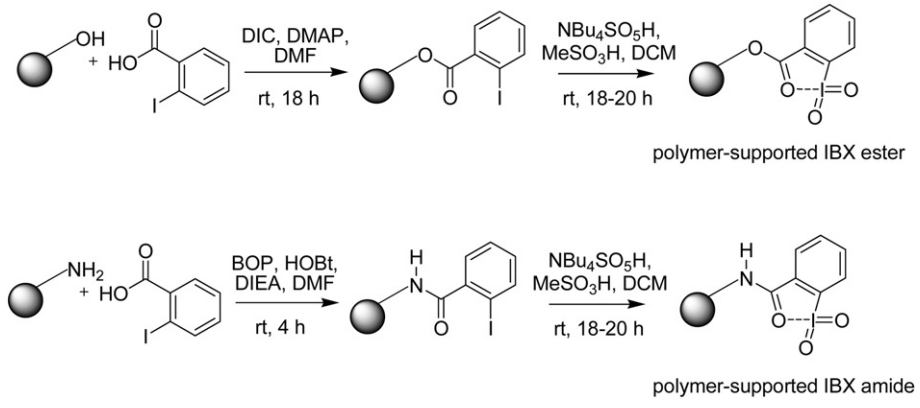


Figure 8.

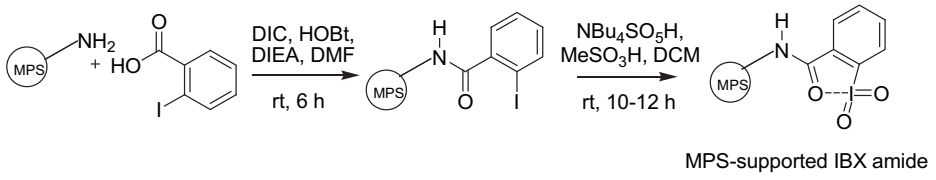
Lee et al.[108] proposed a very simple method of preparing a polymer-supported IBX ester and amide, in two steps, involving the coupling of 2-iodobenzoic acid to a hydroxyl- or amino-functionalized polystyrene (PS) bead, followed by subsequent oxidation on the beads (Scheme 205). These polymer-supported IBX reagents were found to be mild and efficient oxidants for the conversion of various alcohols into the corresponding aldehydes or ketones. The reactions were performed in DCM for 1 h at 25 °C. The ratio of resin-bound IBX and alcohol was 2:1. The polymer-supported IBX amide was found to exhibit particularly fast and efficient oxidative activities toward a series of alcohols, compared to the polymer-supported IBX ester.

properties, as a result of the gel-type and the hydrophobic nature of the polymer backbone. They reported that the oxidation of long-chain alkyl alcohols took a long time to complete, as these alcohols diffused slowly into the inner reactive sites of the resin. When the gel-type PS-IBX resin is not fully solvated, the alcohols experience diffusion resistance and, therefore, slowly diffuse into the inner reactive sites of the resin. Moreover, in a poor solvent system, the polymer matrix of the gel-type PS-support disintegrates and blocks the internal reactive sites. Therefore, in order to improve the properties of the IBX resin, Lee et al.[109] synthesized a macroporous polystyrene-supported IBX (MPS–IBX) amide, as depicted in Scheme 206, and investigated it for oxidative properties using a series of alcohols.

According to Lee et al.,[109] in the case of the MPS-IBX resin, high levels of internal crosslinking created a rigid porous structure, which neither collapsed nor swelled in various solvents. In addition, the internal reactive sites of the macroporous resins were freely accessible across a broad spectrum of solvent polarities, and the alcohols were free to move into the resin reaction sites. Therefore, it was possible to use the MPS–IBX amide resin for oxidizing alcohols in a variety of solvents, as long as the solvents were not oxidized. Lee et al.[109] performed oxidation reactions in various solvents such as acetonitrile, THF, acetone, and diethyl ether (100 mg of bead/1 ml) at 25 °C. The MPS–IBX amides were found to be compatible with all solvents. However, when THF was used as the solvent, lactol and lactone were formed with the MPS–IBX amide. This was probably due to the oxidation reaction of THF by the MPS–IBX amide. The profiles of the benzyl alcohol oxidation reaction in several solvents were compared using either the gel-type PS–IBX amide resin or the MPS–IBX amide resin. Both resins in DCM showed similar oxidative properties. However, in acetone, diethyl ether, and THF, only the MPS–IBX amide resin revealed strong oxidative properties toward benzyl alcohols. A series of other alcohols including long-chain alkyl alcohols and primary alcohols were rapidly converted into the corresponding aldehydes and ketones using the MPS–IBX amide resin. The re-



Scheme 205.

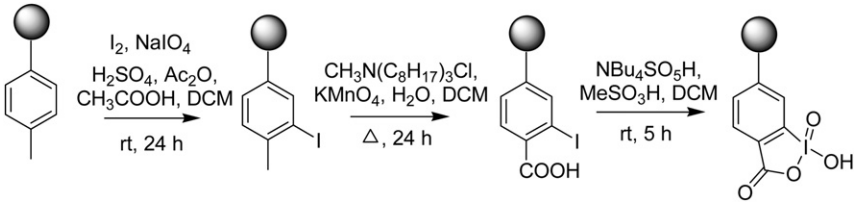


Scheme 206.

Lee et al.[109] also reported that the oxidation activity of a gel-type polystyrene (PS)-supported reagent strongly depends on the solvents employed, because the PS resin has different swelling

duced MPS–IBX amide resin was regenerated by oxidation with tetrabutylammonium-oxone, and no loss of activity was observed, even after five regenerations.

A three-step protocol for the preparation of a polymer-supported IBX reagent from poly(*p*-methylstyrene) was reported by Sutherland et al.[110] (Scheme 207). Poly(*p*-methylstyrene) was prepared from *p*-methylstyrene and divinylbenzene (8 mol %) using a standard suspension polymerization technique. Oxidation reactions of a series of alcohols using this polymer-supported IBX reagent were performed in DCM at 25 °C. The ratio of resin-bound IBX to alcohol was 2:1. The corresponding carbonyl compounds were obtained in excellent yields and purity.

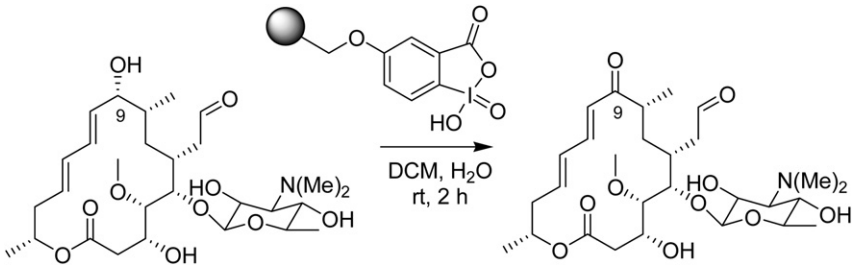


Scheme 207.

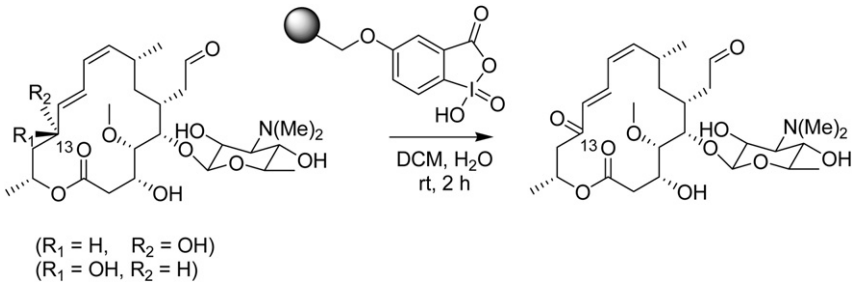
Hertweck et al.[111] successfully employed a polymer-bound IBX reagent to oxidize allylic –OH groups of highly functionalized macrolides. The 9- and 13-keto leucomycines represent valuable key intermediates in the synthesis of biologically active macrolide derivatives. A crucial step in their synthesis involves the oxidation of allylic 9- and 13-OH groups, which can be accomplished by the well-known oxidant for allylic alcohols, manganese(IV) oxide. However, this reagent provides the desired products only in unsatisfactory yields (~20%). Hertweck et al.[111] demonstrated that allylic 9- and 13-OH groups of these highly functionalized macrolides could be selectively oxidized with polymer-supported IBX in good-to-very good yields (up to 61% isolated yield, compared to <20% using manganese dioxide) without the need of protecting groups (Schemes 208 and 209).

Harding et al.[112] reported the application of polymer-bound IBX for the oxidation of threonine-containing protected peptides and polypeptides to the corresponding keto-peptides, which underwent hydroxylation at the threonine α-C position (Scheme 210). Quantitative conversion into the α-hydroxy ketone required 10 equiv of polymer-bound IBX and heating at 45 °C for two days. The elevation in temperature resulted in some minor leaching of the polymer resin into the solution of the crude products.

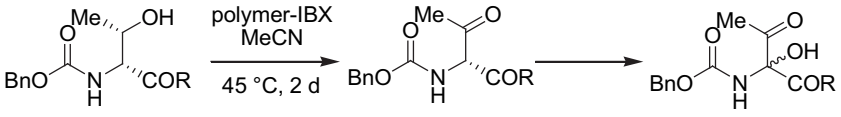
The unusual hydroxylation mediated by IBX at the threonine α-C provided a new class of peptide derivatives. Scheme 211 shows the proposed mechanism for this transformation. The oxidation at the α-C of threonine residues occurs due to the presence of a highly acidic proton, which is α to two carbonyl groups once the hydroxyl group on side chain is oxidized to the ketone.



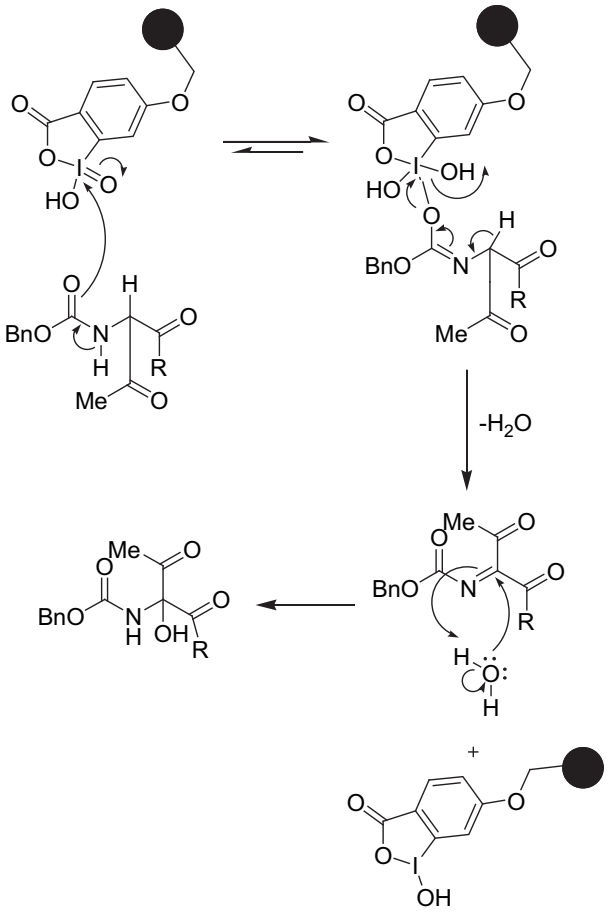
Scheme 208.



Scheme 209.



Scheme 210.

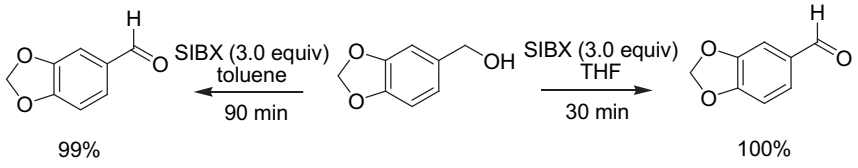


Scheme 211. Proposed mechanism for unusual hydroxylation mediated by IBX at threonine α-C.

8. Stabilized IBX (SIBX), a non-explosive formulation of IBX

The utility and selectivity of 2-iodoxybenzoic acid (IBX) in oxidation reactions have been amply demonstrated by many synthetic transformations. However, industrial applications of IBX are limited because IBX suffers from major safety concerns related to its violent decomposition under impact and/or heating. It thus became desirable to find a means of stabilizing IBX to enable its safe utilization in chemical synthesis, particularly in process chemistry. To address this limitation Quideau et al.[113,114] reported an oxidizing system referred to as SIBX (stabilized IBX). SIBX is a non-explosive formulation of IBX that can be used as a suspension in a variety of standard organic solvents including refluxing ethyl acetate and THF to safely oxidize alcohols into aldehydes and ketones. Like IBX, SIBX is not soluble in most standard organic solvents. It readily dissolves in DMSO and is only sparingly soluble in *N*-methylpyrrolidone (NMP). This formulation of IBX is a white powder composed of a mixture of benzoic acid (22%), isophthalic acid (29%), and *o*-iodoxybenzoic acid (49%).

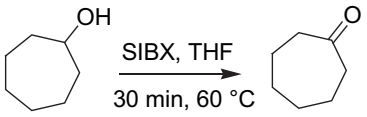
Quideau et al.[113] oxidized a variety of alcohols using SIBX and found that, in all cases, yields were comparable with those obtained with IBX. SIBX worked very well in solvents like THF and toluene in which IBX gave intractable dark-colored reactions. Oxidation of piperonyl alcohol with SIBX in THF and toluene furnished the corresponding aldehyde in 99 and 100% yields, respectively (Scheme 212). However, Quideau et al.[113] also reported that SIBX is not stable over a prolonged period of time, either in THF at 60 °C or in toluene at 80 °C (100 mg in 1.0 ml solvent under nitrogen).



Scheme 212.

Cycloheptanol was oxidized by SIBX into cycloheptanone in a good yield of 77% in only 30 min in THF at 60 °C (Scheme 213). Of particular note is the fact that no dehydrogenation product was observed. This is in contrast to observations made by Nicolaou et al.[50] on the formation of α,β-unsaturated carbonyl compounds from saturated alcohols with the use of IBX in DMSO. With SIBX (2.0–3.0 equiv), however, even when the reaction was performed in DMSO at 60 °C or 90 °C, only cycloheptanone was formed.

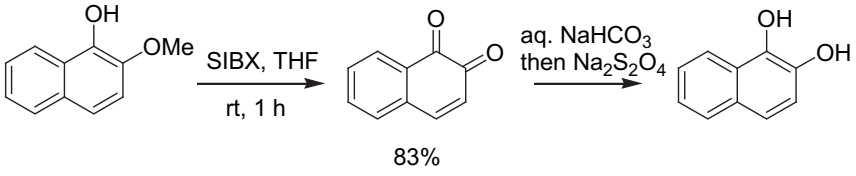
For oxidation of most of the aliphatic alcohols (except primary alcohols), the SIBX formulation is no different from IBX. Most yields



Scheme 213.

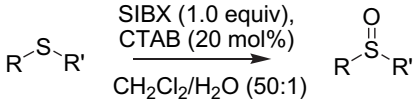
are comparable to those obtained with IBX. No silica gel chromatography is required to remove the carboxylic acid stabilizers, as they can be efficiently removed by slightly basic aqueous washes. In addition, the main IBX by-product, iodosylbenzoic acid (IBA), can be recovered by filtration and recycled via oxidation into IBX with oxone.

SIBX can also be used to perform oxygenative demethylation of 2-methoxyarenols into *o*-quinones and catechols. SIBX-mediated demethylation of 2-methoxynaphthol gave rise to the stable naphthoquinone, which was reduced to the catechol derivative, naphthalene-1,2-diol (Scheme 214).[113] A mechanistic description of this SIBX-mediated demethylation is similar to that of IBX-mediated *ortho*-oxygenation of phenols described by Pettus et al.[42]



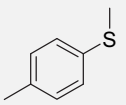
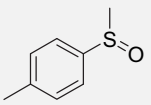
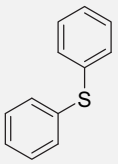
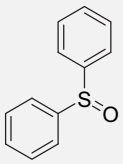
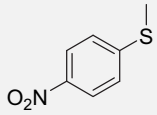
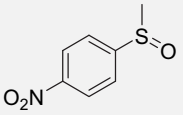
Scheme 214.

SIBX was also found to rapidly and safely oxidize sulfides into sulfoxides in reversed micellar solvent systems in the presence of a quaternary ammonium salt (i.e., cetyltrimethylammonium bromide, CTAB) without any overoxidation into sulfones. Quideau et al.[115] showed that several sulfides could be oxidized under CTAB-induced reversed micellar conditions in dichloromethane–water (50:1) (Scheme 215 and Table 10). Methyl *p*-tolyl sulfide (Table 10, entry 1) and diphenyl sulfide (Table 10, entry 2) were rapidly converted into the corresponding sulfoxides in 82 and 84% yields.



Scheme 215.

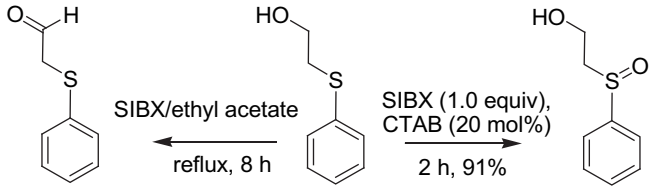
Table 10
Oxidation of sulfides into sulfoxides using SIBX in presence of CTAB in DCM–water (50:1)

Entry	Sulfide	Sulfoxide	Time (h)	Yield (%)
1			1	82
2			4	84
3			12	74

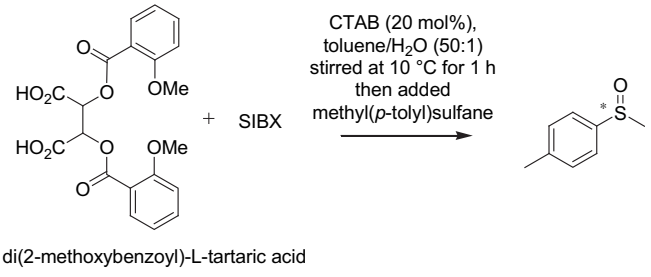
Oxidation of electron-poor sulfides such as methyl *p*-nitrophenyl sulfide (Table 10, entry 3) furnished methyl *p*-nitrophenyl sulfoxide in 74% yield, but the reaction was much slower. Diphenyl disulfide was found to be refractory to any oxygenation.

It is interesting to note that, in the case of sulfides having a primary hydroxyl group, SIBX expressed chemoselectivity in the reversed micellar system. Thus, phenylthioethanol was converted into the corresponding sulfoxide in 91% yield with the hydroxyl group untouched, whereas it furnished the aldehyde in quantitative yield in refluxing ethyl acetate in the absence of CTAB (Scheme 216).

The SIBX-mediated sulfoxidation is solvent dependent and is most effective in a bi-phasic solvent system. Quideau et al.[115] observed that, in anhydrous toluene, sulfoxidation was extremely slow and moderate yielding, whereas in a 50:1 toluene–water system, it was complete in close to 2.0 h and with excellent yield. This sulfoxidation protocol was even faster in dichloromethane–water (50:1), but it slowed down in a more polar solvent system such as ethyl acetate–water (50:1). SIBX was also shown to induce an asymmetric sulfoxidation in high chemical yield and moderate enantioselectivity (up to 50% ee) by simple addition of an external chiral source. When SIBX and the chiral source (di(2-methoxybenzoyl)-L-tartaric acid) were allowed to mix at 10 °C for 1 h in the reversed micellar solvent system before adding the starting sulfide, the sulfoxidation proceeded smoothly in 24 h, giving an excellent chemical yield and an enantiomeric excess up to 50% (Scheme 217).[115]



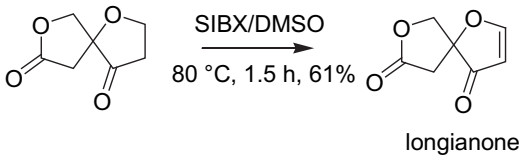
Scheme 216.



di(2-methoxybenzoyl)-L-tartaric acid

Scheme 217.

Stratakis et al.[116] presented a simple, efficient, and bioinspired route to longianone using an easily accessible furan diol, 2-(3-(hydroxymethyl)furan-2-yl)ethanol. In their synthetic approach, Stratakis et al.[116] successfully used SIBX to perform the oxidation of dihydrolongianone to longianone in good yield (Scheme 218). Their attempts to carry out dehydrogenation of spirocyclic dihydrolongianone with other oxidizing systems like TESOTf–$Ph_3C^+BF4^-$ and PhSeCl–O_3 were unsuccessful. The reaction of



Scheme 218.

dihydrolongianone with 2.0 equiv of SIBX in DMSO at 80 °C gave 70% conversion into longianone after 1.5 h. Stabilized IBX (SIBX) was found to be significantly more effective than IBX to bring about this conversion. Stratakis et al.[116] reported that, by using 3.0 equiv of IBX in DMSO, the dehydrogenation proceeded relatively fast (~70% conversion after 1 h), yet with a <60% mass balance. After 12 h, no starting material could be detected, yet the reaction mass balance and the product yield dropped dramatically to <10%, indicating that IBX caused decomposition of the product.

9. Conclusions

Although 2-iodoxybenzoic acid (IBX) is a reagent with a caution tag for its explosive nature, it has proliferated in synthetic organic chemistry, due to its versatile applications. IBX is a reagent, which will continue to surprise. It has been prolifically used for the mild and chemoselective oxidation of alcohols containing various sensitive functional groups to the corresponding carbonyl compounds. In addition to the oxidation of alcohols, a plethora of other IBX-mediated oxidative transformaions have been demonstrated by many synthetic chemists. Owing to the discovery of a variety of novel applications, IBX is becoming an increasingly important reagent in synthetic organic chemistry.

Ionic liquids have been used efficiently as polar solvents for the oxidation of alcohols and for other oxidative transformations using IBX. The synthesis of polymer-bound IBX will undoubtedly be of paramount importance for rapid combinatorial chemistry in the near future. Further, tailor-made SIBX, a non-explosive version of IBX, has been found to be as effective and selective as IBX for different transformations in various solvents.

We are sure that hypervalent iodine chemistry, in particular that involving IBX, will continue to attract significant research activity in the future. We hope and anticipate that this review will provide an additional stimulus for the application of IBX in synthesis, and the discovery of new transformations with this reagent will surely be the basis for different and improved synthetic strategies and concepts.

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