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Synthetic Methods

2-Iodoxybenzoic Acid—A Simple Oxidant with a Dazzling Array of Potential Applications

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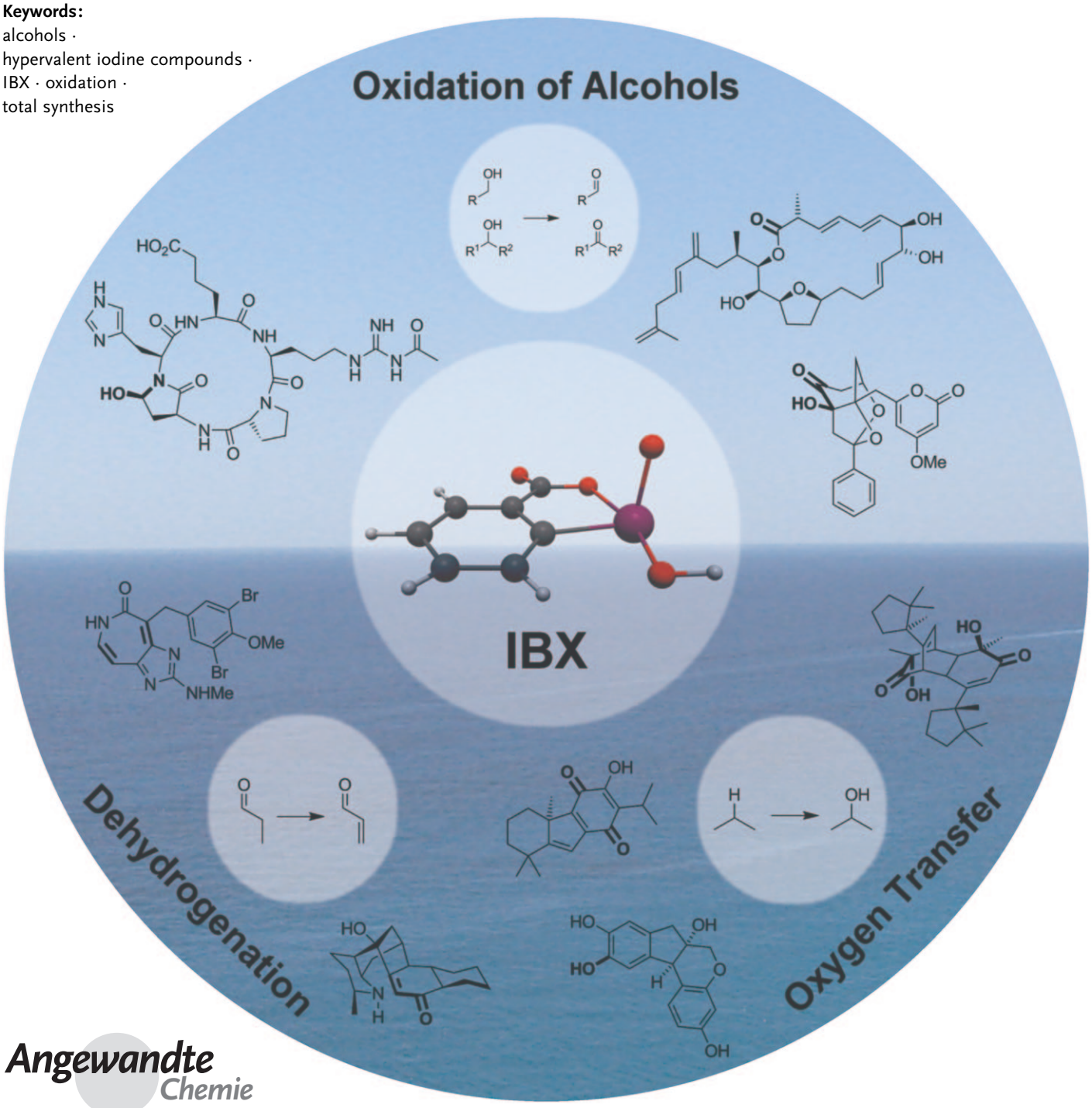
alcohols · hypervalent iodine compounds · IBX · oxidation · total synthesis



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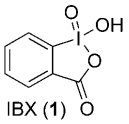
Since its discovery by Christoph Hartmann and Victor Meyer in 1893, 2-iodoxybenzoic acid (IBX) has emerged as a rather ubiquitous oxidant for organic synthesis. The past decade has seen the development of a large variety of applications that go far beyond the simple oxidation of alcohols. This Review is concerned with the synthetic potential of IBX, with particular emphasis on uncommon reactivity patterns and novel fields of application.

From the Contents

1. Introduction

In 1893, Victor Meyer was the first to observe the formation of *o*-iodosobenzoic acid (*o*-iodosylbenzoic acid, IBA) upon treatment of *o*-iodobenzoic acid with fuming nitric acid. Further oxidation by alkaline permanganate solution gave *o*-iodoxybenzoic acid (*o*-iodylbenzoic acid, IBX, **1**), a material he referred to as "Jodobenzoesäure".[1] The properties of the acid were aptly described as follows: "*Depending on the purity of the starting material, the acid is obtained in the form of white to light yellowish needles which decomposed violently with a loud report around 233°. … It possesses strongly acidic properties, unlike the iodoso compound that is an extremely weak acid. It is distinguished from the latter by its intensely acidic taste…*".[1a] Furthermore, it was already reported in these seminal studies that *o*-iodoxybenzoic acid is reduced by alcohols. For almost one century, no importance was attached to this observation in the field of organic chemistry. Instead, pharmacological studies on the oxidizing action of IBX were undertaken during the early 20th century: For example, it was shown that IBX is capable of oxidizing hemoglobin and that its intravenous injection into rabbits results in a significant decrease in blood pressure.[2]



IBX (**1**)

In the meantime, synthetic organic chemistry benefited from the development of a large variety of oxidation methods.[3] Among them, the Swern procedure,[4] oxidations with chromium(VI) compounds such as pyridinium chlorochromate (PCC),[5] and the Dess–Martin oxidation[6] are particularly well-established and reliable. Maybe stimulated by the synthetic utility of the Dess–Martin periodinane, an iodine(V) compound introduced in 1983, a recent upsurge in activity surrounding the chemistry of polyvalent organoiodine compounds began in the early 1990s and persists to this day. Hypervalent iodine reagents have now transmuted from chemical curiosities into valuable synthetic tools for a vast and constantly growing array of different applications. Accordingly, the continuing interest in polyvalent iodine(III) and iodine(V) compounds is reflected in numerous review articles that have appeared over the past years.[7,8] This Review will focus on IBX,[9] which is one of the oldest iodine(V) compounds but has found an increasing number of applications in recent years. Besides the oxidation of alcohols to carbonyl compounds, a large variety of unique oxidative transformations have been developed, thus rendering IBX an almost universally applicable oxidizing agent. The ready availability of IBX, along with its stability towards moisture and oxygen, make it a particularly appealing oxidation reagent. Other iodine(V) compounds derived from IBX will be discussed briefly. Furthermore, novel and uncommon fields of application in redox processes will be emphasized.

2. Structure, Preparation, and Derivatives

2.1. Structure

The name *o*-iodoxybenzoic acid (or 2-iodylbenzoic acid) does not represent the true structure of IBX (**1**), which exists exclusively in its tautomeric form as the cyclic benziodoxole oxide (1-hydroxy-1-oxo-1*H*-1λ^5-benzo[*d*][1,2]iodoxol-3-one according to the IUPAC nomenclature). A cyclic structure was proposed for IBX as early as 1960, since its IR spectrum does not exhibit any absorption that would be expected for a free iodoxy group (720 ± 5, 745 ± 5, $765 \pm 5\ cm^{-1}$) or a carboxylic acid.[10] The proposed structure was later confirmed by X-ray structural analysis. Structural data have been obtained for crystals of racemic IBX as well as for conglomerates in which each crystal contained only iodine atoms of the same absolute configuration.[11] The molecule is planar, with the exception of O4, which points out of the plane and thus gives rise to the chirality of IBX. Two additional intermolecular I···O contacts to neighboring molecules in the crystal results in an octahedral geometry around the iodine center (Figure 1).

IBX is an iodine(V) compound which, according to IUPAC recommendations, belongs to the class of aryl λ^5-iodanes. The bonding in polyvalent iodine species of this type is described in terms of three-center four-electron (3c-4e)

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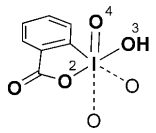


Figure 1. Molecular structure of IBX. I–O3 1.925 Å, I–O4 1.784 Å, O2-I-O3 163.43°.[11a]

bonds that are designated as "hypervalent".[7f,12] In the bonding model, there is generally assumed to be three different types of bonds in IBX: Being the least electronegative ligand, the phenyl group is attached to the iodine atom through an ordinary covalent bond. One of the two remaining doubly occupied, nonhybridized 5p orbitals of the iodine forms a linear 3c-4e bond with both the hydroxy and the carboxylate ligand (Figure 2). Such highly polarized

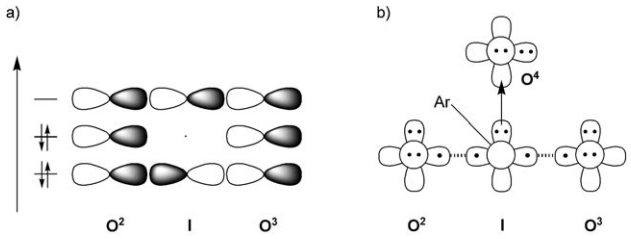
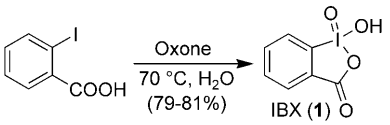


Figure 2. Hypervalent bonding in IBX. a) Qualitative molecular orbital diagram of the 3c-4e bond;[7d] b) structure of IBX.[13]

hypervalent bonds are weaker than regular covalent bonds, thus providing an explanation for the increased electrophilicity of the iodine atom. The bonding between the iodine atom and the oxo ligand located outside the plane is best described as a dative donor–acceptor bond (I^+–O^-),[13] which results in a high electron density at the oxygen atom.

2.2. Preperation of IBX

The original protocols for the synthesis of IBX relied on the oxidation of *o*-iodosobenzoic acid (IBA) by potassium permanganate[1] or chlorine gas,[14] but a range of different oxidants also facilitates the direct oxidation of *o*-iodobenzoic acid. For example, the preparation of IBX from *o*-iodobenzoic acid by using chlorine and aqueous sodium hypochlorite[15] or aqueous sodium periodate[16] as the oxidizing agent has been reported. In 1936, Greenbaum first reported the oxidation of *o*-iodobenzoic acid by potassium bromate in aqueous sulfuric acid, a procedure which probably constitutes the most common access to IBX.[17] Over the years, numerous modifications of this protocol resulted in the continuous development of improved procedures for the preparation of IBX.[18] It should be noted that IBX has been reported to be explosive upon impact or when heated above 200 °C;[1,19] however, this property was partly attributed to the presence of traces of bromate impurities.[20] The oxidation of *o*-iodobenzoic acid by using oxone ($2\,KHSO_5$-$KHSO_4$-K_2SO_4; Scheme 1) is particularly practical and suitable for the large-



Scheme 1. Preparation of IBX according to the procedure of Santagostino and co-workers.[21]

scale preparation of crystalline IBX.[21] This procedure, developed by Santagostino and co-workers, uses only water as the solvent and avoids toxic reagents or waste products.

IBX is a relatively strong acid on an organic scale: By using potentiometric titration methods, a pK_a value of 2.40 was obtained for IBX in aqueous solution; for IBX in DMSO, the corresponding value was found to be $pK_a^{DMSO} = 6.65$.[22,23] However, the solubility of IBX is mostly confined to DMSO; in the majority of organic solvents, IBX is insoluble at room temperature. The electrochemical reduction of IBX, IBA, and other hypervalent iodine compounds has been studied by means of voltammetric methods in dilute aqueous solution.[24]

2.3. IBX Derivatives and Their Synthetic Applications

As already indicated above, there are safety concerns regarding the potentially violent decomposition of IBX upon impact or at high temperatures, thus, rendering IBX unattractive for industrial applications.[19] A formulation composed of a mixture of benzoic acid (22 %), isophthalic acid (29 %), and *o*-iodoxybenzoic acid (49 %) has been developed

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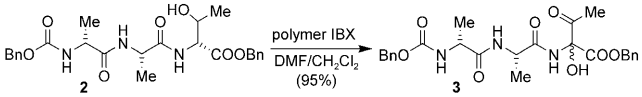
Alexander Duschek was born in Ingolstadt, Germany, in 1980. He studied chemistry at the Technische Universität München, where he completed his diploma thesis in 2007 under the guidance of Dr. S. F. Kirsch. Since then, he has been working on his PhD in the same group. Besides investigations concerning the reactivity of hypervalent iodine compounds, his research also encompasses the development of novel transition-metal-catalyzed carbocyclizations and their application to total synthesis.

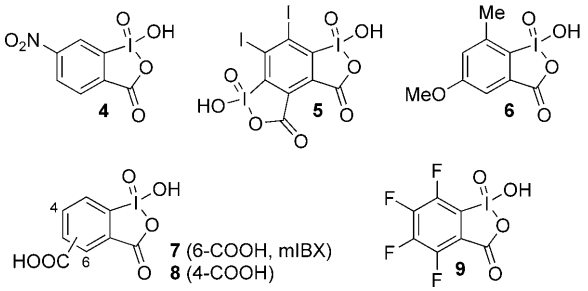
as a non-explosive alternative to IBX with similar oxidative properties. Accordingly, this stabilized form of IBX ("SIBX") has found numerous applications in the oxidation of alcohols,[25] the hydroxylation of phenols,[26] and other oxidative processes.[27]

The solubility problem of IBX in organic solvents (which will be discussed in more detail below) means that IBX oxidations are frequently associated with tedious work-up procedures and appear not to be suitable for automated high-throughput applications. Advantageously, various polymer-supported IBX derivatives have been synthesized which combine ease of application with high activity in the oxidation of alcohols.[28,29] The reduced form can be recovered by simple filtration and regenerated by oxidation with oxone. For example, polymer-supported IBX was employed successfully in an oxidative transformation of threonines, which proceeded with oxidation of a secondary alcohol to the ketone and subsequent α-hydroxylation (Scheme 2).[30]



Scheme 2. Oxidation of threonine derivatives by polymer-supported IBX.[30]

The first IBX derivative, *o*-iodoxy-*p*-nitrobenzoic acid (**4**), was described as early as 1908.[31a] Further derivatives with differently functionalized arene moieties (for example, **5**) followed, many of which remained laboratory curiosities (Scheme 3).[31] The deliberate addition of ancillary substituents to the aromatic core can improve the solubility without diminishing the oxidative properties. Hence, the methyl-substituted IBX derivative **6** is slightly soluble in acetone, acetonitrile, ethyl acetate, and tetrahydrofuran, thereby enabling the oxidation of alcohols and sulfides to the corresponding carbonyl compounds and sulfoxides in these solvents at room temperature.[32] Thottumkara and Vinod demonstrated that the introduction of an additional carboxylic acid functionality results in the formation of water-soluble IBX derivatives such as mIBX (**7**) and **8**. Benzylic and allylic alcohols are efficiently oxidized by mIBX in water or aqueous THF.[33] Isomer **8** turned out to be more broadly applicable.



Scheme 3. IBX derivatives bearing additional substituents at the aromatic core.

When dissolved in aqueous DMF, **8** displayed reactivity similar to that of IBX towards alcohols.[34] However, the reaction does not proceed as cleanly in other aqueous solvent mixtures. Tetrafluoro-IBX (**9**, FIBX) was developed by Wirth and co-workers and seems to hold even greater synthetic potential.[35] This reagent facilitates the ordinary oxidation of alcohols in aqueous acetonitrile or other solvents. Also, a range of other oxidative processes that are covered in the following section are possible.

In numerous iodoxyarenes formally derived from IBX, the carboxylic acid unit is replaced by other donor groups (Figure 3).[36] In addition to a number of IBX analogues that are not discussed in detail herein,[37] IBX amides (**10**),[38] IBX esters (**11**),[39] ethers of the type **12**,[40] acylamides of the type **13**,[41] sulfonamides of the type **14**,[42] and sulfonates of the type **15**[43] have been prepared and characterized (Scheme 4). The readily available IBX amides (**10**) and IBX esters (**11**), which are soluble in organic solvents, have proven to be useful oxidants for alcohols[38,39b] and sulfides.[39b,c] However, studies on their application to other oxidative processes remain quite limited.[44]

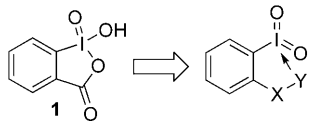
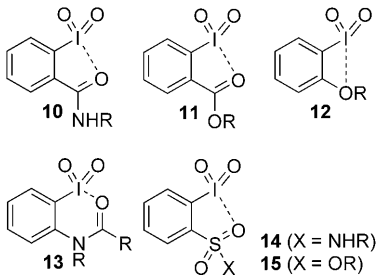


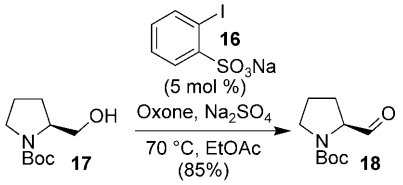
Figure 3. General structure of iodoxyarenes related to IBX.



Scheme 4. Selected IBX analogues.

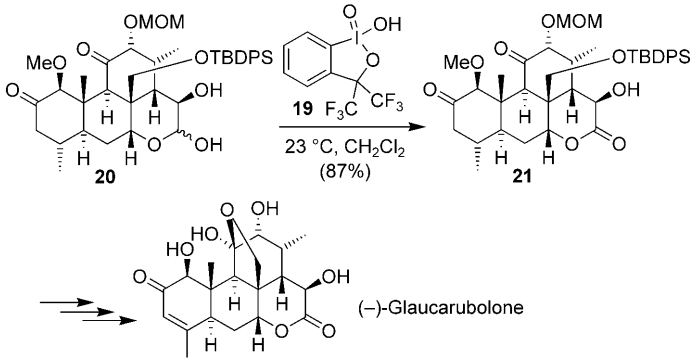
In this context, the activity of 2-iodoxybenzenesulfonic acid (IBS) as a catalyst for the oxidation of alcohols is particularly noteworthy. The oxidation of alcohols to the corresponding carbonyl compounds is accomplished in the presence of 0.05–0.5 mol% IBS, which is formed in situ from 2-iodobenzenesulfonic acid or its sodium salt **16** by oxidation with oxone (Scheme 5).[45] Under suitable reaction conditions, this protocol developed by Ishihara et al. also allows the transformation of carbonyl compounds into the corresponding enones and the oxidative rearrangement of allylic alcohols.[46]

Applications of IBX derivatives to the total synthesis or modification of biologically active natural products are still rather scarce. Whereas SIBX has only occasionally been employed as an oxidant in the synthesis of complex pro-



Scheme 5. IBS-catalyzed oxidation of alcohols.[45]

ducts,[47] the use of polymer-supported IBX is becoming increasingly popular.[48] As a consequence of their ease of handling, immobilized IBX reagents are attractive reagents, in particular for the oxidation of complex substrates on a small scale. An increasing number of applications can be expected in the future. Other IBX analogues have rarely found any synthetic application. A noteworthy exception is 1-hydroxy-1,3-dihydro-3,3-bis(trifluoromethyl)-1,2-benziodoxol-1-oxide (**19**), which was first described by Dess and Martin in 1991.[20] For example, **19** was successfully employed as a mild oxidant in a number of total syntheses by Grieco and coworkers to effect the oxidation of both simple alcohols and lactols in dichloromethane (Scheme 6).[49,50]



Scheme 6. Oxidation of lactols by periodinane **19**.[49b] MOM = CH_2OCH_3; TBDPS = $SiPh_2tBu$.

3. Oxidation of Alcohols

Despite the multitude of different oxidative processes that are known to be mediated by IBX, the selective transformation of primary and secondary alcohols into their corresponding carbonyl counterparts is still by far the most important application of this multifaceted reagent (Figure 4). Therefore, the mechanism of alcohol oxidation by IBX has been the subject of detailed experimental and theoretical investigations.

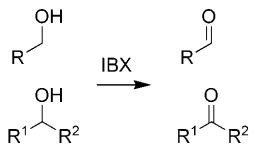
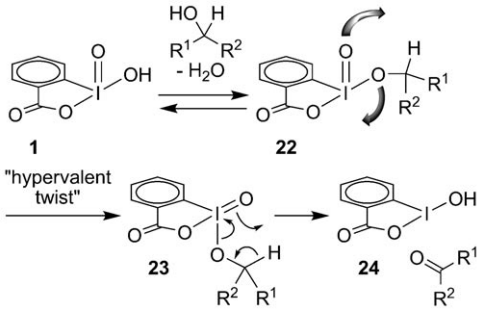


Figure 4. Oxidation of primary and secondary alcohols to carbonyl compounds by IBX.



Scheme 7. "Hypervalent twist" mechanism.[52]

Reversible ligand exchange at the electrophilic iodine atom proceeds with loss of one molecule of water to form intermediate **22** (Scheme 7), in which the alkoxy ligand assumes the position previously occupied by a hydroxy group. Adducts of this type have been observed in [D_6]DMSO by means of ^{1}H NMR spectroscopy, and equilibrium constants for their formation from IBX and different alcohols have been determined. Rate constants for the subsequent conversion of these intermediates into IBA **24** and the carbonyl compounds are also known. This disproportionation was found to be the rate-limiting step in the oxidation of aliphatic alcohols.[51]

Theoretical studies based on density functional theory indicate that, for electronic reasons, formation of the final products can not occur directly from intermediates with the structure shown in **22**. Instead, calculations have revealed that this should proceed via intermediate **23**, which arises from **22** by reorganization of the alkoxy and oxo ligands. Intermediate **23** has so far eluded spectroscopic detection. The oxidation product is released through elimination of IBA under formation of the linear 3c-4e bond (O–I–O) and the T-shaped geometry typical for trivalent iodine. In this mechanistic picture, the coordinated motion of the oxo and alkoxy ligands termed "hypervalent twisting" is regarded as the actual rate-determining step. According to calculations, its activation barrier is significantly larger than the corresponding values for the remaining steps [ligand exchange (**1**→**22**): 9.1 kcal mol^{-1}; twisting (**22**→**23**): 12.1 kcal mol^{-1}; elimination (**23**→**24**): 4.7 kcal mol^{-1}].[52]

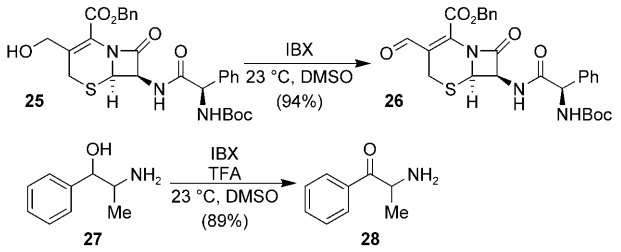
3.1. Reactivity

3.1.1. Simple Oxidation of Alcohols and Diols

Hartmann and Meyer observed the reduction of IBX by ethanol as early as 1893.[1a] Sixty years later, Caraway and Hellerman described the oxidation of ascorbic acid in a dilute aqueous solution of IBX with concomitant formation of IBA.[53] However, it took another 40 years until the use of IBX as an oxidant in organic synthesis was studied systematically. For a long time, IBX was only regarded as an insoluble compound, for which there was no synthetic application except serving as the precursor for the popular Dess–Martin periodinane (DMP).[54] The insolubility of IBX in common

organic solvents resulted in a suitable reaction medium being unavailable that would have allowed an examination of the synthetic potential of IBX. This situation suddenly changed in 1994: In their groundbreaking publication, Frigerio and Santagostino reported that dimethyl sulfoxide (DMSO) is capable of completely dissolving IBX at room temperature, even at relatively high concentrations (up to 1.5 M).[55] Unlike DMP, IBX is not susceptible to hydrolysis.[56] Furthermore, oxidation of DMSO to dimethyl sulfone by IBX is a very slow process at room temperature, thus rendering solutions of IBX in DMSO stable for several days.[57] Moreover, it was demonstrated that a solution of IBX in DMSO at room temperature can be used as an exceptionally mild oxidant for the highly selective transformation of primary and secondary alcohols into carbonyl compounds.[55] Remarkably, the reaction of primary alcohols with IBX in DMSO results exclusively in the formation of the corresponding aldehydes, and overoxidation to carboxylic acids is not observed.[58]

In their first studies, Frigerio and Santagostino already demonstrated that IBX displays a remarkable chemoselectivity towards the oxidation of alcohols, a property that turned out to be extremely useful for the synthesis of complex molecules. Other functional groups such as carbon–carbon multiple bonds, thioethers, tertiary alcohols, and oxidizable heterocycles such as furans, pyridines, or indoles usually remain untouched (Scheme 8).[55,57] In addition, tertiary



Scheme 8. Selected examples of chemoselective alcohol oxidation.[57] TFA = CF_3COOH.

amines do not interfere;[57] this feature has proven to be highly advantageous in the synthesis of alkaloids.[59] Primary and secondary amines, however, require temporary blocking by protonation with trifluoroacetic acid to prevent side reactions (Scheme 8).[57] Moreover, the oxidation of alcohols by IBX tolerates a wide variety of other functional groups such as allenes,[60] azides,[61] cyclopropanes,[62] diazo compounds,[63] epoxides,[64,65] phosphates,[66] phosphonates,[67] silanes,[68] germanes,[69] stannanes,[70] trifluoroborates,[71] iron and rhenium complexes,[72,73] as well as a large number of nitrogen- and sulfur-containing heterocycles.[74–84] Furthermore, most commonly employed protecting groups are compatible with IBX, the use of which in organic synthesis is steadily increasing as a result of these advantages.

The oxidation of diols by IBX generally follows the patterns ilustrated in Figure 5. Compared to other commonly employed oxidants, IBX has proven to be particularly useful for the selective oxidation of 1,2-diols[55,57] to the corresponding α-hydroxy aldehydes,[85] α-hydroxy ketones,[86,87] or α-

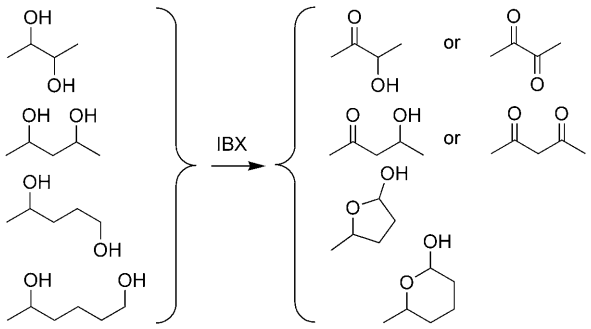
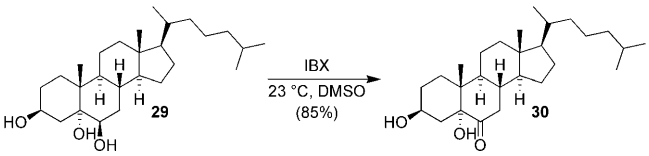


Figure 5. Reactiviy of 1,*n*-diols in the presence of IBX.

diketones (Scheme 9).[88] Cleavage of glycols is usually not observed, although it is a common side reaction when other reagents such as DMP are employed.[89] α-Hydroxy carbonyl compounds obtained by other synthetic routes may also be oxidized by IBX to yield the corresponding α-diketones,[90] α-

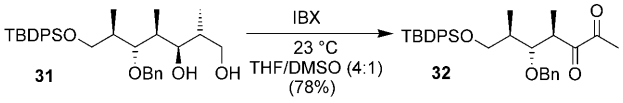


Scheme 9. Selective oxidation of a 1,2-diol.[57]

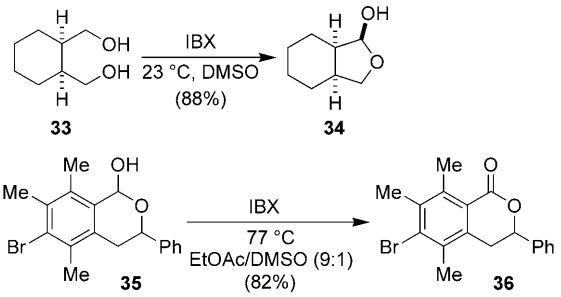
keto aldehydes,[55] α-keto amides,[91] or α-keto esters.[92–94] If both a 1,2-diol and additional oxidizable hydroxy groups are present in the same molecule, the glycol unit is oxidized preferentially.[55] However, under specific reaction conditions, in particular at elevated temperatures or in the presence of trifluoroacetic acid, glycol cleavage may also occur during IBX oxidations.[51,95]

The reaction of 1,3-diols with IBX frequently furnishes the corresponding β-hydroxy carbonyl compounds,[96] which might yield β-dicarbonyl compounds upon further oxidation.[97–101] As an exception, IBX oxidation of 1,3-diols with one primary and one secondary hydroxy group or the respective β-hydroxy carbonyl compounds typically does not afford enolizable β-keto aldehydes in good yields.[102] Although the expected formyl ketone is formed as an intermediate, it rapidly undergoes oxidative cleavage[103,104] to afford only 1,2-diketones in the presence of an excess of IBX (Scheme 10).[102]

Both 1,4- and 1,5-diols can be converted into lactols by selective oxidation with IBX and subsequent cyclization of the hydroxy carbonyl compound thus formed (Scheme 11).[105,106] Further oxidation of lactols to lactones is



Scheme 10. Oxidative cleavage of a 1,3-diol with a primary and secondary hydroxy group to the 1,2-diketone by IBX.[102] Bn = CH_2Ph; TBDPS = $SiPh_2tBu$.

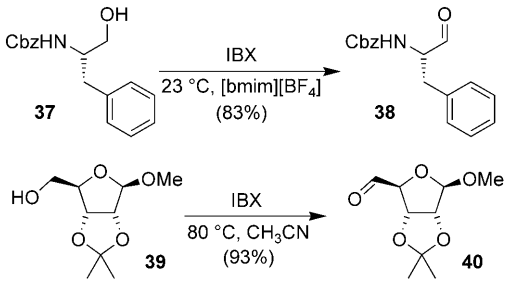


Scheme 11. Oxidation of lactols[105a] and lactones.[107a]

also feasible at elevated temperatures or in the presence of an excess of IBX.[93,107] However, the formation of lactones from lactols is considerably slower than the preceding oxidation of the diol to the lactol.[105b] The oxidative cyclization of *Z*-configured but-2-en-1,4-diols in the presence of IBX gives access to furan derivatives.[108] In analogy to the formation of lactols, the oxidation of 1,4- and 1,5-amino alcohols yields the five- or six-membered cyclic hemiaminals.[109–115] In the case of hemiaminals containing a protected nitrogen atom, further oxidation with IBX gives rise to the corresponding lactams.[116]

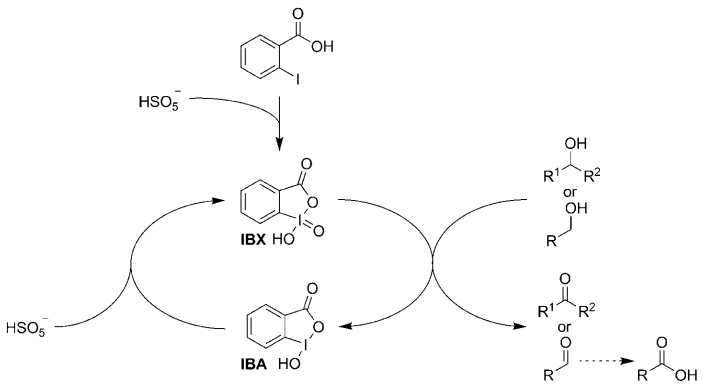
3.1.2. *Alternative Protocols*

The necessity of using DMSO as the solvent has long been regarded as a major drawback of IBX, in particular when compared to DMP, which is sensitive to moisture but soluble in dichloromethane. Unsurprisingly, intensive research in this area resulted in the proposal of numerous other solvents besides DMSO for use as reaction media in IBX-mediated oxidations at room temperature. For example, oxidations can also be performed in trifluoroacetic acid,[95a] dimethylformamide,[117] *tert*-butanol,[118] various ionic liquids,[119] and aqueous mixtures.[120] In a variation of particular synthetic importance, alcohols were shown to be oxidized at higher temperatures and in good to excellent yields when using suspensions of IBX in less-polar organic solvents such as acetonitrile, acetone, ethyl acetate, benzene, dichloroethane, or chloroform (Scheme 12).[121] Oxidations under solvent-free conditions are also possible at 60–70 °C.[122] Mixtures of DMSO and organic cosolvents are particularly practical for the oxidation of substrates that display insufficient solubility in pure DMSO or when reaction temperatures below the melting point of DMSO are required.[55,123]

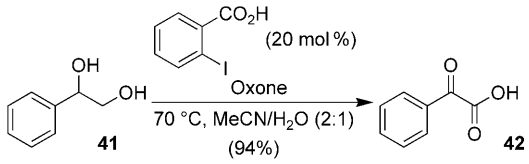


Scheme 12. Selected alternatives to DMSO: Solutions of IBX in ionic liquids[119b] and in acetonitrile at reflux.[121a] [bmim][BF_4] = 1-butyl-3-methylimidazolium tetrafluoroborate.

In recent years, further enhancement of the conventional oxidation by using stoichiometric amounts of IBX resulted in the development of improved procedures that only require catalytic amounts of IBX (or *o*-iodobenzoic acid). The oxidation of *o*-iodobenzoic acid and reoxidation of IBA formed in the course of the reaction is either effected by oxone in aqueous acetonitrile[124] or in a biphasic mixture of water and ethyl acetate under phase-transfer catalysis (Scheme 13).[125] Since only catalytic quantities of commercially available *o*-iodobenzoic acid are required, both the preparation and isolation of IBX become pointless. Frequently, however, this procedure for the oxidation of aliphatic primary alcohols results in the formation of the corresponding carboxylic acid instead of the desired aldehyde (Scheme 14). This overoxidation can be avoided by replacing oxone with tetraphenylphosphonium monoperoxysulfate (TPPP), thus allowing the reaction to be conducted in anhydrous media.[126]



Scheme 13. Oxidation of primary and secondary alcohols by using catalytic quantities of *o*-iodobenzoic acid in the presence of stoichiometric amounts of persulfate.

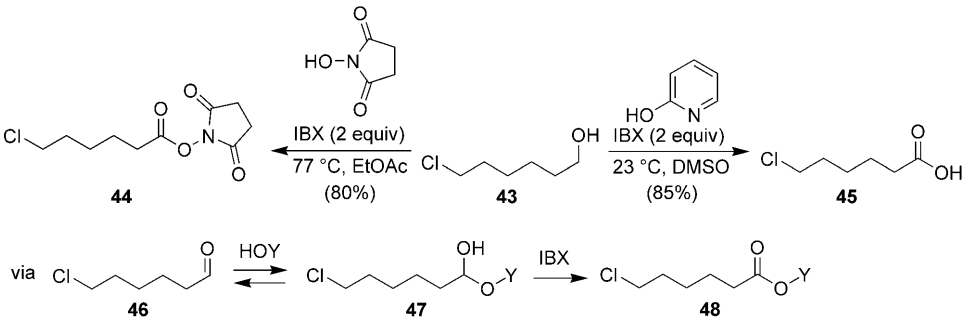


Scheme 14. Oxidation to the carboxylic acid by using a catalytic amount of *o*-iodobenzoic acid.[124]

3.1.3. *Oxidative One-Pot Procedures*

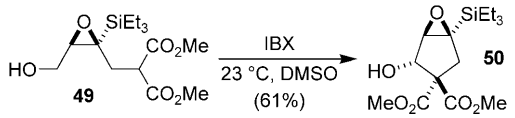
In numerous procedures, the nascent aldehyde compounds obtained from the IBX oxidation of primary alcohols are directly subjected to synthetically valuable follow-up reactions. For example, the protocol developed by Giannis and co-workers permits the oxidation of primary alcohols (or aldehydes) to carboxylic acids by use of IBX in DMSO in the presence of *N*-hydroxysuccinimide (NHS) or 2-hydroxypyr-

idine (HYP).[127] When the reaction is carried out in ethyl acetate, *N*-hydroxysuccinimide esters can be isolated, thus providing direct access to active esters of carboxylic acids (Scheme 15).[128] During the course of this reaction, the initially formed aldehyde **46** undergoes addition of a suitable oxygen nucleophile (HOY). Hence, subsequent oxidation provides the active ester, which in turn may be hydrolyzed to give the free carboxylic acid.



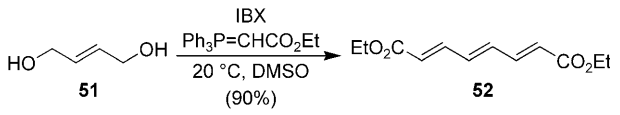
Scheme 15. Reaction conditions for the formation of active ester **44**[127] or carboxylic acid **45**[128a] from primary alcohol **47**.

Carbonyl intermediates generated by oxidation with IBX are also used for the assembly of cyclic systems in a protocol that relies on the oxidation of hydroxymalonates of type **49**. The formation of an aldehyde intermediate is followed by intramolecular nucleophilic attack with closure of the malonate ring to afford cyclopentanol **50** as the final product (Scheme 16).[129]



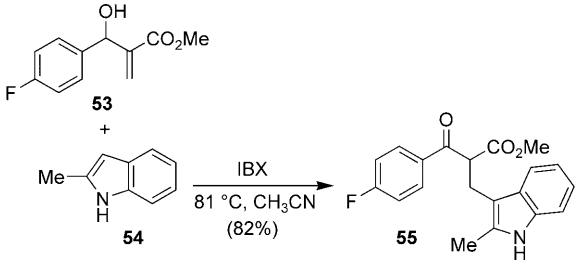
Scheme 16. IBX-mediated oxidation to aldehydes followed by cyclization to cyclopentanols.[129]

Since IBX in DMSO tolerates the presence of numerous functionalized reagents that are reactive towards carbonyl groups, carbonyl compounds created by means of IBX oxidation can conveniently be employed in other one-pot procedures. For example, carbonyl olefination products are directly accessed from the corresponding alcohols when stabilized Wittig ylides are used to trap aldehyde intermediates (Scheme 17).[130] In this way, the isolation of volatile or unstable intermediates can be obviated in a highly efficient manner.[131]

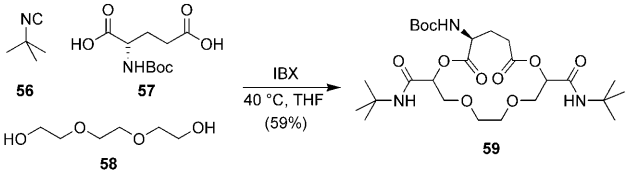


Scheme 17. IBX oxidation combined with carbonyl olefination.[130b]

The generation of carbonyl groups by IBX oxidation has been successfully combined with condensation reactions to access heterocycles such as pyridines directly from alcohols.[132] Furthermore, there is an impressive number of examples that demonstrate the oxidation of allylic alcohols coupled with the subsequent addition of various nucleophiles to the intermediate α,β-unsaturated carbonyl compounds (Scheme 18).[133,134] In a particularly interesting oxidative variant of the Passerini multicomponent reaction, the prerequisite aldehyde component is generated in situ by oxidation of the corresponding primary alcohol with IBX (Scheme 19).[135] In addition, a number of protocols make use of IBX to directly oxidize alcohol intermediates generated in the course of the reaction.[136,137] For example, a combination of IBX and I_2/H_2O



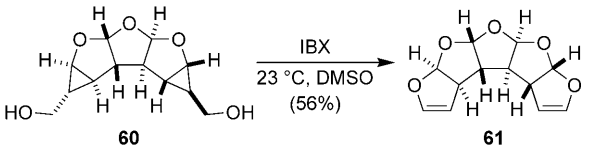
Scheme 18. IBX oxidation coupled with 1,4-addition of indoles to Michael acceptors formed as intermediates.[134a]



Scheme 19. Formation of a 15-membered macrocycle in an oxidative IBX-mediated Passerini reaction.[135b]

can be used for the direct transformation of alkenes into 2-iodoketones without isolation of the initially formed halohydrins.[137] Fanciful applications of this simple principle appear to have no limits.

A method developed by Werz and co-workers exploits a ring expansion reaction for the *anti*-selective synthesis of oligoacetals. The oxidation of cyclopropylmethanol derivatives such as **60** probably gives rise to non-isolable cyclopropylaldehyde intermediates. These "push-pull-substituted" cyclopropanes containing both electron-donating and electron-withdrawing substituents are unstable and spontane-



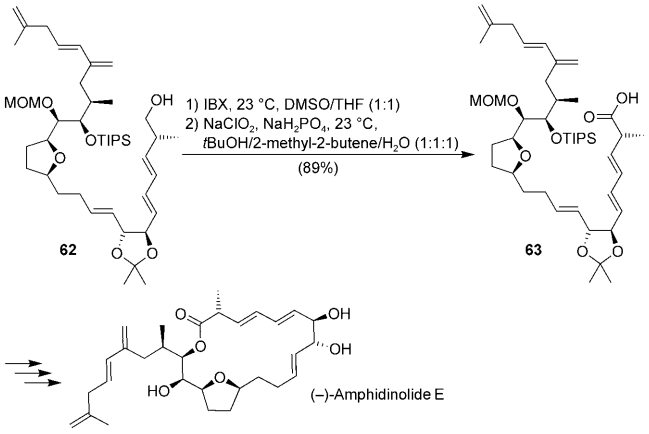
Scheme 20. Oxidative synthesis of *anti*-fused oligoacetals.[138]

ously undergo rearrangement under ring expansion to give the five-membered ring (Scheme 20).[138] A modification of this reaction yields spiroketals.[139]

3.2. Selected Applications in Total Synthesis

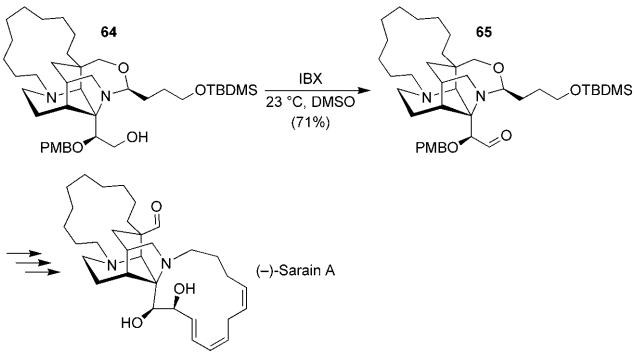
In recent years, IBX has become one of the most frequently used oxidants in the total synthesis of biologically active natural products. Therefore, it is neither intended nor possible to cover the entire literature in this area in this section. Only representative examples are discussed below. The examples were selected to illustrate that IBX is especially valuable for transformations involving complex and sensitive substrates whose selective oxidation quite often turns out to be problematic when other oxidants are employed.

Of particular advantage for total synthesis is that oxidations using IBX in DMSO have been proven to occur under exceptionally mild conditions. As an impressive example, oxidation of the α-chiral homoallylic alcohol **62** with IBX proceeds cleanly without any epimerization or isomerization of the double bond (Scheme 21).[140] In contrast, DMP failed to deliver satisfactory results in this total synthesis of (−)-amphidinolide E.



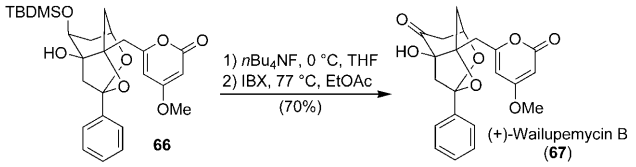
Scheme 21. Oxidation with IBX in the total synthesis of the macrolide (−)-amphidinolide E.[140] MOM = CH_2OCH_3; TIPS = $SiiPr_3$.

In the course of the total synthesis of the alkaloid (−)-sarain A by Overman and co-workers, the oxidation of the amino alcohol **64** in the presence of both a tertiary amine and an *N*,*O*-acetal turned out to be extremely difficult. Eventually, IBX was found to be the only oxidant that could furnish the desired aldehyde **65** in good yields (Scheme 22).[141]



Scheme 22. Oxidation of basic substrates in the synthesis of alkaloids exemplified by an advanced intermediate in the total synthesis of (−)-sarain A.[141] TBDMS = $SiMe_2tBu$; PMB = $CH_2C_6H_4p$-OMe.

The unique reactivity of IBX in the oxidation of 1,2-diols has been utilized in various total syntheses.[85–88,93] One intriguing example can be found in the total synthesis of (+)-wailupemycin B (**67**) by Bach et al. (Scheme 23).[142] The 1,2-diol intermediate obtained from **66** was converted in the final step of this synthesis into the natural product by using IBX. This oxidation proceeds cleanly in ethyl acetate at reflux without cleavage of the glycol moiety.

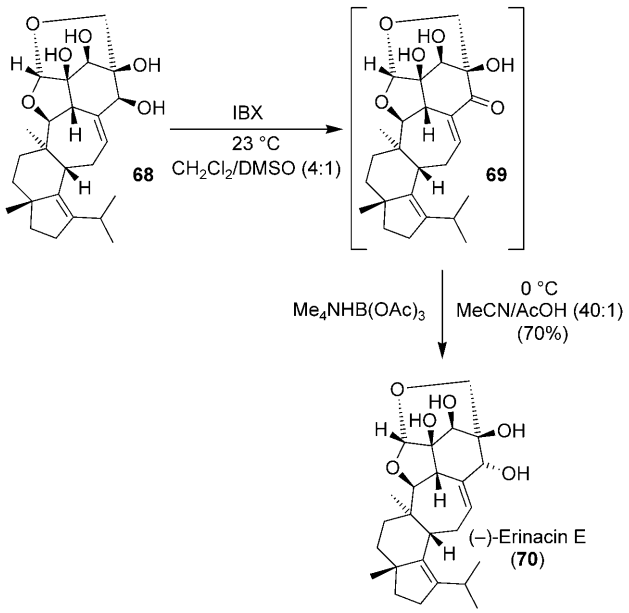


Scheme 23. The final oxidation in the total synthesis of (+)-wailupemycin B.[142] TBDMS = $SiMe_2tBu$.

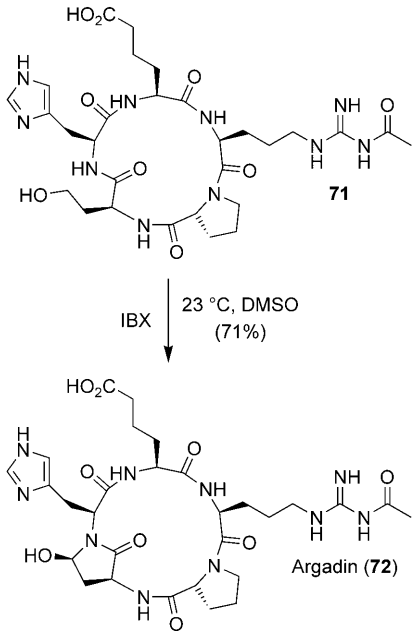
Another example is the selective oxidation of the 1,2,3,4-tetraol unit in **68** to provide hydroxy ketone **69** (Scheme 24). The configuration of the secondary alcohol was inverted through a subsequent stereoselective reduction of the newly formed carbonyl group, thus successfully completing the total synthesis of (−)-erinacin E (**70**).[87] This elegant sequence circumvents tedious protecting-group manipulations.

Besides the selective oxidation of 1,4- and 1,5-diols to the respective lactols initally described by Corey and Palani,[105,106] there are numerous examples of the analogous formation of cyclic hemiaminals in the total synthesis of complex natural products.[109–115] For example, Eggleston and co-workers employed an oxidative ring closure of this type in the final step of the total synthesis of the potent chitinase inhibitor argadin (**72**, Scheme 25).[143] Remarkably, the transformation of the cyclic peptide into the target compound was achieved selectively in the absence of any protecting-group manipulations.

Further applications in total synthesis that make use of the oxidation of alcohols by IBX are not discussed at this point. However, a multitude of conceptually related total syntheses can be found in Section 3.1.



Scheme 24. Selective oxidation of a 1,2,3,4-tetraol in the total synthesis of (−)-erinacin E.[87]

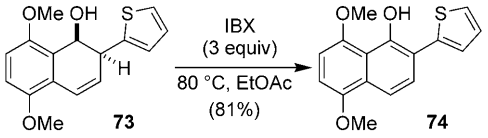


Scheme 25. Oxidative hemiaminal formation in the total synthesis of argadin.[143]

4. Other Types of Dehydrogenation

Although the oxidation of alcohols to carbonyl compounds is undoubtedly the most important application of IBX as an oxidant, recent years have seen the establishment of different oxidative processes that formally correspond to dehydrogenations.

For example, the formal dehydrogenation of 1,2-dihydro-1-naphthols such as **73** in the presence of IBX leads to the corresponding 2-substituted 1-naphthol oxidation products (Scheme 26).[144] This aromatization developed by Chen and

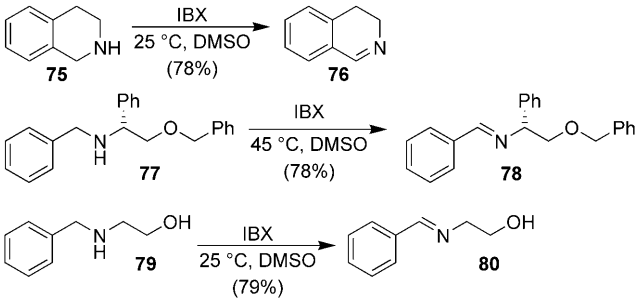


Scheme 26. Selective oxidation of dihydronaphthols to naphthols.[144]

Martin provides excellent yields by using ethyl acetate as the solvent; subsequent oxidative dearomatization, as described in Section 5.2, is not observed under these conditions. Other carbocycles[145] and in particular heterocycles are also aromatized efficiently by formal dehydrogenation.[146] For example, the reaction of cyclic amines with IBX directly produces imidazoles, isoquinolines, pyridines, or pyrroles.[147] In the presence of IBX, 1,4-dihydropyridines undergo aromatization to the corresponding pyridines.[148]

4.1. Oxidation of Benzylic Amines and Related Reactions

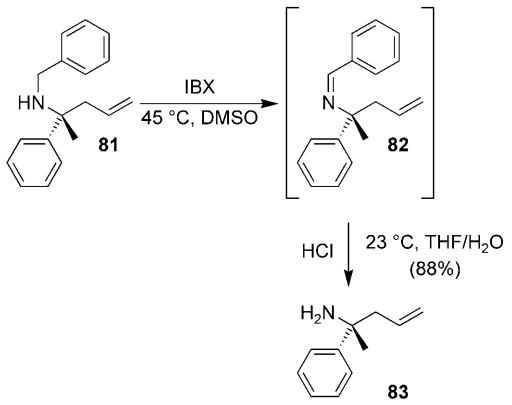
The oxidation of reserpine reported in 1994 was the first reaction of a benzylic amine with IBX ever reported.[149] Detailed investigations by Nicolaou et al. later demonstrated the generality of IBX-mediated oxidations of benzylic amines; in a reaction that parallels the oxidation of alcohols to carbonyl compunds, benzylic amines are transformed into the respective imines (Scheme 27).[147,150] The remarkable



Scheme 27. Oxidation of secondary benzylic amines.[147]

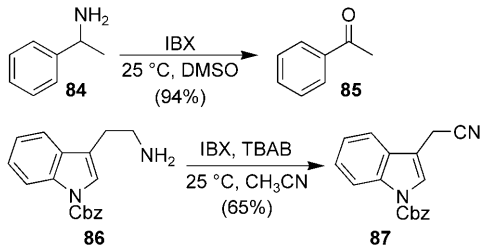
chemoselectivity of this transformation allows the oxidation of secondary benzylic amines even in the presence of primary alcohols or free phenols. Secondary hydroxylamines are oxidized to oximes under these conditions. Although the mechanism of this oxidation has not yet been elucidated in full detail, initial investigations suggest an ionic mechanism similar to the one that operates in the oxidation of alcohols.

Shibasaki and co-workers utilized the oxidation of a benzyl-protected secondary amine followed by acidic hydrolysis of imine **82** to achieve deprotection of the amine (Scheme 28).[151] In the presence of an alkene moiety, catalytic hydrogenation, which is typically employed for the deprotection of benzylated amines, would not have been possible without concomitant reduction of the double bond.



Scheme 28. Deprotection of benzylated amines.[151]

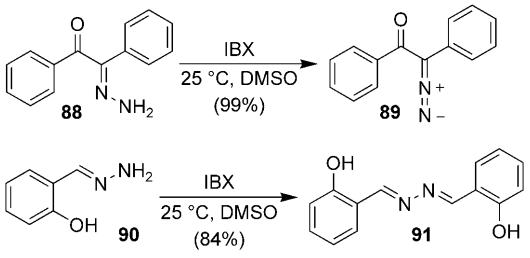
Imines formed from primary amines either undergo hydrolysis to the corresponding carbonyl compound[147] or further dehydrogenation to the nitrile under the reaction conditions (Scheme 29).[152] The role of tetrabutylammonium



Scheme 29. Oxidation of primary amines by IBX.[147,152] TBAB = nBu$_4$NBr.

bromide as a stoichiometric additive in the synthesis shown in Scheme 29 is not entirely clear. As will be discussed in more detail in Section 5.3, it seems likely that bromine or tribromide formed in situ through oxidation of bromide ions by IBX may be the actual oxidant in this transformation.

Hydrazines and hydrazones are also oxidized by IBX with initial formation of diazo compounds. If the diazo function in the product is stabilized by conjugation with a carbonyl group, the diazo ketone can indeed be isolated (Scheme 30).[147] In other cases, the diazo intermediate rapidly undergoes further reactions, and dimerization products are obtained.[147] Synthetic applications of this particular reactivity of IBX have not been reported so far.



Scheme 30. Oxidation of hydrazones.[147]

4.2. Dehydrogenation of Aldehydes and Ketones

From a synthetic point of view, the direct dehydrogenation of aldehydes and ketones to the respective α,β-unsaturated carbonyl compunds introduced by Nicolaou et al. is one of the most fundamental discoveries in the field of IBX-mediated reactions (Figure 6).[153–156] Both oxidizable carbonyl compounds and, provided that one additional equivalent of IBX is employed, the corresponding alcohols may serve as suitable substrates.

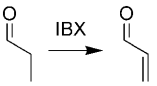
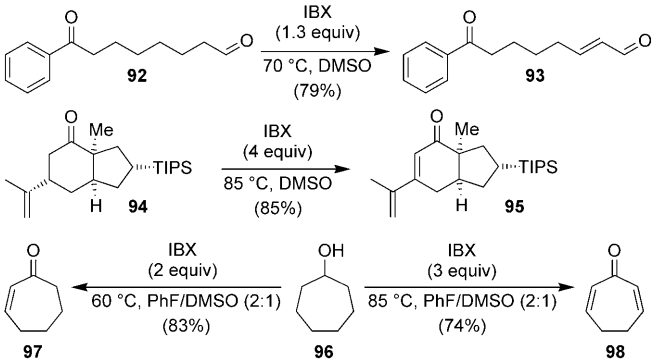


Figure 6. Reactivity of carbonyl compounds.

Some examples of this reaction type are summarized in Scheme 31. Typically, the reaction only takes place at elevated

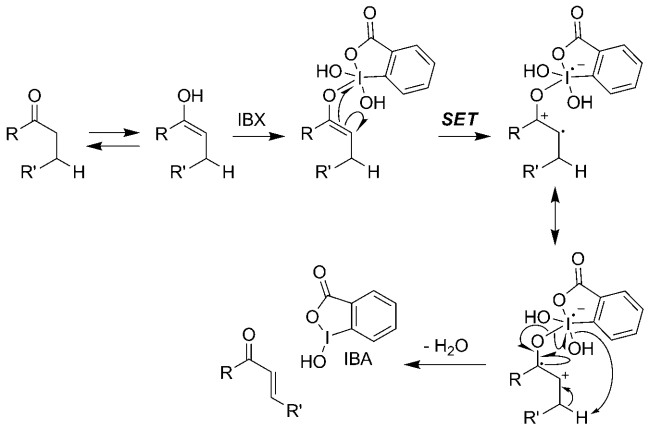


Scheme 31. Examples of dehydrogenation of carbonyl compounds.[153,154] TIPS = SiiPr$_3$.

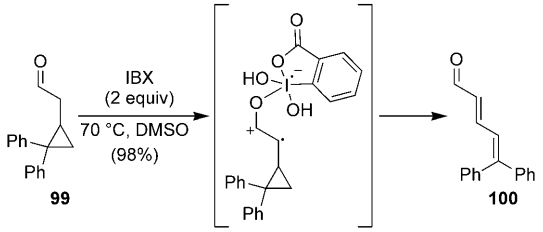
temperatures (> 65 °C). When multiple oxidizable positions are present, the suitable choice of the reaction conditions may allow selective dehydrogenation at one particular site. For example, aldehydes can be dehydrogenated in the presence of ketones. Depending on the amount of IBX employed, ketones may be transformed into enones such as **97** or dienones such as **98**. The reaction is accelerated by the addition of catalytic amounts of acid.[154] The addition of fluorobenzene improves the solubility of certain substrates in DMSO; however, the amount of fluorobenzene in the reaction medium should be kept to a minimum since the rate of the reaction significantly decreases as the amount of fluorobenzene increases.[154]

Although an ionic mechanism cannot be fully excluded at this time, the results of detailed mechanistic studies strongly support the assumption of a single-electron-transfer (SET) reaction. A radical cation is formed initially in the reaction. As depicted in Scheme 32, rearrangement of this intermediate liberates IBA and also results in the formation of the α,β-unsaturated carbonyl compound. The intermediacy of radical species was substantiated by the observation that cyclopropane derivative **99** undergoes ring opening to the conjugated diene **100** under the reaction conditions, as would be expected for 2,2-diphenylcyclopropylmethyl radicals (Scheme 33).

The reaction can be carried out under considerably milder conditions by using an improved procedure for the dehydrogenation of carbonyl compounds. Simple addition of a

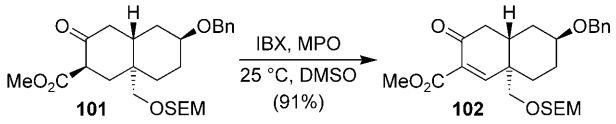


Scheme 32. Dehydrogenation of carbonyl compounds.[154]



Scheme 33. Evidence for radical intermediates in the IBX-mediated dehydrogenation of carbonyl compounds.[154]

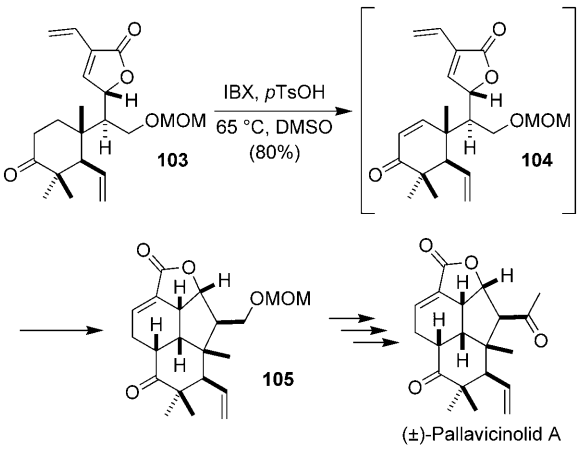
stoichiometric amount of an *N*-oxide allows dehydrogenation to occur readily at room temperature, thus also enabling sensitive substrates to be oxidized to enones (Scheme 34).[155] 4-Methoxypyridine-*N*-oxide (MPO), which forms a well-defined complex with IBX, has proven to be particularly



Scheme 34. Dehydrogenation at ambient temperature in the presence of an *N*-oxide.[155] SEM = $Me_3Si(CH_2)_2OCH_2$.

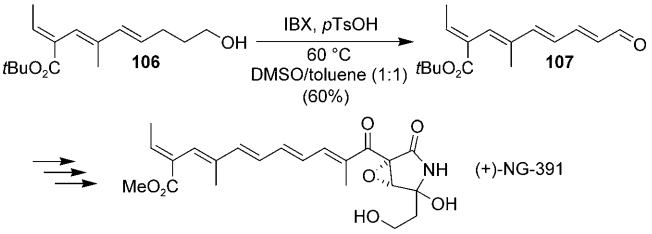
suitable for this purpose. The exact origins of the significant rate acceleration at room temperature remain unclear. With respect to the transformation depicted in Scheme 34, it is noteworthy that these reaction conditions do not result in hydroxylation, which would be the expected mode of reaction in the absence of MPO (see Section 5.3). Silyl enol ethers are also smoothly oxidized to the corresponding enones by IBX·MPO.[156]

Since its first description in 2000, the IBX-mediated dehydrogenation of ketones has found numerous applications in total synthesis. This reaction was utilized in a particularly elegant manner in the total synthesis of (±)-pallavicinolide A.[157] A dehydrogenation directly followed by an intramolecular Diels–Alder reaction was the key step for the stereoselective assembly of the complex tetracyclic carbon



Scheme 35. Dehydrogenation and intramolecular Diels–Alder reaction as the key step in the total synthesis of (±)-pallavicinolide A.[157] MOM = CH_2OCH_3.

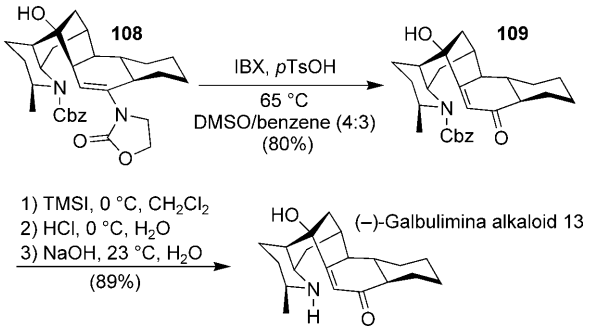
framework (Scheme 35). The oxidation of cyclic ketones and silyl enol ethers to the corresponding cyclic enones by IBX has gained widespread popularity in particular, as evidenced by the large number of applications in total synthesis that have been reported in recent years.[158,159] Even though it is used less frequently, the dehydrogenation of aldehydes is equally practical. For example, the reaction of primary alcohol **106** with IBX gave conjugated tetraenal **107** as an advanced intermediate in the total synthesis of NG-391 (Scheme 36).[160]



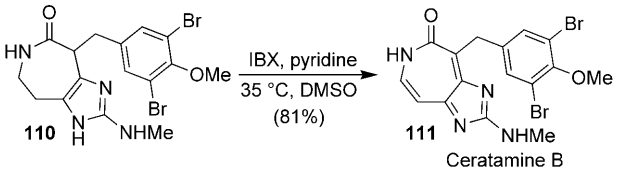
Scheme 36. Oxidation of a primary alcohol to the α,β-unsaturated aldehyde in the total synthesis of NG-391.[160]

An interesting modification of the protocol for IBX-mediated dehydrogenation was employed by Movassaghi et al. during the final stages of the total synthesis of galbulimima alkaloid 13.[161] Enone **109** was obtained directly from vinyl carbamate **108** in 80% yield by using IBX and excess *p*-toluenesulfonic acid. Subsequent cleavage of the Cbz group gave the natural product (Scheme 37).

Another variant of this reaction was used for the formation of the unsaturated imidazo[4,5-*d*]azepine ring system in the antimitotic natural product ceratamine B.[162] Lactam **110** was transformed into the unsaturated natural product **111** by formal removal of four hydrogen atoms. Coleman et al. showed that this double dehydrogenation proceeds under very mild conditions in 81% yield (Scheme 38). The oxidative transformation of lactam **110** is also noteworthy because other attempts to use IBX for the



Scheme 37. Direct transformation of a vinyl carbamate into an enone during the final stages of the total synthesis of galbulimina alkaloid 13.[161] Cbz = $PhCH_2OC(O)$.



Scheme 38. Twofold dehydrogenation to ceratamine B.[162]

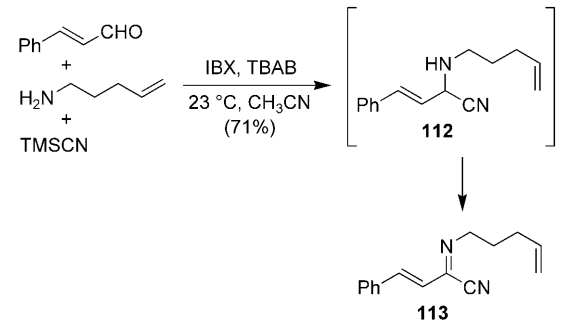
conversion of lactams,[163] lactones,[164] or esters[165] into their α,β-unsaturated counterparts have so far been unsuccessful.

4.3. One-Pot and Multicomponent Reactions Proceeding with Dehydrogenation

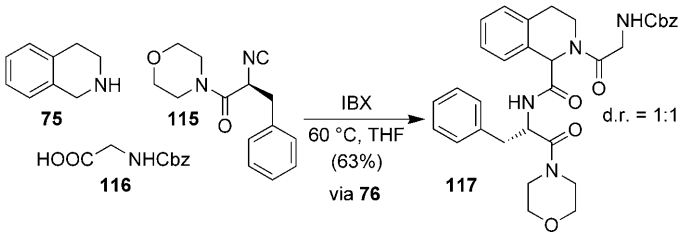
The IBX-mediated dehydrogenation of substrates other than alcohols has also been incorporated into a number of one-pot and multicomponent reactions. For example, the dehydrogenation of nitrogen-containing heterocycles is the key step in a one-pot procedure for the direct synthesis of substituted pyrazoles from aldehydes, aromatic hydrazines, and β-keto esters.[166] A further sequence facilitates the direct conversion of aldehydes into nitriles in aqueous ammonia. After condensation to the imine, both aromatic and aliphatic aldehydes are oxidized by IBX, thus yielding the corresponding nitriles in a single step.[167]

The oxidative Strecker reaction developed by Zhu and coworkers seems to be particularly advantageous.[168] The aminonitrile intermediate is directly oxidized in the presence of IBX to the α-iminonitrile (Scheme 39). The stoichiometric addition of tetrabutylammonium bromide is required in this three-component reaction to ensure high yields (see also Section 5.3). In cycloaddition reactions with isocyanides, iminonitriles such as **113** serve as starting materials for the synthesis of highly substituted pyrroles.[168b]

Moreover, Ngouansavanh and Zhu devised an appealing procedure for oxidative Ugi reactions wherein the imine component **76** is formed in situ by oxidation of the secondary benzylic amine **75** by IBX (Scheme 40).[169] Under operationally simple reaction conditions, this three-component reaction connects a carboxylic acid and an isonitrile with an amine.



Scheme 39. Synthesis of α-iminonitriles.[168] TBAB = nBu_4NBr.



Scheme 40. Oxidative Ugi reaction.[169] Cbz = $PhCH_2OC(O)$.

5. Oxidations by Oxygen Transfer

A large category of oxidations mediated by IBX proceed through transfer of oxygen to the substrate. As shown in Figure 7, one can be differentiate between three classes of such C,H oxidations: a) benzylic oxidation, b) hydroxylative phenol dearomatization, and c) α-hydroxylation of carbonyl compounds.

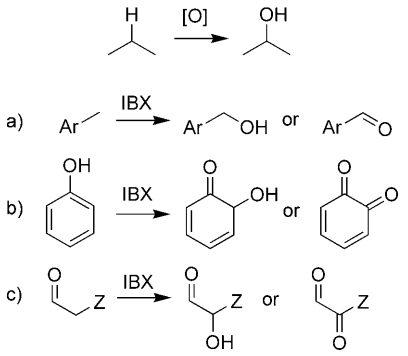
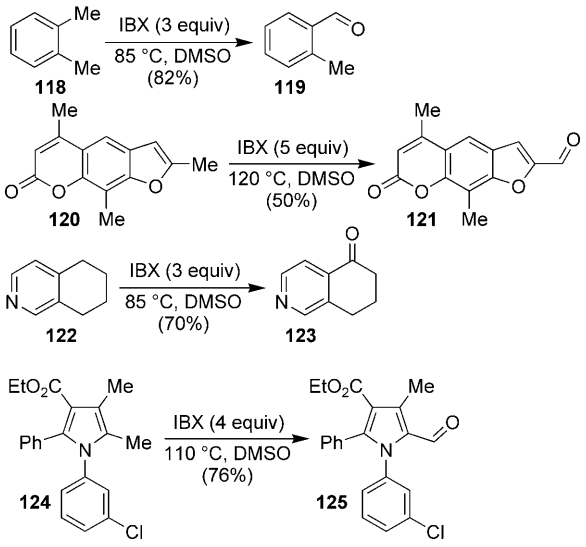


Figure 7. Different types of IBX oxidations proceeding through oxygen transfer.

5.1. Benzylic Oxidation

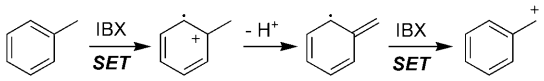
The selective oxidation of benzylic positions by IBX was first reported by Nicolaou et al. in 2001.[170] A clean reaction occurs at 75–90 °C in pure DMSO or in mixtures of DMSO and fluorobenzene. In all cases, carbonyl compounds are obtained as sole products. As exemplified in Scheme 41, suitable aromatic systems frequently possess electron-donating substituents that result in a high oxidation potential.



Scheme 41. Benzylic oxidations.[154,171]

When two competing oxidizable positions are present, usually only one of them will be oxidized since the newly formed carbonyl group significantly decreases the reactivity of the second position towards further benzylic oxidation (**118**→**119**). Benzylic positions of heterocycles can also be oxidized smoothly by IBX.[154,171] A variant in which IBX is formed in situ from oxone and catalytic amounts of *o*-iodobenzoic acid has also been employed successfully in benzylic oxidations of simple substrates.[172]

Detailed mechanistic investigations by Nicolaou et al. indicate that an inital SET process generates a radical cation that is further transformed into a benzylic cation in a second SET step (Scheme 42).[154] However, it remains unclear how



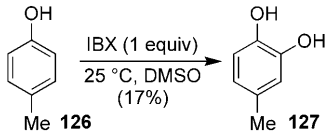
Scheme 42. Postulated mechanism of benzylic oxidation.[154]

the oxygen atom is introduced. In principle, water, DMSO, and IBX may be considered as potential sources of oxygen. However, the addition of water to the benzylic cation appears rather unlikely since the reaction also proceeds rapidly in anhydrous DMSO.

IBX is also capable of converting simple benzylic and allylic bromides into the corresponding carbonyl compounds in DMSO.[173] This reaction does not seem to proceed through alcohol intermediates.[173c]

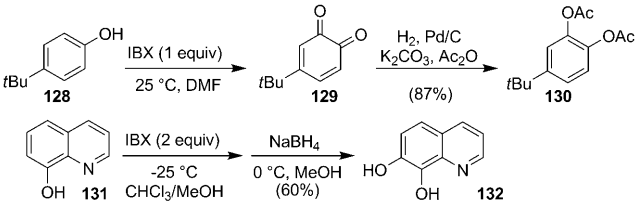
5.2. Oxidation of Phenols

In conjunction with their breakthrough studies regarding benzylic oxidation, Nicolaou et al. also investigated the IBX-mediated oxidation of *p*-cresol.[154] Here, it was observed that bisphenol **127** was obtained in low yield even at room temperature (Scheme 43). Interestingly, this rapid oxidation



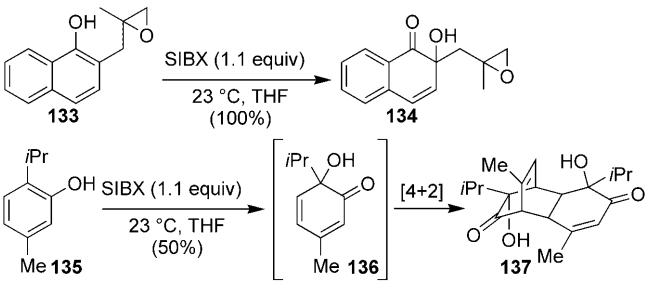
Scheme 43. Oxidation of *p*-cresol.[154]

of *p*-cresol by IBX was already utilized for biochemical purposes in 1981 to purify IBA from trace impurities of IBX.[174] In 2002, systematic NMR studies by Pettus and coworkers demonstrated for the first time that IBX is capable of transforming phenols cleanly and regioselectively into *o*-quinones even at room temperature.[175] As a consequence of their limited stability, the *o*-quinones were directly hydrogenated and subsequently acylated to finally provide catechols as isolable products from the overall sequence (**128**→**129**→**130**; Scheme 44). Alternatively, reduction to the catechols can be achieved during work-up with aqueous $Na_2S_2O_4$.

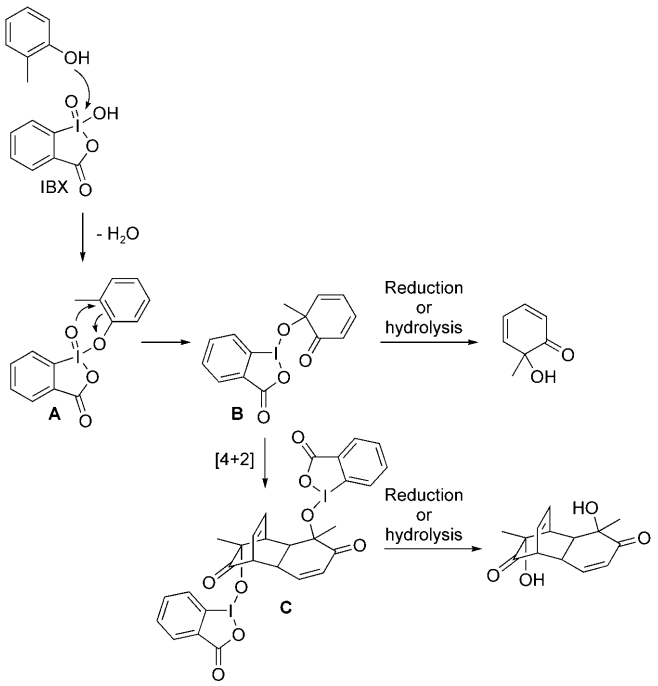


Scheme 44. Synthesis of catechols by using IBX.[175a,177]

The finding that IBX can hydroxylate phenols led to a dramatic extension of the reactivity portfolio of IBX.[176] For example, it was shown that numerous catechols are easily accessible if the reduction of the quinone intermediates is carried out with $NaBH_4$ in methanol at 0 °C (Scheme 44).[177] Even more interesting, the oxidation of 2-alkyl phenols by IBX results in regioselective dearomatization to provide the corresponding tertiary alcohols.[26,175] While the hydroxylation of 2-alkyl naphthols yields stable products such as **134** (Scheme 45), the dearomatization of 2-alkyl phenols is typically followed by dimerization through spontaneous [4+2] cycloaddition.[178] Work-up is performed best with TFA to achieve hydrolytic cleavage of the IBA units.



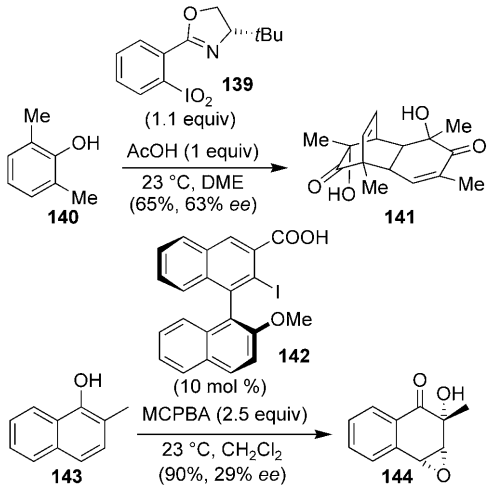
Scheme 45. Dearomatization of 2-alkyl phenols. In these reactions, SIBX was employed rather than IBX.[178]



Scheme 46. Mechanism of dearomatization of 2-alkyl phenols.[175a]

A plausible mechanism for dearomatizations of this type is depicted in Scheme 46. It is assumed that ligand exchange results in intermediate **A**, with the phenol directly bound to the iodine(V) center. Oxygen is now delivered intramolecularly to the phenol, while the I^V species is concurrently reduced to I^{III}. IBA derivative **B** can either directly release the tertiary alcohol or undergo a further dimerization to **C**. Pettus and co-workers were able to isolate the I^{III} intermediate of type **C** in the conversion of 2,6-dimethylphenol in the presence of IBX.[175a]

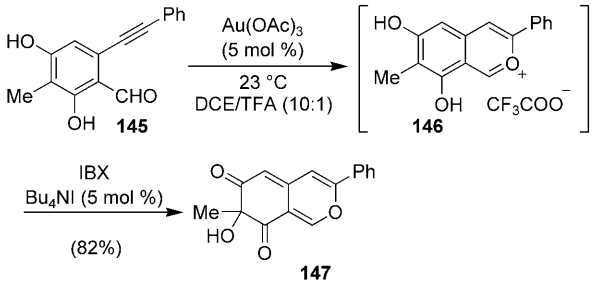
As a consequence of their potential importance for future developments in the field, two variants of the dearomatization that most likely proceed in a related manner should be briefly mentioned, even though IBX is not the oxidizing agent in these cases. For example, the asymmetric dearomatization of phenols can be achieved by using the chiral iodine(V) compound **139** as the oxidant (Scheme 47).[179] Boppisetti and Birman achieved 63% *ee* and a yield of 65% in the oxidative transformation of 2,6-dimethylphenol. The addition of acetic acid proved useful to activate the otherwise unreactive iodoxy compound. Notably, complete conversion resulted in the formation of an aryl iodide (I^I) as the only reduced iodine form rather than providing the expected iodosyl compound (I^{III}). Furthermore, Quideau et al. demonstrated in an impressive study that chiral *o*-iodobenzoic acids such as **142** can be transformed in situ into reactive oxidants for the asymmetric dearomatization of phenols by simple treatment with *m*-chloroperbenzoic acid (MCPBA).[180] Although the enantioselectivities achieved so far are only moderate in the best cases, the method has great potential. On the basis of mass spectrometric investigations, the authors assume I^V intermediates. However, it can also be argued that iodoxy-I^V species are actually involved. Indeed, it is reported



Scheme 47. Asymmetric dearomatizations.[179,180]

that iodobenzene is oxidized by peracids;[181] on the other hand, *o*-iodobenzoic acid is typically only oxidized to the oxidation state of *o*-iodosylbenzoic acid (IBA).[40c,182]

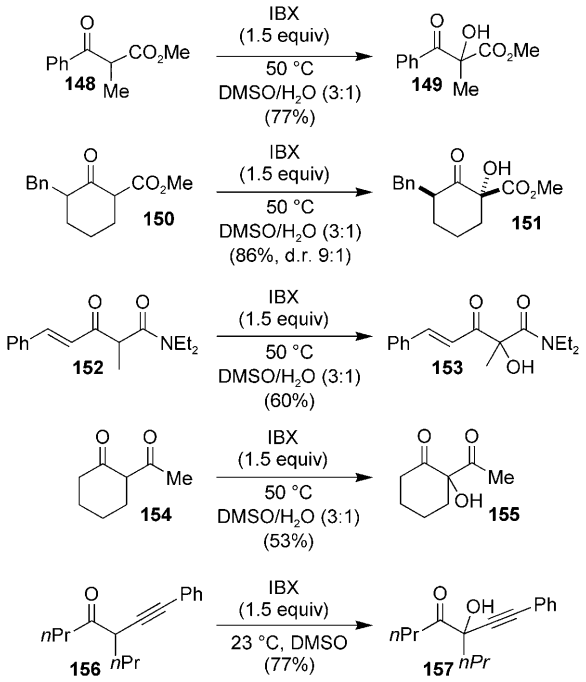
The dearomatization of other aromatic systems such as anilines[183] and indoles[184] also works fine when using IBX. Porco and co-workers showed that 2-benzopyrilium salts as **146** are easily oxidized by IBX in 1,2-dichloroethane(DCE)/TFA (Scheme 48).[185] The use of tetrabutylammonium iodide as a phase-transfer catalyst was essential for the success of the reaction. The starting benzopyrilium salt was obtained through Lewis acid catalyzed cyclization of *o*-alkynyl benzaldehyde **145** and directly submitted to further conversion.[186]



Scheme 48. Oxidation of 2-benzopyrilium salts.[185]

5.3. α-Hydroxylation of Carbonyl Compounds

The direct α-hydroxylation of carbonyl groups is possible with IBX when the α position is sufficiently activated by suitable functional groups.[187] Duschek and Kirsch demonstrated that β-keto esters such as **148** or **150** are converted into the corresponding tertiary alcohols in good yields on treatment with IBX (Scheme 49).[188] Although the reaction in pure DMSO was invariably accompanied by the formation of significant amounts of α,β-unsaturated compounds originating from concomitant dehydrogenation (see Section 4.2), the addition of water was found to completely suppress this competing reaction pathway. In particular, a 3:1 mixture of DMSO and water turned out to be optimal, whereas a higher

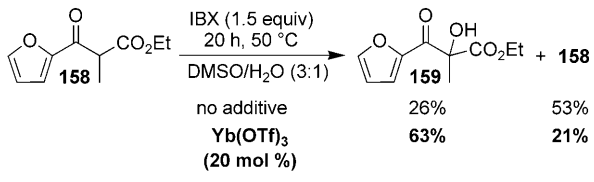


Scheme 49. α-Hydroxylation of carbonyl compounds according to Kirsch and co-workers.[188,189]

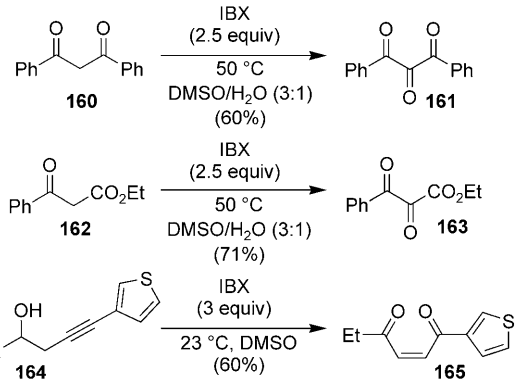
water content resulted in problems because of the poor solubility of both the substrate and IBX. The IBX-facilitated α-hydroxylation of ketones is not limited to substrates possessing an ester moiety in the α position. In preliminary studies it was discovered that, for example, amides (such as **152**) and ketones (such as **154**) react in an analogous manner. However, in these cases the yields were more modest than generally observed in the corresponding reactions of β-keto esters. Of particular synthetic value is that α-alkynyl carbonyl compounds such as **156** undergo α oxygenation when treated with IBX.[189] The tertiary alcohols obtained by this oxidative process are useful starting materials for the direct synthesis of 3(2*H*)-furanones und 3-pyrrolones.[190]

In some cases the reaction turned out to be too slow to be synthetically viable. For example, treatment of **158** with IBX for 20 h gave rise to the desired alcohol **159** in only 26% yield (Scheme 50). Interestingly, the addition of 20 mol% of a suitable Lewis acid such as $Yb(OTf)_3$ resulted in substantially higher yields, possibly as a result of increased enolization of the substrate.

Moreover, the oxidation of diketones and keto esters not bearing an additional substituent in the α position also proceeds smoothly under the standardized reaction condi-



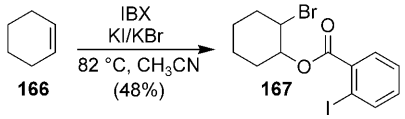
Scheme 50. Effect of added $Yb(OTf)_3$.[188]



Scheme 51. Direct access to triketones, diketo esters, and (*Z*)-enediones by IBX oxidation.[188,191]

tions (IBX, 50 °C, $DMSO/H_2O$ (3:1); Scheme 51). A secondary hydroxy group that is presumably generated in a first step would subsequently undergo further oxidation to give the corresponding ketone **161**, which can be isolated as a mixture with various amounts of its hydrate. In contrast to this observation, α-alkynyl carbonyl compounds lacking the additional substituent in the α position do not provide access to the corresponding 1,2-diketo compound. Instead, a rapid rearrangement results in the formation of (*Z*)-enediones such as **165** as the major products.[191]

Besides oxygen, thiocyanates,[192] bromides,[193] and iodides[194] were successfully transferred onto C=C bonds and aromatic compounds in the presence of IBX. An example of this reactivity is shown in Scheme 52. However, when IBX



Scheme 52. Halooxygenation of alkenes. The diastereoselectivity of the reaction is not given.[194a]

oxidations are conducted in the presence of halides, such as iodides and bromides, one should carefully discuss the exact role of the salts added as the halide sources. In was already reported in the first studies on the reactivity of IBX in 1893 that IBX (just like IBA) oxidizes iodides with formation of I_2.[1,2,53] More recent studies explicitly point out, for example, that IBX is capable of releasing Br_2 from LiBr.[133d,173d] When performing oxidations mediated by IBX in the presence of iodides or bromides of whatever origin, one must then consider that IBX might primarily oxidize the halides. Depending on the reaction medium, the actual reactants might then be halide-derived neutral species (X_2), anionic species (X_3^-), or cations (X^+; see Refs. [193,194]). This is also true for reactions that utilize stoichiometric amounts of phase-transfer catalysts such as tetrabutylammonium iodide or tetrabutylammonium bromide in addition to the oxidizing agent IBX (see Refs. [120bc,152b,168]).It appears quite

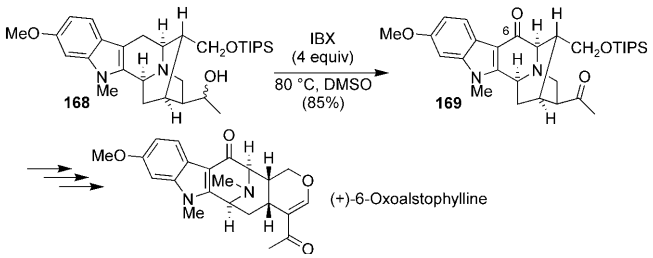
possible that in transformations of this type (in addition to a few reactions discussed in Section 6) IBX acts by oxidizing the halides first,[195] although neither the activation of IBX through the halide nor the phase-transfer catalysis can be ruled out.

5.4. Selected Applications in the Synthesis of Complex Systems

The ability of IBX to oxidize distinct substrates by oxygen transfer was used early on in the synthesis of complex compounds. Selected representative examples are summarized below.

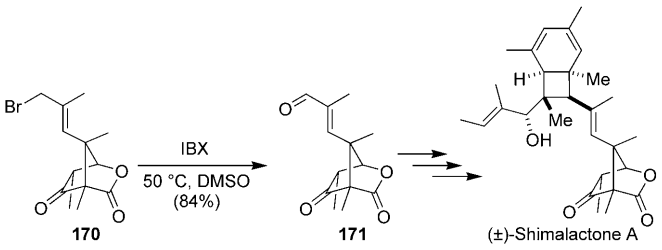
5.4.1. Benzylic Oxidation

The IBX-mediated oxidation of benzylic positions only found sporadic use in synthesis. As a prominent example, a late-stage introduction of the carbonyl group at C6 by use of IBX provides an easy entry into the synthesis of (+)-6-oxoalstophylline (Scheme 53).[196] In the case of (+)-6-oxoalstophylline, the oxidation of the secondary alcohol moiety proceeds in EtOAc in the presence of one equivalent of IBX. A further three equivalents of IBX are added to the reaction mixture for the subsequent benzylic oxidation at 80 °C in DMSO.



Scheme 53. Synthesis of (+)-6-oxoalstophylline by benzylic oxidation with IBX.[196] TIPS = Si(*i*Pr)$_3$.

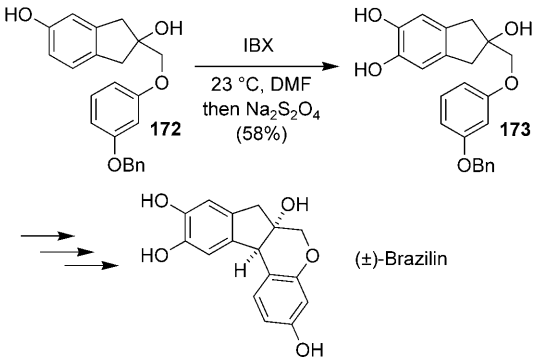
The oxidation of allylic bromides was the key step in the biomimetic synthesis of shimalactone A developed by Trauner and co-workers (Scheme 54).[197] The oxidation of allylic bromides was also successfully employed for the construction of complex materials.[198]



Scheme 54. Synthesis of shimalactone A.[197]

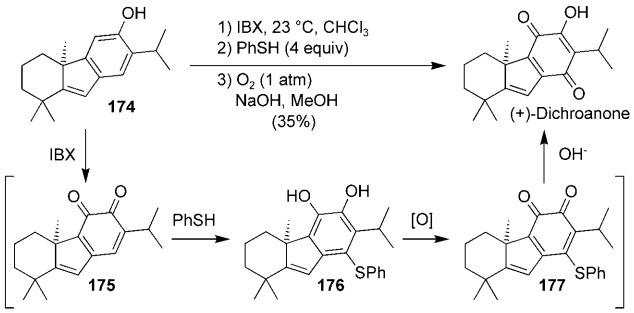
5.4.2. Oxidation of Phenols

All the variants of the oxidation of phenols discussed above were applied to the total syntheses of natural products. In particular, the oxidation to *o*-quinones originally developed by Pettus and co-workers and subsequent reduction provides a flexible and frequently used entry to catechols.[199–201] A representative example is the total synthesis of brazilin in which the oxidation of phenol **172** by IBX is the key step.[199l] Remarkably, the high regioselectivity (4:1) of the oxidation favors the desired *o*-quinone that is further reduced to catechol **173** in 58% yield upon work-up with $Na_2S_2O_4$ (Scheme 55). To finally obtain brazilin the *o*-quinone was reformed and isomerized with Hünig's base to give the tetracyclic core structure.



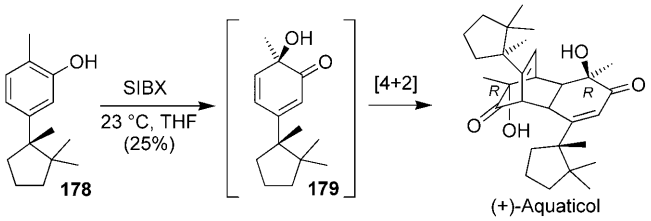
Scheme 55. Total synthesis of brazilin.[199l]

The final step of the protecting-group-free total synthesis of (+)-dichroanone also relied on the IBX-mediated oxidation of phenols (Scheme 56).[202] McFadden and Stoltz treated *o*-quinone **175** directly with thiophenol without further work-up. It is assumed that catechol intermediate **176** is formed upon 1,4-addition and tautomerization. Although the catechol moiety proved to be highly labile, oxidation by oxygen in the presence of base gave the natural product, presumably through intermediate **177**. This unique sequence proceeds in 35% yield; hydroxylative dearomatization was not observed under the reaction conditions.



Scheme 56. Total synthesis of (+)-dichroanone.[202]

The hydroxylative dearomatization of *o*-alkyl phenols was employed by Quideau and co-workers as the key step in the concise biomimetic total synthesis of (+)-aquaticol (Scheme 57).[203] The oxidation of phenol **178** by SIBX resulted in a mixture containing the *R*,*R* natural product (25%) and the *S*,*S* diastereomer (25%), also formed from **179**. Furthermore, the catechol resulting from the competing *o*-quinone formation was obtained in 22% yield. Purification of the reaction mixture was achieved by reversed-phase HPLC.

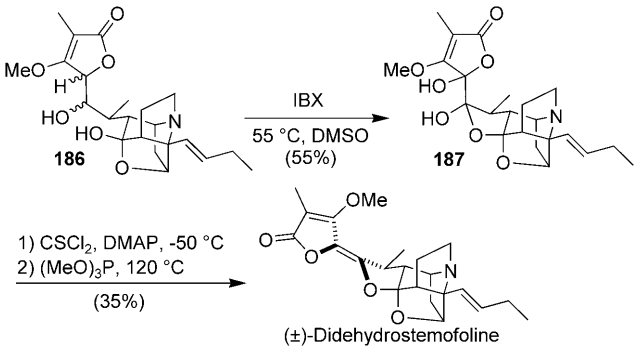


Scheme 57. Total synthesis of (+)-aquaticol.[203]

5.4.3. α-Hydroxylation of Carbonyl Compounds

The direct α-hydroxylation of carbonyl compounds has only rarely been applied to the total synthesis of biologically active compounds. A striking exception are the alkaloid syntheses developed by Nagasawa and co-workers, many of which rely on IBX to transfer oxygen to the α position of a carbonyl group (Scheme 58). For example, in the total synthesis of batzelladine A, alcohol **180** was oxidized with an excess of IBX.[204] In addition to enal **181**, which is required for completion of the synthesis of the natural product, oxygenation led to tertiary alcohol **182** in 11% yield. IBX-mediated hydroxylation of ketone **183** was the key step in the total synthesis of (−)-decarbamoyloxysaxitoxin.[205] As shown in Scheme 58, the two-step sequence consisting of Swern oxidation followed by IBX oxidation at 70 °C in DMSO was ideal to transform alcohol **183** into aminal **185** in good yield. However, hemiaminal **185** was only isolated in 28% yield when IBX was used for both oxidation steps. A closely related transformation was utilized for the total synthesis of (+)-dibromophakellin.[206]

Overman and co-workers used an excess of IBX in DMSO at 55 °C for the hydroxylation of 4-methoxy-2(5*H*)furanone **186** (Scheme 59).[207] In the course of this reaction the secondary alcohol was oxidized and converted into lactol **187**. Condensation of the major diastereoisomer with thiophosgene and subsequent elimination in the presence of $(MeO)_3P$ led to the completion of the total synthesis of didehydrostemofoline.

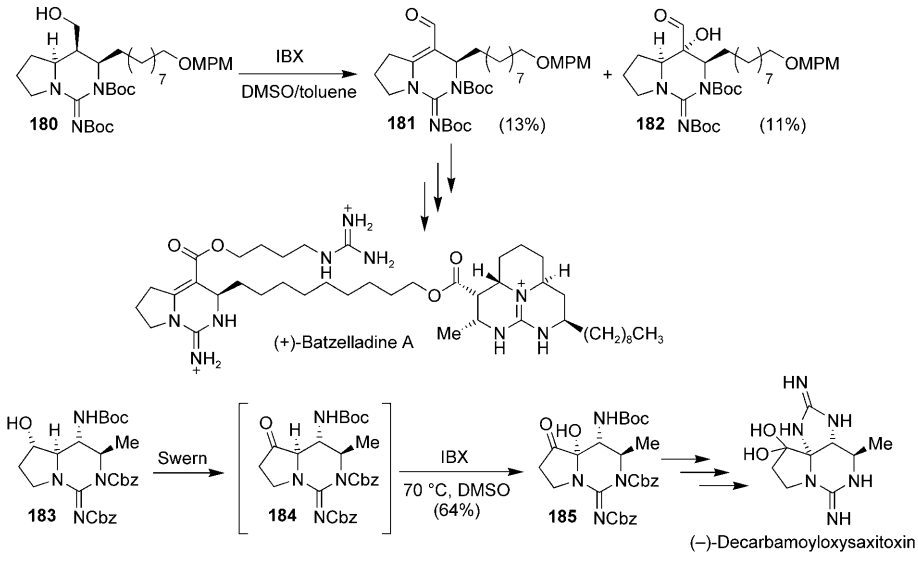


Scheme 59. Total synthesis of didehydrostemofoline.[207]

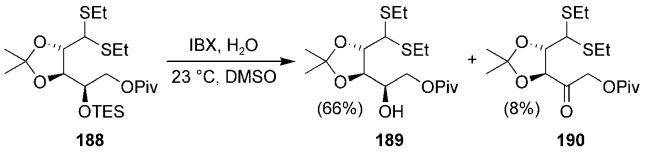
6. Miscellaneous Reactions of IBX

This section deals with those reactions mediated by IBX that do not fall into any of the categories discussed above. Besides the oxidative properties of IBX, its considerable acidity certainly plays a pivotal role in many of the transformations described below. For example, triethylsilyl ethers[208] are hydrolyzed in the presence of IBX.[209] Usually, the deprotected alcohol is immediately oxidized to the corresponding carbonyl compound. However, since cleavage of the triethylsilyl moiety occurs more rapidly than alcohol oxidation, the subsequent oxidation of the hydroxy group may be suppressed in the presence of water (Scheme 60).

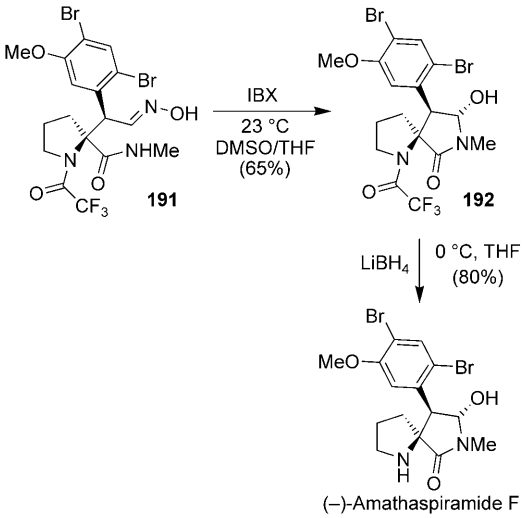
Oximes derived from aldehydes and ketones as well as tosyl hydrazones can be transformed into the parent carbonyl compounds in good yields under relatively mild reaction conditions by using IBX.[210,211] An interesting example can be found in the total synthesis of the alkaloid (−)-amathaspiramide F (Scheme 61). Here, the reaction of oxime **191** with IBX gave hemiaminal **192**, which was further converted into the natural product by removal of the trifluoroacetyl



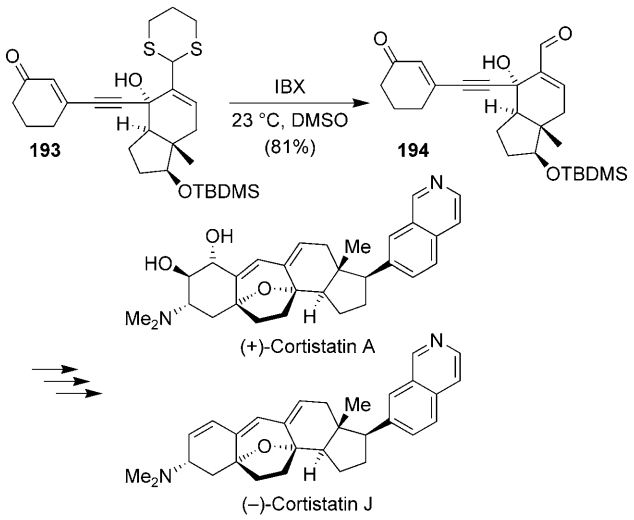
Scheme 58. Syntheses of alkaloids according to Nagasawa and co-workers.[204,205]



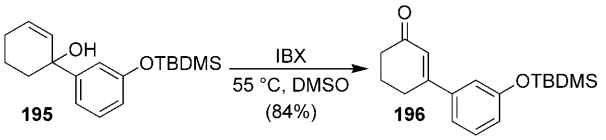
Scheme 60. Rapid cleavage of TES ethers by IBX.[208] TES = $SiEt_3$; Piv = tBuC(O).



Scheme 61. Deprotection of an oxime in the total synthesis of (–)-amathaspiramide F.[211a]



Scheme 62. IBX-mediated deprotection of dithianes.[216] TBDMS = $SiMe_2t$Bu.



Scheme 63. Oxidative rearrangement of tertiary allylic alcohols.[218] TBDMS = $SiMe_2t$Bu.

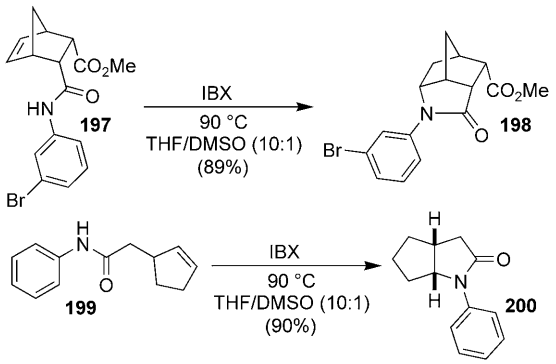
group.[211a] The hydrolysis of *O*,*S*-acetals,[212] *O*,*O*-acetals,[213] and tetrahydropyranyl (THP) ethers[214] is also observed in the presence of IBX under quite specific reaction conditions.

The release of ketones or aldehydes from the corresponding thioketals and thioacetals by using IBX in aqueous media constitutes a particularly appealing alternative to traditional procedures that often require the use of toxic heavy-metal salts.[215] Interestingly, dithianes containing α-hydrogen atoms seem to be deprotected via vinyl sulfide intermediates, which can be isolated under certain conditions. Nicolaou et al. utilized this mild procedure to convert dithiane **193** into aldehyde **194**, a common key intermediate in the total synthesis of both cortistatin A and cortistatin J (Scheme 62).[216] Occasionally, rearrangements are observed in similar reactions with IBX. Besides being deprotected to the corresponding carbonyl compound, 1,3-dithiolanes and 1,3-dithianes may also undergo ring expansion to form dihydro-1,4-dithiines und dihydro-1,4-dithiepines.[217]

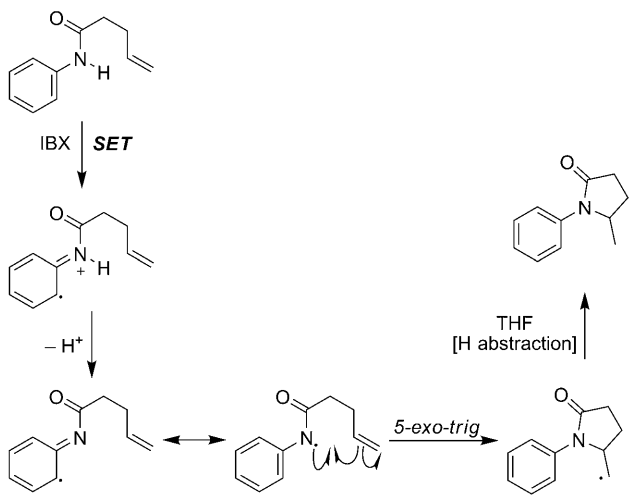
Tertiary allylic alcohols in five- and six-membered ring systems undergo oxidative rearrangement in the presence of IBX in DMSO to the corresponding α,β-unsaturated ketones. A representative example of this transformation is shown in Scheme 63; notably, the reaction takes place without requiring chromium-based reagents of high toxicity.[218] A closely related reaction that involves the use of IBX in the presence of $InCl_3$ leads to α,β-unsaturated lactones.[219]

The cyclization of unsaturated *N*-aryl amides in the presence of IBX represents a reaction type, the synthetic potential of which has certainly not yet been fully explored. Detailed studies by Nicolaou et al. demonstrated that C–N bond formation occurs at elevated temperature through a reactivity of IBX that is fundamentally different from most of the reactions discussed previously.[220,221] Representative examples of this type of reaction are shown in Scheme 64. The 5-*exo* cyclization occurs in a mixture of THF and DMSO at 90 °C in the presence of excess IBX, and allows the synthesis of a large variety of nitrogen-containing five-membered rings.

The results of mechanistic studies point to a radical mechanism (Scheme 65).[220c,221] An initial single-electron transfer (SET) leading to the formation of a radical cation is assumed to be the rate-determining step. The actual



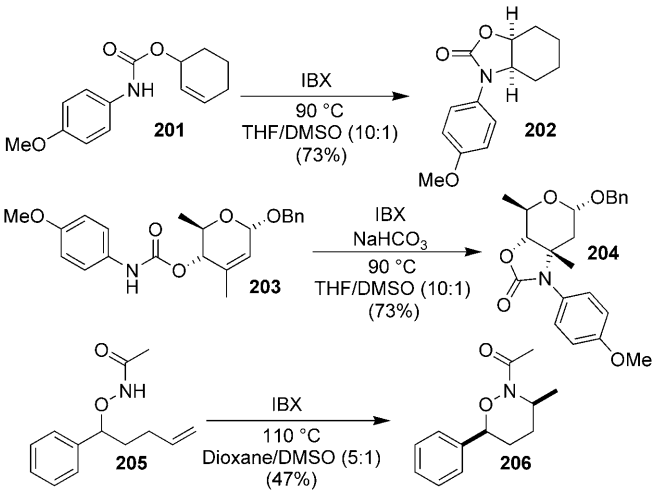
Scheme 64. IBX-mediated 5-*exo*-cyclization of *N*-aryl amides.[220c]



Scheme 65. Mechanism of radical cyclization of anilides.[221]

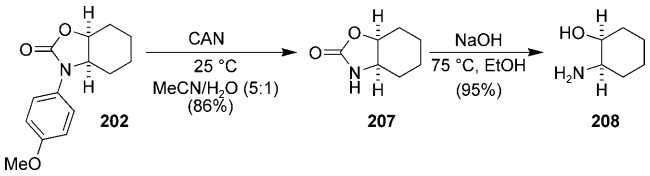
oxidizing agent is most probably a complex containing THF bound to IBX. The loss of a proton from the radical cation gives a radical which then undergoes 5-*exo* cyclization. Subsequent abstraction of a hydrogen atom yields the final product. Experiments in deuterated solvents clearly show that the cosolvent THF is the source of the hydrogen atom incorporated in this step; in the absence of THF, no reaction is observed.

This procedure can also be applied to unsaturated *N*-aryl carbamates, which are readily obtained by the addition of allylic alcohols to aryl isocyanates (Scheme 66). When applied



Scheme 66. Cyclization of allylic carbamates and related reactions.[220c]

to cyclic substrates, the reaction proceeds with excellent stereoselectivity, as illustrated for the conversion of **201** and **203**. In combination with an oxidative deprotection step involving cerium ammonium nitrate (CAN) and subsequent basic hydrolysis, this protocol provides a convenient access to *cis*-1,2-amino alcohols such as **208** (from **202**; Scheme 67). Janza and Studer reported a related transformation based on



Scheme 67. Simple access to *cis*-1,2-amino alcohols from the products of IBX-mediated cyclization of carbamates.[220c] CAN = cerium(IV) ammonium nitrate.

the action of IBX on acylated alkoxyamines to generate alkoxyamidyl radicals that then give rise to heterocycles by 5-*exo* and 6-*exo* cyclization (**205**→**206**).[222]

Various other transformations induced by IBX are also worth mentioning: For example, the reaction of α-disubstituted primary amides with IBX gives isocyanate intermediates which undergo subsequent oxidative cleavage to ketones.[223] When the same reaction conditions are applied to α-monosubstituted primary amides, dehomologation with loss of one carbon atom is also observed, although in this case with formation of nitriles.[224] The reaction of *cis*-2,4-enyn-1-ols with IBX leads to the formation of 2-acyl furans.[225] Thioamides dimerize to 1,2,4-thiadiazoles in an oxidative cyclization mediated by IBX.[226] In some cases, the IBX oxidation of benzylic positions has resulted in the isolation of unexpected products arising from double bond isomerization.[227]

7. Concluding Remarks and Summary

A full century passed between the seminal works of Hartmann and Meyer and the first application of IBX as an oxidant in organic synthesis. Nevertheless, during this period there have been several attempts to use IBX and its derivatives for a range of other purposes.

The potential use of IBA, IBX, and several derivatives as catalysts for the hydrolytic cleavage of organic phosphates was examined in detail when aiming to develop reagents for the decontamination of chemical warfare agents.[228] In analytical chemistry, titrations with salts of IBX in acidic aqueous solution were used for the quantitative determination of oxidizable substances such as thiols and amines.[149,229] Early examples also show that the oxidation of phenols to quinones was applied to the qualitative and quantitative detection of free phenolic hydroxy groups.[230]

In studies conducted during the early 20th century both IBA and IBX were found to possess bactericidal activity. This observation is not overly surprising considering their known oxidizing properties.[231] In numerous animal experiments that may appear rather bizarre from today's perspective, aqueous solutions of IBX and its salts were injected into rabbits and dogs to probe the influence of these substances on respiratory function and the immune system.[2,232] Moreover, in the first half of the 20th century, a number of authors even recommended the medicinal use of IBX and its salts for the treatment of arthritic diseases.[233] In fact, both the ammonium and calcium salts of IBX were temporarily marketed as drugs

under the trade names "Amiodoxyl" or "Oxoate".[234] Their therapeutic usefulness, however, was soon cast into doubt, and severe side effects were reported.[235] To the best of our knowledge, the last reports on such treatments were in 1950, when a clinical trial showed that these preparations based on IBX are no more effective than aspirin.[236] Afterwards, the "iodoxybenzoates" fell into oblivion for about 30 years.

For more than a decade now, IBX has enjoyed great popularity as an oxidant in organic synthesis. A huge amount of methodological studies as well as an ever increasing number of applications in the total synthesis of complex natural products bear testimony to the great reliability put on this reagent. IBX has now become one of the most important tools in the synthetic chemist's repertoire for the mild oxidation of alcohols. The power of attraction of IBX also keeps steadily growing because of its ability to make many further oxidative processes possible that are currently not feasible through the use of alternative reagents. Hence, IBX has emerged as an almost universally applicable oxidizing agent that permits the dehydrogenation of various functional groups as well as the transfer of oxygen atoms to phenols, benzylic sites, and the α positions of carbonyl groups. Furthermore, IBX is capable of inducing one-electron-transfer processes that result in the generation of radical species, the full synthetic potential of which seems still to be underexploited. There remains a need for a detailed understanding of the underlying effects that are responsible for the propensity of IBX to oxidize such a diverse array of substrates by various alternative pathways. In terms of practicability, many synthetically useful processes still require significant improvements. Further refinement of the existing methods discussed above and additional applications involving new types of substrates can be expected in the near future.

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