Hypervalent Iodine Reagents for the Oxidation of Alcohols and Their Application to Complex Molecule Synthesis

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Abstract: Hypervalent iodine(V) derivatives such as 2-iodoxybenzoic acid (IBX) and Dess–Martin periodinane [DMP; 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one] have been used widely for the oxidation of alcohols to aldehydes and ketones during the last decade because of their high chemoselectivity, mild reactivity, and high yielding process. This review focuses on the recent progress in the oxidation of alcohols to carbonyl compounds using IBX, DMP, and other hypervalent iodine reagents, and their application to total syntheses of a variety of complex natural products.

Keywords: alcohols; aldehydes; hypervalent compounds; IBX; iodine; ketones; oxidation

1 Introduction

The recent demand for highly efficient and environmentally benign syntheses of fine chemicals and pharmaceuticals has encouraged the development of mild, safe, and highly chemoselective oxidizers. Hypervalent iodine reagents are now used extensively in organic synthesis as a mild, safe, and economical alternative to heavy metal reagents such as lead(IV), thallium(III), and mercury(II).[1] In particular, hypervalent iodine(III)-induced oxidation reactions of phenols and related compounds have been applied to the total syntheses of a wide variety of biologically active natural products.[2] On the other hand, hypervalent iodine(V) reagents, namely, Dess–Martin periodinane (DMP; **2**) and its precursor, 2-iodoxybenzoic acid (IBX; **1**) have emerged as mild and highly selective reagents for the oxidation of alcohols to carbonyl compounds and for other synthetically useful oxidative transformations during the last decade. In particular, IBX has attracted much attention as a cheaper and more stable alternative to DMP despite its sparse solubility and explosive nature. Therefore, various derivatives of IBX, which are highly soluble, non-explosive, and/or recyclable, have recently been developed. This review deals with recent progress in the oxidation of alcohols using IBX and other hypervalent iodine(III) and iodine(V) reagents including their scope and limitation, and their synthetic applications to complex molecule synthesis. Other oxidative transformations and applications to natural product synthesis using IBX and other hypervalent iodine reagents are discussed in other recent reviews by us and others.[1,2]

2 Hypervalent Iodine Reagents for Oxidation of Alcohols

2.1 Iodine(V) Compounds: Benzoiodoxole Oxides

2-Iodoxybenzoic acid [IBX, 1-hydroxy-1,2-benziodoxole-3(1*H*)-one 1-oxide; **1**] was first synthesized in 1893,[3] but has been rarely used in organic synthesis, probably due to its insolubility in most organic solvents. In 1983 Dess and Martin transformed IBX into the highly soluble Dess–Martin periodinane (DMP; **2**), and first introduced the use of DMP to facilitate the oxidation of alcohols.[4] Subsequently, DMP has been used extensively in synthetic organic chemistry due to its mild reactivity and chemoselectivity. In 1994 Frigero and Santagostino reported that IBX, which is a cheaper and

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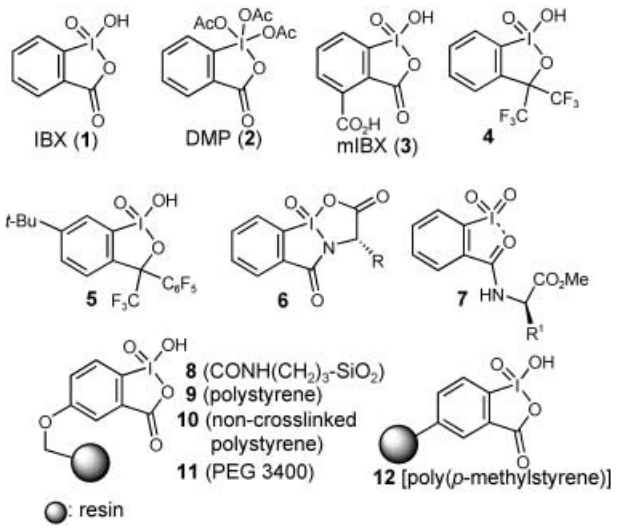


Figure 1. Benziodoxole oxides for the oxidation of alcohols.

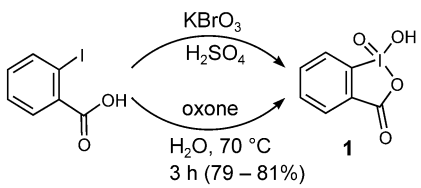
much more stable alternative to DMP, could also be utilized in the oxidation of alcohols in dimethyl sulfoxide (DMSO).[5] Since then, a variety of benzoiodoxole oxide derivatives including polymer-supported IBX analogues have been developed as mild, stable, and useful oxidizers for alcohols to the corresponding aldehydes and ketones (Fig. 1).

*2.1.1 2-Iodoxybenzoic Acid (IBX; **1**)*

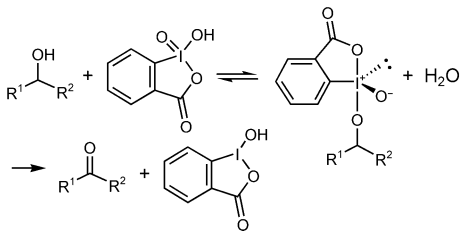
IBX (**1**) is commonly prepared by oxidation of 2-iodobenzoic acid with potassium bromate ($KBrO_3$) in an aqueous solution of sulfuric acid. Santagostino and coworkers reported a new convenient method for preparing highly pure **1** from 2-iodobenzoic acid using oxone ($2\,KHSO_5$-$KHSO_4$-K_2SO_4) (Scheme 1).[6] The latter procedure reduced the toxic and explosive contaminants.

CAUTION! Compound **1** was reported to be explosive under excessive heating ($>200\,^{\circ}C$) or impact.

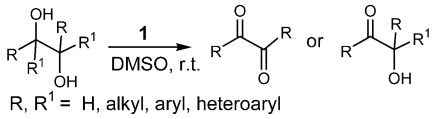
IBX (**1**) mildly and rapidly oxidizes primary and secondary alcohols to the corresponding aldehydes and ketones even in the presence of other non-hydroxy functional groups such as silyl ethers, allyl group, alkenes, alkynes, acetals, thioethers, thioketals, amines, amides, pyridines and indoles in DMSO or DMSO/tetrahydrofuran (THF) solution. The reaction can be considered to proceed *via* a fast pre-equilibrium induced by the ligand exchange (hydroxy-alkyloxy) on the iodine atom, Eq. (1).[5] The oxidation of 1,2-diols with IBX can be controlled to produce α-hydroxyketones and 1,2-diketo derivatives without oxidative cleavage of the glycol C–C bond, Eq. (2).



Scheme 1. Preparation of IBX (**1**).



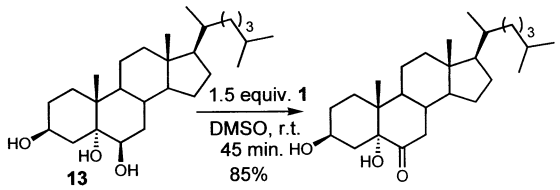
(1)



(2)

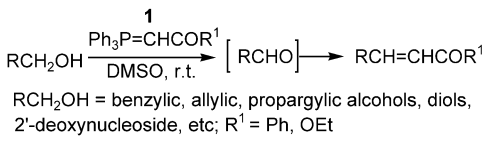
Selective oxidation of the primary alcohol can also be realized using **1** in DMSO for the oxidation of primary-secondary 1,4- or 1,5-diols, Eq. (3).[7] Triol **13** was oxidized selectively at the secondary alcohol of 1,2-diol in the presence of the isolated secondary alcohol, Eq. (4).[5]

(3)



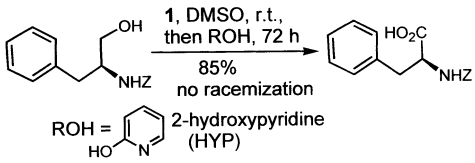
(4)

In addition, IBX oxidation exhibits a high degree of chemoselectivity for the oxidation of primary alcohols to aldehydes in the presence of either secondary alcohols or other oxidizable moieties. Benzylic, allylic, and propargylic alcohols can be oxidized by **1** in the presence of stabilized Wittig ylides to generate α,β-unsaturated esters in a one-pot procedure. This is useful when the intermediate aldehydes are unstable and difficult to isolate, Eq. (5).[8]



(5)

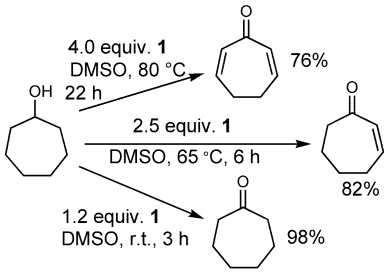
Primary alcohols are oxidized easily by **1** in the presence of certain *O*-nucleophiles such as 2-hydroxypyridine (HYP) and *N*-hydroxysuccinimide (NHS) to give carboxylic acids in DMSO at ambient temperature in high yields.[9] This procedure is applicable to the direct oxidation of an *N*-protected β-amino alcohol to the corresponding amino acid without racemization, Eq. (6).



(6)

IBX (**1**) can also be used as a suspension in various solvents. Simply heating (80 °C) a solution of the alcohols in the presence of suspended **1** in a wide variety of solvents such as ethyl acetate, chloroform, dichloroethane, acetone, benzene, and acetonitrile followed by filtration and removal of the solvent gives excellent yields of the corresponding carbonyl compound.[10] The ionic liquid 1-butyl-3-methylimidazolium chloride ([bmim]Cl) was utilized as the reaction medium for the IBX oxidation of alcohols in the presence of water.[11] Aqueous oxidation of alcohols with **1** catalyzed by β-cyclodextrin have been developed. Using this system, a series of alcohols are oxidized in water/acetone (86:14) at room temperature in excellent yields.[12]

Furthermore, Nicolaou and co-workers reported the one-step synthesis of α,β-unsaturated carbonyl compounds from saturated alcohols and carbonyl compounds by using an excess IBX under heating (60–80 °C), Eq. (7).[13]

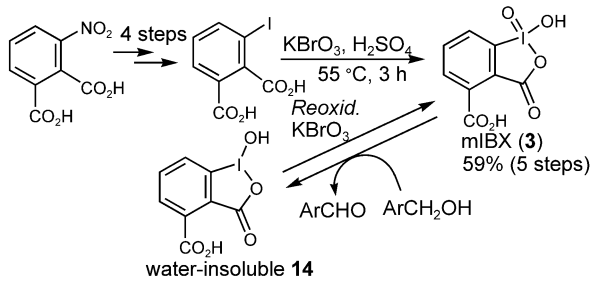


(7)

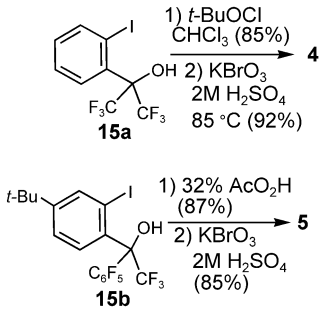
The stabilized IBX (SIBX), which is a non-explosive white-powder formulation of IBX composed of a mixture of benzoic acid (22%), isophthalic acid (29%), and IBX itself (49%), was also developed.[14] SIBX can be used as a suspension in a variety of standard organic solvents such as refluxing EtOAc and THF to safely oxidize alcohols into the corresponding carbonyl compounds.

2.1.2 IBX Analogues

A variety of IBX analogues, which are soluble, non-explosive, and/or recyclable, has recently been developed.



Scheme 2. Preparation of mIBX (**3**).



Scheme 3. Preparation of IBX analogues **4** and **5**.

Modified IBX (mIBX; **3**), which is synthesized from commercially available 3-nitrophthalic acid, is a water-soluble derivative of IBX.[15] mIBX (**3**) selectively oxidizes benzylic and allylic alcohols to the corresponding ketones and aldehydes in water, while non-allylic/benzylic alcohols cannot be oxidized. An important aspect of this oxidation protocol is the near insolubility of **14**, the reduced form of **3**. Thus, only filtration and a subsequent removal of solvent are required for the work-up. In addition, recycle of **3** is also possible by re-oxidation of **14** using $KBrO_3$ (Scheme 2).

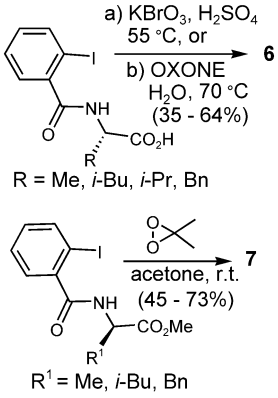
1-Hydroxy-1,3-dihydro-3,3-bis(trifluoromethyl)-1,2-benziodoxole 1-oxide (**4**)[4b] and 6-(1,1-dimethylethyl)-1,3-dihydro-1-hydroxy-3-(pentafluorophenyl)-3-(trifluoromethyl)-1,2-benziodoxole 1-oxide (**5**),[16] which are soluble analogues of IBX, are prepared from the corresponding iodoalcohols **15a**,**b** by two-step oxidation, respectively, as shown in Scheme 3.

Reagent **4** reacts with alcohols in a similar fashion to DMP **2**, and sometimes gives successful results where **2** failed to give satisfactory results (see Section 3.1).

Reagent **5** is stable, non-explosive and soluble in a wide range of common organic solvents such as hexanes, ether, dichloromethane, acetone, acetic acid, and water. Its *t*-butyl group supposedly disrupts the polymerization believed to lead to an explosion. Compound **5** can be used for general oxidation of primary and secondary alcohols containing various non-hydroxy functional groups such as ethers, thioethers, amino, vinyl, and halides.[16]

Two types of IBX amides (**6**, **7**), which are readily prepared from various 2-iodobenzamides, were recently reported by Zhdankin and co-workers (Scheme 4).

IBX amides **6**, which are non-explosive and soluble in dichloromethane and other common non-polar organic solvents, slowly react with benzyl alcohol in chloroform at 50 °C affording benzaldehyde in *ca.* 90% yield. A catalytic amount of trifluoroacetic acid accelerates the reaction rate.[17] Reactivities of IBX amides **7** are similar only in certain aspects to both IBX and DMP. Compounds **7** cleanly oxidize benzyl alcohols and secondary alcohols to benzaldehydes and ketones in $CHCl_3$ at room temperature. However, oxidation of 1,2-diol with **7** yields C–C bond cleavage products.[18] Several chiral, non-racemic IBX amides **7** were prepared, and the oxidative kinetic resolution of racemic *sec*-phenethyl alcohol was investigated using chiral, non-racemic **7** ($R^1 = Bn$) but gave unsatisfactory results ($\sim$9% ee).

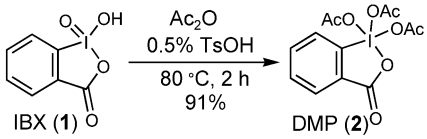


Scheme 4. Preparation of IBX amides **6** and **7**.

2.1.3 Dess–Martin Periodinane (DMP; 2)

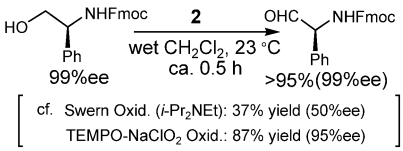
DMP (**2**)[4] is readily prepared from IBX (**1**) on a 100-g scale by using acetic anhydride (Ac_2O) and 0.5% TsOH (Scheme 5).[19] In addition, **2** is currently commercially available from Sigma-Aldrich and other chemical companies.

DMP (**2**) can be used widely for the selective oxidation of alcohols containing sensitive functional groups, such as unsaturated alcohols, carbohydrates, polyhydroxy derivatives and polyethers, silyl ethers, amines and amides, azide, various nucleoside derivatives, selenides, tellurides, phosphine oxides, homoallylic and homopropargylic alcohols, and fluoro alcohols.



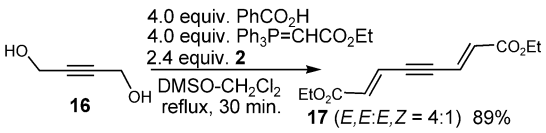
Scheme 5. Preparation of DMP (**2**) from IBX.

Meyer and Schreiber reported that the DMP oxidation is accelerated by the addition of water.[20] DMP **2** is especially useful for the oxidation of the optically active, epimerization sensitive substrates such as *N*-protected β-amino alcohols without loss of enantiomeric excess, while epimerization proceeds partly in Swern oxidation or the TEMPO-catalyzed oxidation, Eq. (8).[21]



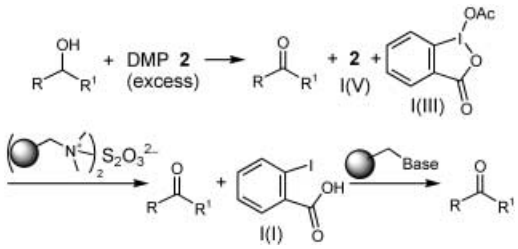
(8)

The DMP oxidation/Wittig homologation sequence in one pot directly provides the Wittig adducts in high yields even when the initially formed aldehydes are highly unstable. For instance, in the oxidation of propargylic diol **16**, the Wittig adduct **17** was obtained in 89% yield without isolating a highly unstable dialdehyde, 2-butynedial, Eq. (9).[22]



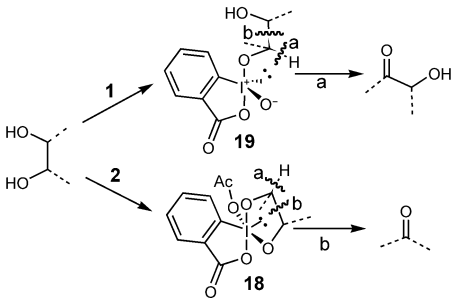
(9)

Parlow and co-workers developed a simple and efficient method for sequestering byproducts and excess reagent from the solution phase using a thiosulfate resin in the oxidation of various primary and secondary alcohols with **2**, Eq. (10).[23]



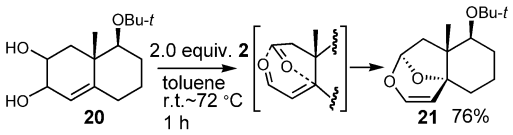
(10)

The characteristic difference between the reactivities of **1** and **2** was revealed in the oxidation of 1,2-diols. That is, **1** oxidizes 1,2-diols to 1,2-diketones or α-ketols, while **2** generally cleaves the glycol C–C bond in the same manner as tetrapropylammonium perruthenate (TPAP) or pyridinium chlorochromate (PCC) reagents. Mechanistic studies have provided insight into the different product distributions from 1,2-diols using **1** and **2**. That is, while **2** gives spirobicyclic periodinane adducts **18**, **1** binds reversibly with the 1,2-diol thereby forming open-chain iodic monoesters **19**, probably reflecting the different electronic characteristics of the ligands in the oxidants, Eq. (11).[24]



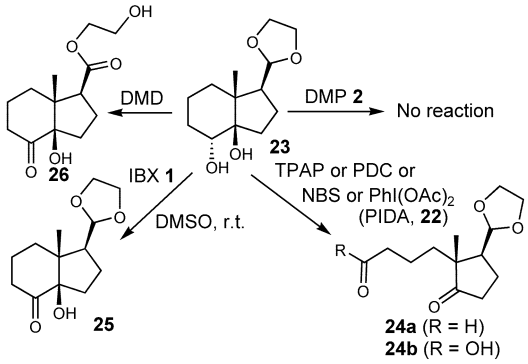
(11)

Oxidation of 1,2-diol **20** with **2** in toluene affords the isolable and stable tricyclic enol ether **21** *via* a tandem glycol cleavage-intramolecular [4 + 2] cycloaddition reaction, Eq. (12).[25]



(12)

However, the ability of glycol-fission by **2** is not much stronger than those by TPAP, PCC, pyridinium dichromate (PDC), and phenyliodine diacetate (PIDA, **22**). In fact, oxidation of 1,2-diol **23** using a variety of oxidizers was examined, Eq. (13).[26] No reaction proceeded when using **2**, while other oxidants such as TPAP, PDC, *N*-bromosuccinimide (NBS)-dimethyl sulfide, and **22** gave rise to products **24a**,**b** derived from glycol C–C bond cleavage. On the other hand, the IBX oxidation of **23** afforded **25** quantitatively, and the oxidation of **23** with dimethyldioxirane (DMD) gave **26**.

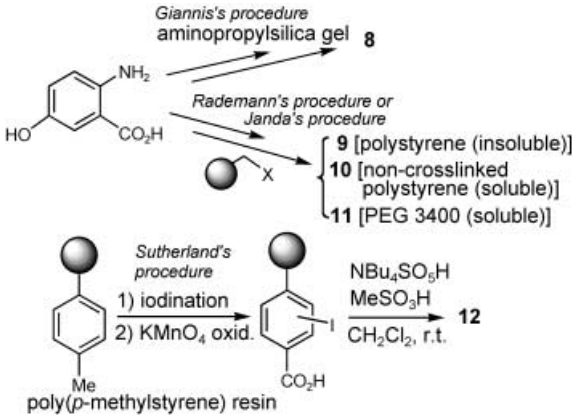


(13)

2.1.4 Polymer-Supported Benzoiodoxole Oxides

In order to realize facile reaction work-up and efficient recycling of the reagent, several polymer-supported IBX have been developed.

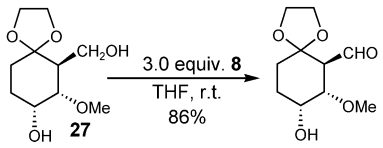
Previously reported polymer-supported IBX reagents **8**–**11** are mostly prepared by coupling to an appropriately functionalized solid support such as aminopropyl silica gel,[27] chloromethyl polystyrene,[28] soluble non-



Scheme 6. Preparation of polymer-supported benzoiodoxole oxides.

cross-linked polystyrene, and PEG-based supports[29] after elaboration starting from 2-amino-5-hydroxybenzoic acid. Another type of solid-supported IBX, **12**, can be prepared in only three steps from poly(*p*-methylstyrene)[30] (Scheme 6).

Silica-supported IBX **8** can be used for the oxidation of alcohols in THF as well as DMSO at room temperature.[27] Reactions proceeds faster in THF than DMSO. In addition, the presence of water (1 – 10%) has no negative influence on the yields and reaction times. In the oxidation of **27**, **8** oxidizes the primary alcohol moiety selectively to the corresponding aldehyde without oxidation of the secondary alcohol moiety even when **8** is added in three-fold excess, Eq. (14). In fact, oxidation of aliphatic secondary alcohols, except for 2-methylcyclohexanol, such as menthol and 3-methyl-2-butanol with **8** gave the ketones only in poor yields (< 5%) even after longer reaction times (48 h).



(14)

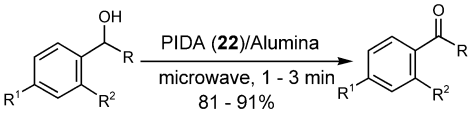
Polymer-supported IBX **9** is capable of converting various alcohols including benzylic, pyridyl, allylic, and *N*-protected amino alcohols, except for menthol, efficiently and in good to excellent yields into the corresponding alcohols in dichloromethane at room temperature.[28] However, at elevated temperatures, the benzylic position of the resin in **9** can be oxidized by an IBX moiety. Benzyl alcohols can be converted to benzaldehydes with solid-supported IBX **12** in dichloromethane in good yields. However, oxidation of a primary alkanol with **12** proved to be more difficult and a lower yield was obtained.[30]

2.2 Iodine(III) Compounds

In spite of the utility and popularity of **1** and **2**, a serious disadvantage of such iodine(V) reagents is their explosive nature, and therefore these potentially dangerous reagents should not be stocked. Thus, a facile and efficient use of the readily available and relatively stable iodine(III) reagents in place of iodine(V) reagents has been long desired. In contrast to the glorious utilization of iodine(V) reagents for the oxidation of alcohols, iodine(III) reagents normally have very low reactivity toward alcohols. The few successful examples of the oxidation of alcohols using iodine(III) reagents that have been performed are described below.

*2.2.1 Phenyliodine Diacetate [(Diacetoxyiodo)-benzene] (PIDA; **22**)*

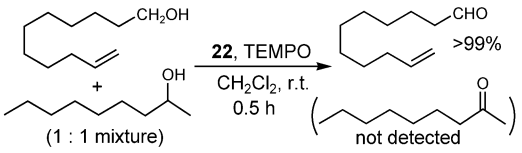
PIDA (**22**) is commercially available from Sigma-Aldrich and other chemical companies. In the absence of additives, benzylic and allylic alcohols are oxidized with **22** in refluxing dioxane to aldehydes without causing further oxidation to carboxylic acids.[31] However, aliphatic alcohols are not oxidized efficiently under such conditions. On the other hand, benzylic alcohols are rapidly oxidized to carbonyl compounds by alumina-supported PIDA under microwave irradiation, Eq. (15).[32]



(15)

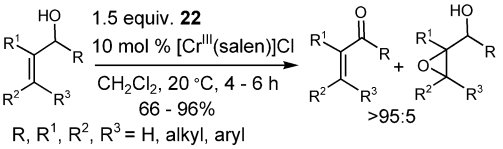
R = H, Et, C_6H_5CO, 4-$MeOC_6H_4CO$
R^1 = H, Me, OMe; R^2 = H, CH_2OH

Efficient and high-yielding oxidation of alcohols to carbonyl compounds using the combination of **22** and a catalytic amount (10 mol %) of 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) was achieved by Piancatelli, Margarita and co-workers.[33] This procedure exhibits very high selectivity for oxidation of primary alcohols to aldehydes, without any overoxidation to carboxyl compounds, and a high chemoselectivity in the presence of either secondary alcohols or other oxidizable functional groups such as ethers, sulfides, selenides, allyl, furyl, epoxides, and alkenes, Eq. (16). Furthermore, no isomerization to the α,β-unsaturated aldehydes is noted for secondary allylic alcohols, and optically pure epoxides are rapidly oxidized to epoxy aldehydes in high yields without epimerization. The PIDA-TEMPO procedure can be used for the direct oxidation of *N*-protected amino alcohols to the respective amino acids in the presence of water without racemization.[34]



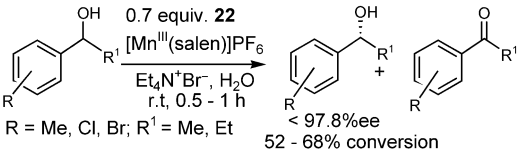
(16)

Several metal-catalyzed oxidation reactions of alcohols with **22** have also been reported. Interestingly, the catalytic oxidation of allylic alcohols with **22**, mediated by the chloride complex of [Cr^{III}(salen)], affords the corresponding enones in excellent chemoselectivity, while nearly equal amounts of enone and epoxide were obtained when using the triflate ([Cr^{III}(sale-the hexafluorophosphate ([Cr^{III}(salen)]PF_6) complex, Eq. (17).[35] Likewise, the oxidation with iodosylbenzene (PhIO; **28**)-[Cr^{III}(salen)]Cl gives enones selectively.[36]



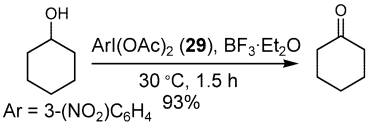
(17)

An efficient oxidative kinetic resolution of benzyl alcohols using **22** and $Et_4N^+Br^-$ in the presence of a catalytic amount (2 mol %) of a chiral [Mn^{III}(salen)] complex was accomplished, Eq. (18).[37] This procedure realized the highly enantioselective kinetic resolution of secondary alcohols in water.



(18)

$BF_3 \cdot Et_2O$ accelerates the oxidation of alcohols with $ArI(OCOCH_3)_2$ (Ar: 3-nitrophenyl; **29**). Oxidation of *sec*-BuOH and cyclohexanol using **29** and $BF_3 \cdot Et_2O$ afforded butan-2-one and cyclohexanone in 92 and 93% yields, respectively, Eq. (19).[38]



(19)

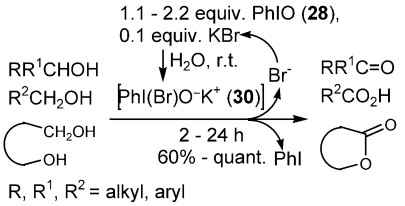
2.2.2 Iodosylbenzene (PhIO; *28*)

Iodosylbenzene (PhIO; **28**) is readily prepared by alkaline hydrolysis of **22**. In addition, **28** is commercially available from TCI and other chemical companies.

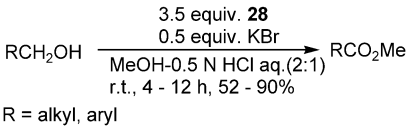
PhIO (**28**) oxidizes a variety of alcohols to the corresponding ketones and carboxylic acids in CH_2Cl_2 in the presence of ruthenium catalysts such as $RuCl_2(PPh_3)_3$, $Ru_3(CO)_{12}$, $RuCl_3 \cdot H_2O$, or rutheno-cene.[39]

Ytterbium(III) nitrate [$Yb(NO_3)_3$] also catalyzed the PhIO oxidation of alcohols in 1,2-dichloroethane to give ketones and aldehydes selectively in good yields.[40]

The combination of **28** and potassium bromide (KBr) in water generates a powerful oxidizer, **30**, for the oxidation of alcohols. Primary alcohols are converted exclusively to the carboxylic acids in good yields, whereas secondary alcohols lead to the corresponding ketones, Eq. (20).[41] In addition, oxidation of diols with the PhIO-KBr system affords the corresponding lactones in high yields. A plausible mechanism of the catalytic activation of **28** is supported by ESI-mass spectroscopic studies of the reactive species **30**.[42] Furthermore, a single-step oxidative transformation of primary alcohols to the corresponding methyl esters using PhIO-KBr was also achieved in aqueous MeOH, Eq. (21).[43]

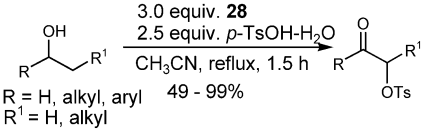


(20)



(21)

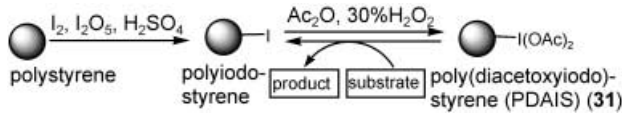
Togo and co-workers recently reported an efficient transformation of alcohols directly to α-tosyloxyaldehydes and α-tosyloxyketones using **28** and *p*-TsOH · H_2O *via in situ* formation of aldehydes and ketones, Eq. (22).[44] This method was applied to the direct preparation of heterocyclic compounds such as thiazoles and imidazoles.



(22)

2.2.3 Poly(diacetoxyiodo)styrene (PDAIS; *31*)

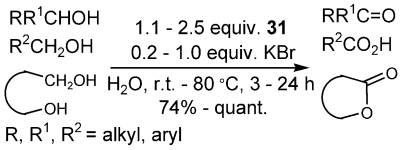
Okawara and co-workers first synthesized the polymer-supported hypervalent iodine reagent, poly(diacetoxyiodo)styrene (PDAIS; **31**) in 1961.[45] In view of green chemistry, **31** has recently attracted much attention due to its recyclability and reactivity similar to that of **22**.[1 m]



Scheme 7. Preparation of PDAIS (**31**).

Reagent **31** is readily prepared from commercially available polystyrene by a two-step procedure [(i) iodination with I_2 and I_2O_5, and (ii) oxidation with hydrogen peroxide and acetic anhydride] (Scheme 7). The loading efficiency of PDAIS can be determined by elemental analysis and/or iodometry.

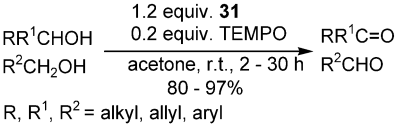
Kita, Tohma, and co-workers demonstrated that **31** can be used for the oxidation of alcohols to carbonyl compounds in water in the presence of KBr, Eq. (23).[41,42] In a similar manner to the PhIO-KBr system, this reaction also gives carboxylic acids and lactones exclusively from primary alcohols and diols.



(23)

The positive features of the use of **31** are summarized as follows: 1) ease of operation; 2) facile recyclability; ease of re-oxidation of the recovered resin (polyiodostyrene) with peracetic acid (30% H_2O_2 and Ac_2O) and repeated use without loss of activity; 3) excellent yields; 4) ecological consciousness (reduced amounts of both organic solvents and waste).

Togo and co-workers reported that TEMPO also catalyzed the oxidation of alcohols using **31** in place of PIDA, Eq. (24).[46]



(24)

2.3 Summarized Table of Hypervalent Iodine Oxidation of Alcohols

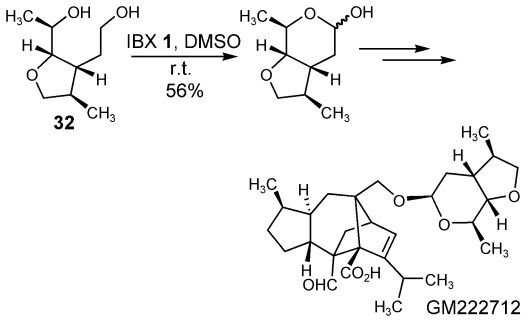
Reaction conditions and the applicable substrates in reported hypervalent iodine(III and V) oxidation reactions of alcohols are summarized in Table 1.

3 Recent Applications to Complex Molecule Synthesis

Due to the broad functional group tolerance and mild and high-yielding reactions, IBX (**1**), DMP (**2**), and their derivatives have been used extensively in the key oxidation steps in the total syntheses of numerous biologically important natural products. Here, we describe several representative and characteristic examples of hypervalent iodine oxidation of alcohols selected from recently reported natural product syntheses.

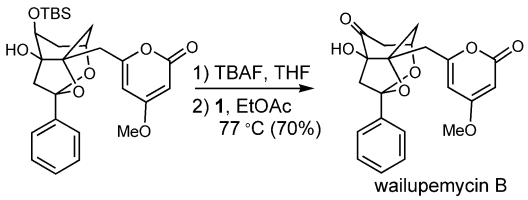
3.1 Application of Benziodoxole Oxides [Iodine(V) Reagents]

The total synthesis of the antifungal agent GM222712 was achieved *via* selective oxidation of the primary alcohol moiety of diol **32** with **1**, Eq. (25).[50]



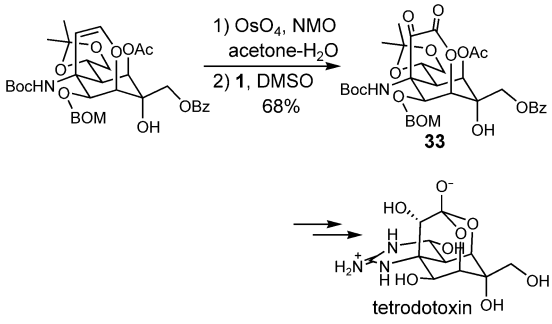
(25)

In the final step of the total synthesis of wailupemycin B, which is an α-pyrone-containing metabolite isolated from *Streptomyces maritimus*, the IBX oxidation of 1,2-diol proceeded in 70% yield without oxidative cleavage of the glycol C–C bond, Eq. (26).[51]



(26)

Likewise, the oxidation of triol using **1** selectively afforded the 1,2-diketo compound **33**, a key precursor to the puffer fish poison, tetrodotoxin, Eq. (27).[52]



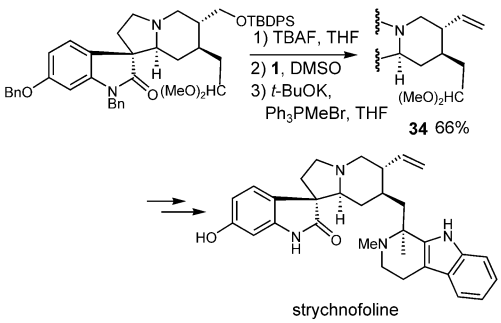
(27)

Table 1. Hypervalent iodine oxidation of alcohols

Run	Reagent	Substrate[a]	Additive	Solvent	T [°C]/time	References
1[b]	IBX **1**	**A, B, P, S, D, AA**	none	DMSO	r.t./0.75 – 48 h	[5,7]
2[c]	**1**	**P, S, D**	none	DMSO	65 – 80/6 – 48 h	[13]
3[b]	**1**	**A, B, P, S**	none	EtOAc [or 1,2-dichloroethane (DCE), CH_3CN]	80/0.5 – 6 h	[10]
4[d]	**1**	**A, B, P**	$Ph_3P{=}CHCOR$	DMSO	r.t./1.5 – 48 h	[8]
5[e]	**1**	**A, B, P, AA**	HYP (or NHS)	DMSO	r.t./16 – 72 h	[9]
6[b]	**1**	**A, B, P, S, D**	H_2O	[bmim]Cl	r.t./5 min	[11]
7[b]	**1**	**A, B, P, S, D**	β-CD	H_2O/acetone	r.t./12 h	[12]
8[b]	SIBX	**A, B, P, S, D**	none	EtOAc (or THF, toluene, DMSO)	r.t. – reflux/0.5 – 6 h	[14]
9[b]	**3**	**A, B**	none	H_2O (or H_2O-THF)	r.t. – 60/3 – 18 h	[15]
10[b]	**4**	**A, B, P, S**	none	CH_2Cl_2	r.t./20 min	[4b,23]
11[b]	**5**	**A, B, P, S**	none	CH_2Cl_2	r.t./0.5 – 2 h	[16]
12[b]	**6**	**B**	none (or TFA)	$CHCl_3$	50	[17]
13[b]	**7**	**B, S, D** (cleavage)	none	$CHCl_3$	r.t./2 – 72 h	[18]
14[b]	**8**	**A, B, P, S**	none	THF	r.t./6 – 12 h	[27]
15[b]	**9**	**A, B, P, S, AA**	none	CH_2Cl_2	r.t./3 h	[28]
16[b]	**9 – 11**	**B, S**	none	CH_2Cl_2	r.t./1 – 6 h	[29]
17[b]	**12**	**B, P**	none	CH_2Cl_2	r.t./5 h	[30]
18[b]	DMP **2**	**A, B, P, S, D** (cleavage), **AA**	none (or TFA)	CH_2Cl_2	r.t.	[4,24]
19[b]	**2**	**B, S, AA**	H_2O	CH_2Cl_2	r.t./0.5 – 4 h	[20,21]
20[f]	**2**	**D**	HOAc	CH_2Cl_2	r.t./15 min	[47]
21[b]	**2**	**A, P, S, D**	$NaHCO_3$	CH_2Cl_2	r.t.	[48,51,63]
22[b]	**2**	**A, P, S**	pyridine (or 2,6-lutidine)	CH_2Cl_2	r.t.	[4,49,60]
23[d]	**2**	**A, P**	$Ph_3P{=}CHCO_2R$, $PhCO_2H$	CH_2Cl_2-DMSO	reflux/0.5 h	[22]
24[b]	**22**	**A, B, D**	none	dioxane	reflux/2 – 12 h	[31]
25[b]	**22**	**B**	Al_2O_3-supported	none	Microwave/0.5 – 3 min	[32]
26[b]	**22**	**A, B, P, S, D, AA**	TEMPO	CH_2Cl_2	r.t./0.1 – 15 h	[33,34]
27[b]	**22**	**A, B**	$[Cr^{III}(salen)]Cl$	CH_2Cl_2	r.t./4 – 6 h	[35]
28[b]	**22**	**B** (kinetic resolution)	Et_4NBr, $[Mn^{III}(salen)]PF_6$	H_2O	r.t./0.5 – 3 h	[37]
29[b]	**28**	**A, B, P, S**	$RuCl_2(PPh_3)_3$	CH_2Cl_2	r.t./5 min – 10 h	[39]
30[b]	**28**	**B, P, S**	$Yb(NO_3)_3$	DCE	80/3 – 12 h	[40]
31[e]	**28**	**B, P, S, D**	KBr	H_2O	r.t./2 – 48 h	[41,42]
32[g]	**28**	**B, P**	KBr, MeOH	H_2O	r.t./4 – 12 h	[43]
33[b]	**28**	**B, P, S**	p-$TsOH \cdot H_2O$	CH_3CN	reflux/1.5 h	[44]
34[b]	**29**	**S**	$BF_3 \cdot Et_2O$		30/0.25 – 1.5 h	[38]
35[e]	**31**	**B, P, S**	KBr	H_2O	r.t. – 80/3 – 24 h	[41,42]
36[g]	**31**	**B, P**	KBr, MeOH	H_2O	r.t./3 – 12 h	[43]
37	**31**	**A, B, P, S**	TEMPO	acetone	r.t./2 – 30 h	[46]

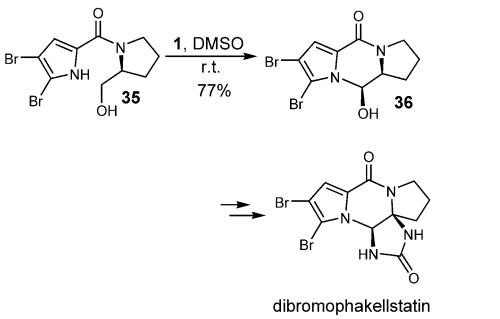
[a] Allylic alcohols: **A**; benzylic alcohols: **B**; primary alcohols: **P**; secondary alcohols: **S**; diols: **D**; amino alcohols: **AA**.
[b] Transformation to ketones or aldehydes.
[c] Transformation to α,β-unsaturated carbonyl compounds.
[d] Transformation to olefination products.
[e] Transformation to ketones or carboxylic acids.
[f] Transformation to cyclic acetoxy acetals or dialdehydes.
[g] Transformation to methyl esters.

Desilylation followed by IBX oxidation and Wittig olefination provided **34**, a key precursor to the antimitotic agent, strychnofoline in 66% (3 steps) without isolation of the labile aldehyde, Eq. (28).[53]



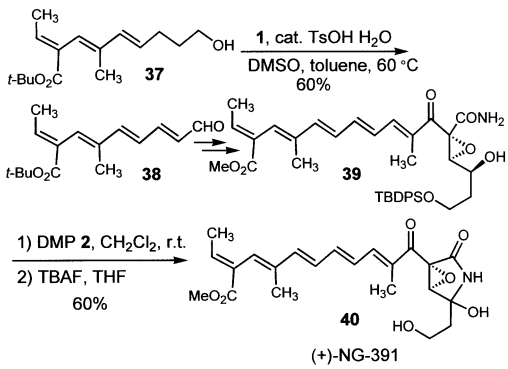
(28)

IBX (**1**) is applicable even in the synthesis of racemization-prone α-aminoaldehydes. Oxidation of enantiopure alcohol **35** with **1** yields the tricyclic *N,O*-hemiacetal **36**, which is a synthetic precursor of the cytotoxic natural product, dibromophakellstatin, without racemization, Eq. (29).[54] Likewise, this procedure was used to construct enantiopure α-piperidine aldehydes in the syntheses of anabaseine analogues.[55]



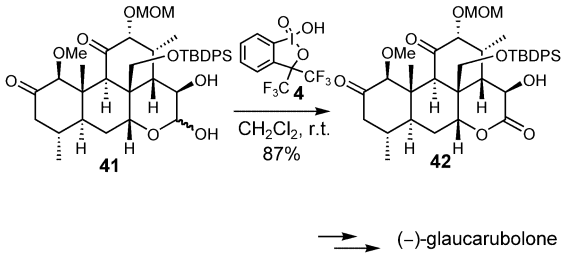
(29)

In the total synthesis of (+)-NG-391, a neuronal cell-protecting molecule, both **1** and **2** oxidations were used. (*E*,*E*,*E*)-Alcohol **37** was effectively oxidized with **1** in the presence of TsOH at 60 °C under Nicolaou's conditions[13] to afford (*E*,*E*,*E*,*E*)-tetraene **38** selectively in 60% yield. In the final stage, oxidation of alcohol **39** with **2** in CH_2Cl_2 followed by desilylation gave epoxy lactam **40** (NG-391) in 60% yield, Eq. (30).[56]



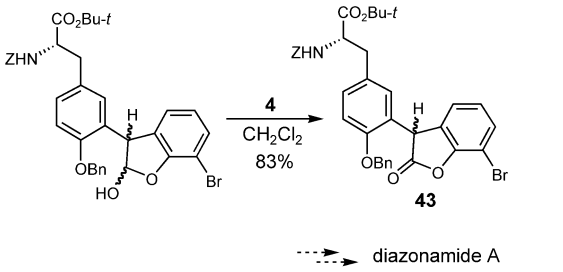
(30)

A soluble IBX analogue, **4**, was used successfully for the oxidation of diol **41** to tetracyclic lactone **42** in the total synthesis of (−)-glaucarubolone by Grieco and coworkers, Eq. (31), while other oxidation conditions (e.g., Fetizon's reagent, MnO_2-$CHCl_3$, Ag_2O-CH_3CN, **2**-CH_2Cl_2) gave only cleavage products.[57] Reagent **4** was also used in total syntheses of the related potential anticancer drugs, the quassinoids.[58]



(31)

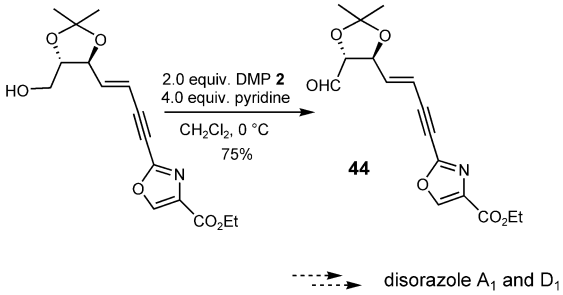
In a similar way, Moody and Lack used **4** in the synthesis of the tyrosine-derived benzofuranone **43**, a potential intermediate for the synthesis of the cytotoxic marine alkaloid diazonamide A, Eq. (32).[59]



(32)

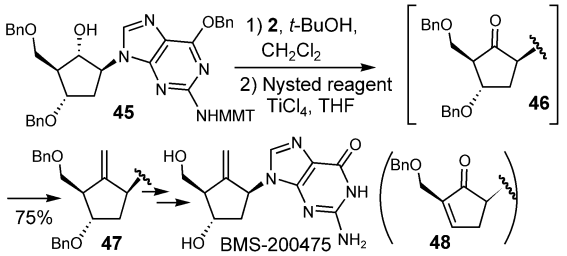
It is worth mentioning that DMP (**2**) was the only reagent applicable in many cases of key oxidation steps in natural product syntheses, when other common oxidation methods including Swern oxidation, Jones oxidation, and other chromium-based procedures, failed. Recent successful examples are described below.

Oxidation with buffered DMP effectively afforded the sensitive aldehyde **44**, an important synthetic intermediate of the natural products disorazole A_1 and D_1, while alternative oxidation methods including PCC, Swern or PIDA-TEMPO oxidation protocols led to significantly lower yields, Eq. (33).[60]



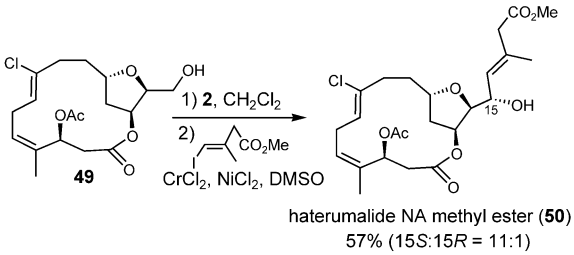
(33)

Combination of DMP oxidation and olefination without isolation of epimerization-prone or unstable aldehydes and ketones can be used widely in total syntheses of various natural products. For instance, oxidation of **45** with **2** cleanly produced ketone **46**. The following methylenation afforded **47**, which is a key precursor in the synthesis of a potent inhibitor of hepatitis B virus, BMS-200475, in good yield, Eq. (34).[61] Moffatt and TPAP-NMMO oxidation protocols mainly led to the undesired cyclopentenone **48** resulting from β-elimination of the 3′-benzyloxy group from **46**.



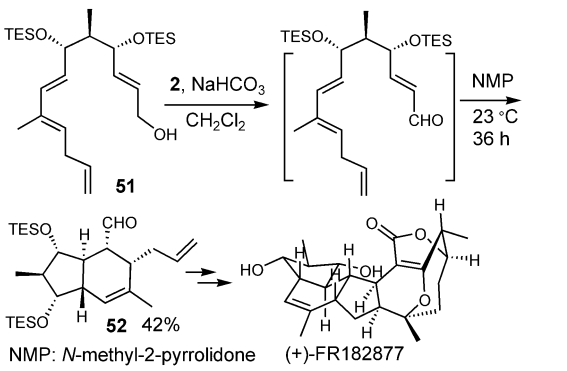
(34)

Another example was shown in the final step of the synthesis of a cytotoxic macrolide, haterumalide NA. Here, alcohol **49** was oxidized with **2** to afford an unstable aldehyde, which was then converted to the olefination product **50** under Nozaki–Hiyama–Kishi coupling conditions, Eq. (35).[62]



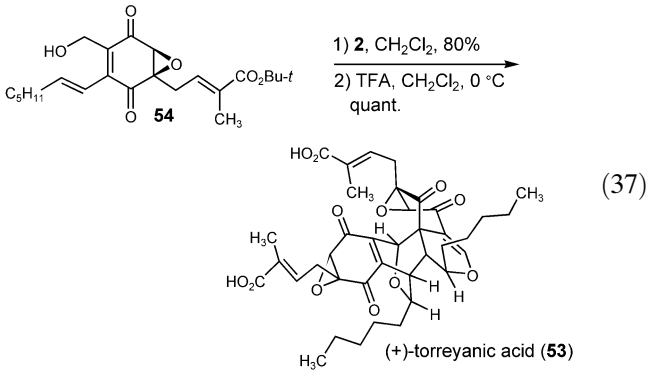
(35)

Several tandem oxidation/Diels–Alder reactions using **1** and **2** have also been applied in natural product synthesis. In the synthetic study toward the potent microtubule-stabilizing agent FR182877, oxidation of **51** with **2** buffered with solid sodium bicarbonate produced bicyclic products **52** *via* a tandem oxidation/intramolecular Diels–Alder reaction, Eq. (36).[63]



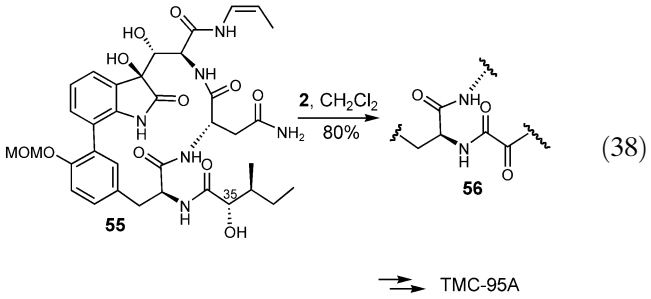
(36)

Porco and co-workers recently reported another interesting tandem intermolecular reaction with **2** in the total synthesis of (+)-torreyanic acid (**53**). In the final step of the synthesis of **53**, the DMP-induced tandem oxidation/electrocyclization/dimerization process starting from **54** followed by treatment with TFA/CH_2Cl_2 afforded **53** in 80% yield, Eq. (37).[64]



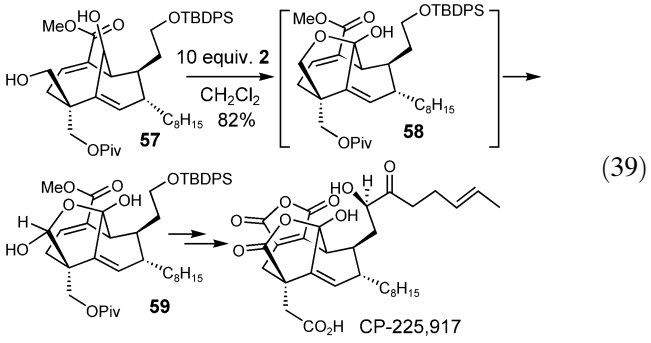
(37)

Several chemoselective oxidations of alcohols with **2** have been used in recent natural product syntheses. Selective oxidation of the C35 alcohol of **55** in the presence of the diol moiety with DMP afforded MOM-protected TMC-95A **56**, a potent proteasome inhibitor, in 80% yield, Eq. (38).[65]



(38)

In the synthetic study of CP molecules, which are lead compounds for potential anticancer and anticardiovascular drugs, sterically hindered secondary alcohol **57** was initially oxidized with **2** in the presence of the primary alcohol moiety to yield the isolable hemiketal **58**. Further oxidation of **58** with **2** formed stable diol **59**, which was not oxidized further with **2**, Eq. (39).[66]

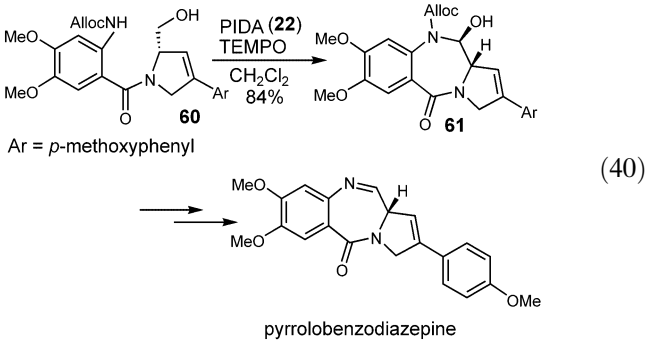


(39)

3.2 Application of Iodine(III) Reagents

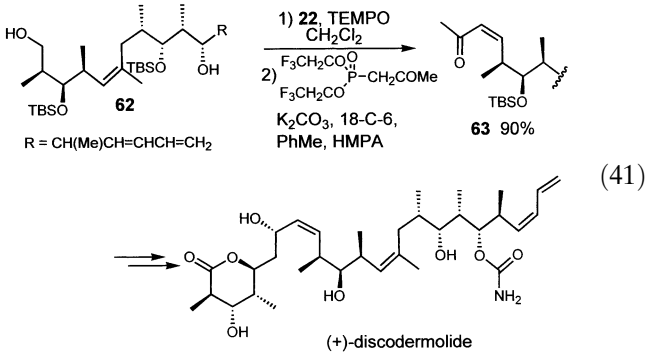
Utilization of iodine(III)-induced oxidation of alcohols in natural product syntheses has not been popular to date. Only the PIDA-TEMPO oxidation protocol[5] has recently been used in several total syntheses of natural products.

Howard and co-workers reported an efficient oxidative cyclization reaction of alcohol **60** to **61** with PIDA-TEMPO in the synthesis of antitumor antibiotics, pyrrolobenzodiazepines, Eq. (40).[67] This method was found to be superior to that of Swern oxidation in several aspects (high yield, no requirement of anhydrous conditions or an inert atmosphere, etc.).



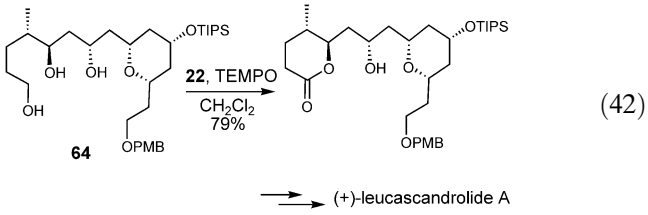
(40)

In the total synthesis of (+)-discodermolide, selective oxidation of the primary alcohol of **62** (12:1 *Z*/*E*) with PIDA-TEMPO in the presence of the secondary alcohol moiety followed by modified Still–Gennari HWE reaction gave (*Z*)-enone **63** in 90% yield, Eq. (41).[68]



(41)

Paterson reported an efficient and chemoselective lactone formation from open-chain triol **64** with PIDA-TEMPO in the total synthesis of the cytotoxic macrolide, (+)-leucascandrolide A, Eq. (42).[69]



(42)

4 Conclusion

IBX and other related hypervalent iodine reagents have realized mild and chemoselective oxidation reactions of alcohols containing various sensitive functional groups to the corresponding carbonyl compounds, and have been utilized during the last decade in total syntheses of numerous biologically important natural products. Furthermore, several new IBX derivatives, that are soluble, recyclable, and non-explosive, as well as polymer-supported hypervalent iodine reagents have recently been developed. These reagents will become increasingly important synthetic tools and will have practical applications in industrial processes for producing pharmaceuticals and agrochemicals due to their low toxicity, ready availability, and recyclability. In addition to the oxidation of alcohols using IBX and other hypervalent iodine reagents, a variety of new reactions have recently been developed by many synthetic chemists.[1k, l,n,2,70] Thus, we are sure that hypervalent iodine chemistry will continue to attract significant research activity in the future.

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