JOC The Journal of Organic Chemistry

Article

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Twist Does a *Twist* to the Reactivity: Stoichiometric and Catalytic Oxidations with *Twisted* Tetramethyl-IBX

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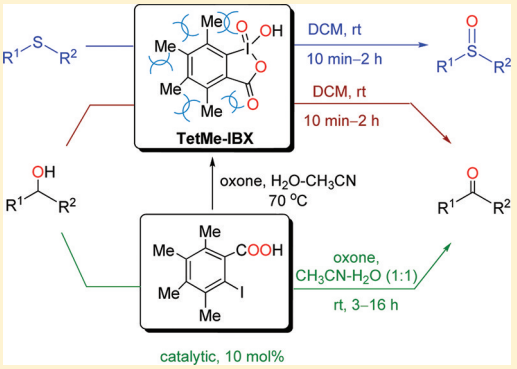
Supporting Information

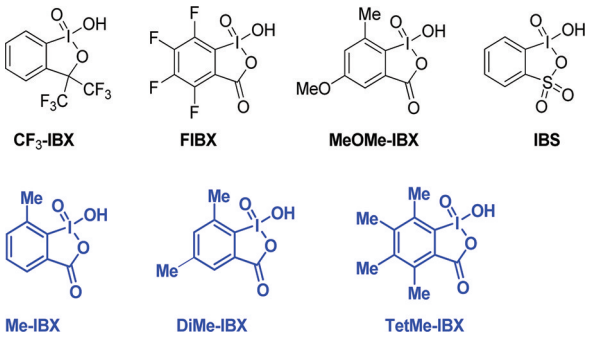
ABSTRACT: The methyl groups in TetMe-IBX lower the activation energy corresponding to the rate-determining *hypervalent twisting* (theoretical calculations), and the steric relay between successive methyl groups *twists* the structure, which manifests in significant solubility in common organic solvents. Consequently, oxidations of alcohols and sulfides occur at room temperature in common organic solvents. In situ generation of the *reactive* TetMe-IBX from its precursor iodo-acid, i.e., 3,4,5,6-tetramethyl-2-iodobenzoic acid, in the presence of oxone as a co-oxidant facilitates the oxidation of diverse alcohols at room temperature.



INTRODUCTION

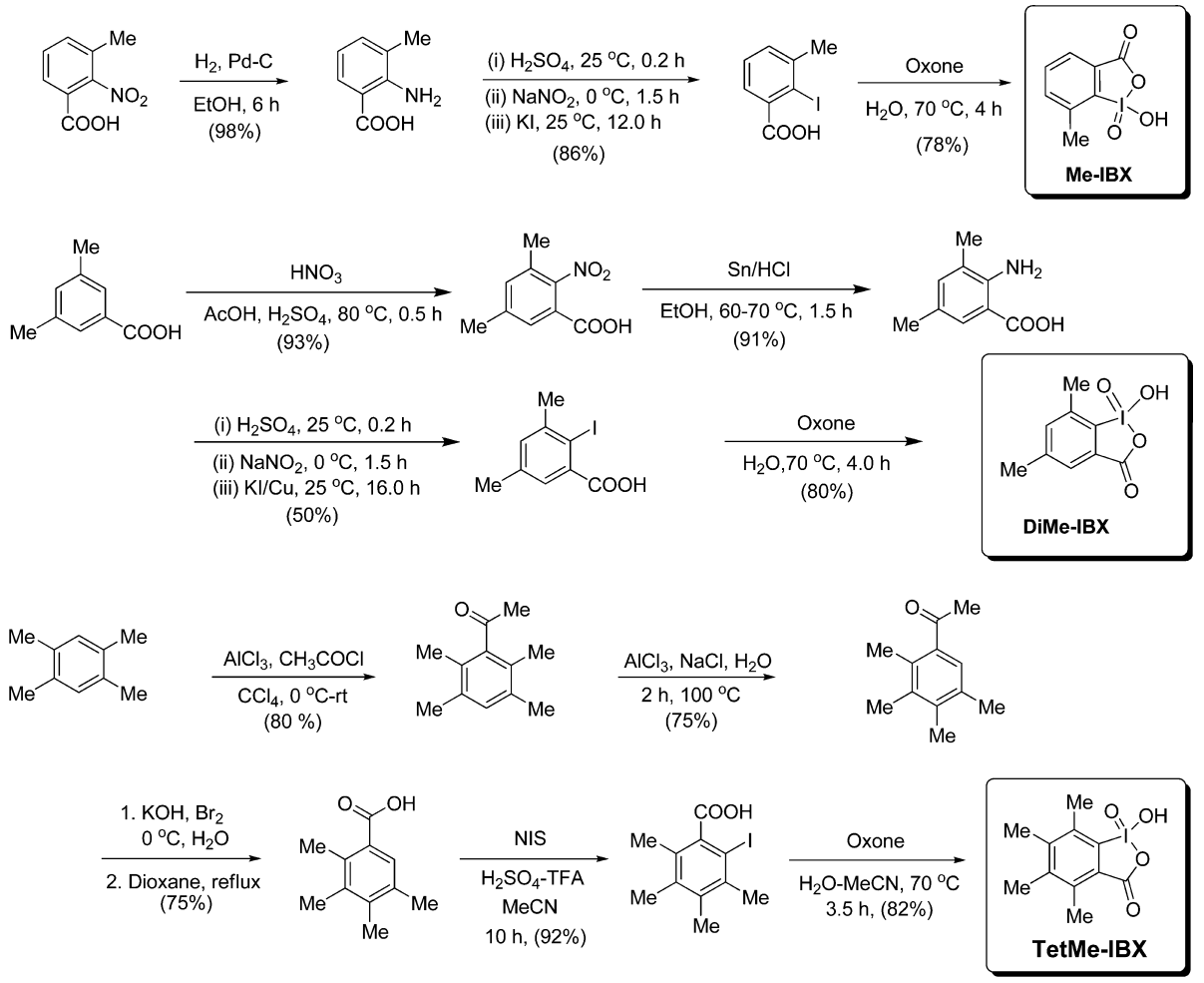
2-Iodoxybenzoic acid, referred to popularly as IBX, is an indispensable organic oxidation reagent in contemporary oxidation chemistry.[1] The reasons for a surge of interest in this reagent are its cheapness, ready accessibility, and environmentally benign characteristics that obviate the use of copious amounts of transition-metal-based reagents. Because of its astounding reactivity, a myriad of organic transformations continue to be unraveled.[2] The use of this simple IBX reagent is, however, plagued by certain drawbacks such as its insolubility in common organic solvents with the exception of polar DMSO, its explosive property at high temperatures,[3] and the need to conduct a majority of the reactions at high temperatures.[4] The insolubility and the explosive nature have been attributed to strong intermolecular interactions (O−H···O hydrogen bonds, C−I···O halogen bonds, and aromatic stacking interactions) that hold the molecules cohesively in the crystal lattice.[5] In view of the innocuous and eco-friendly attributes of IBX, the quest in pursuit of modified IBX analogues that are more reactive, nonexplosive, and common organic solvent soluble continues unabated. In Chart 1 are shown some of the modified IBXs that have been employed in solvents other than DMSO and at room temperature. One of the early modified IBXs reported by Dess and Martin, i.e., bis(trifluoromethyl)-substituted hydroxyiodinane oxide (CF_3-IBX),[6] was shown to oxidize alcohols at rt in acetonitrile; this reagent has, however, not received much attention, presumably because of the difficulty associated with its synthesis. Tetrafluoro-IBX (FIBX) was conceived by Wirth et al. on the basis of better solubility of fluorous compounds in organic solvents in general.[7] They showed that FIBX can indeed be employed in solvents such as acetonitrile. By combining the so-called sterically accelerated hypervalent twisting due to the presence of an *o*-methyl group and improved solubility in common organic solvents brought about as a result of weakening of the intermolecular interactions, the modified MeOMe-IBX was shown by us to be an exceptional reagent for oxidation of alcohols at room temperature.[8] The modified IBXs with significantly enhanced reactivity may allow their synthesis in situ and application catalytically. Ishihara et al. have recently shown that the 2-iodoxybenzenesulfonic acid (IBS),[9] generated in situ from a catalytic amount of the precursor *o*-iodobenzenesulfonic acid in the presence of oxone, can be

Chart 1



Received: March 20, 2011
Published: October 31, 2011

Scheme 1. Synthetic Routes for the Modified IBXs



employed in nitromethane at 70 °C for a range of organic oxidation reactions. Incidentally, the catalytic oxidations at rt by *reactive* IBXs generated in situ are heretofore unprecedented.[10]

In continuing efforts toward exploring the inscrutable reactivity of IBX,[11] we surmised that sterically induced structural deformation and enhanced hypervalent twisting[12] via tetramethyl substitution of the parent IBX as in TetMe-IBX (Chart 1) should render it to be an invaluable reagent for oxidations. Herein, we report that tetramethylation *twists* the structure, in addition to lowering the rate-determining activation barrier associated with hypervalent twisting in alcohol oxidations, as revealed by theoretical (DFT, B3LYP functional) calculations.[13] The steric cascade-induced twisting of the structure manifests in significant solubility to allow oxidation of a variety of alcohols (within a few minutes) and sulfides (in a few minutes to 2 h) in solvents such as DCM at rt. The enhanced reactivity of TetMe-IBX also permits development of a catalytic protocol for facile oxidation of diverse alcohols, which continues to be an intensively investigated transformation.[1e,14]

RESULTS AND DISCUSSION

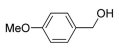
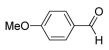
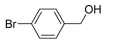
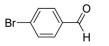
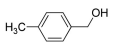
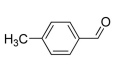
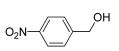
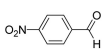
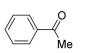
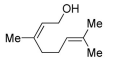
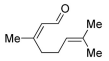
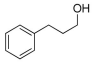
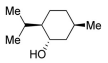
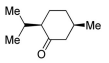
Syntheses of Modified Me-IBX, DiMe-IBX, and TetMe-IBX. For comparison of the oxidation efficiencies of TetMe-IBX, mono- and dimethyl-substituted IBXs, i.e., Me-IBX and DiMe-IBX, were also synthesized along with TetMe-IBX (Scheme 1). Thus, the commercially available 2-nitro-3-methylbenzoic acid was reduced to 3-methylanthranilic acid under catalytic hydrogenation conditions. The resultant amino acid was converted to the corresponding 2-iodo-3-methylbenzoic acid by Sandmeyer reaction. The iodo-acid thus derived was subjected to oxidation with oxone in water at 70 °C to yield Me-IBX in 78% yield. A nitration−reduction−Sandmeyer reaction sequence on the commercially available 3,5-dimethylbenzoic acid led to 2-iodo-3,5-dimethylbenzoic acid, which on oxidation with oxone under standard conditions yielded DiMe-IBX.[15] The modified TetMe-IBX was conveniently prepared from durene. The latter was acetylated to yield acetyldurene,[16] which was subjected to Lewis acid-mediated rearrangement,[17] followed by bromoform reaction[18] to obtain 2,3,4,5-tetramethylbenzoic acid. This compound was subsequently iodinated by NIS in acidic medium to afford the required iodo-acid. Oxidation of the latter under standard conditions with oxone led to the isolation of TetMe-IBX in a respectable yield. It should be mentioned that IBX is known to be explosive as mentioned earlier;[3] in fact, when one attempts to determine the melting point in a capillary, it explodes with an audible noise. In contrast, TetMe-IBX was found to undergo clean visible melting to a colorless liquid without any perceptible hazards.

Oxidation of Alcohols with Modified IBXs. The oxidation of a variety of alcohols by the modified reagents was explored at room temperature in a range of organic solvents that include acetonitrile, dichloromethane, chloroform,

dx.doi.org/10.1021/jo201491q | J. Org. Chem. 2011, 76, 9593–9601

ethyl acetate, etc. As the oxidations were indeed found to occur at rt, DCM was deemed to be a better solvent on the basis of a solvent screening to conduct the oxidations. Thus, by employing 1.2 equiv of Me-IBX, DiMe-IBX, and TetMe-IBX, the oxidations of a variety of alcohols were run in DCM at rt. The results of oxidations are given in Table 1. It is apparent from a perusal of the results that the primary benzylic and allylic alcohols are oxidized to the corresponding aldehydes by TetMe-IBX within a few minutes, whereas the reaction durations are longer for Me-IBX and DiMe-IBX. As monitored by 500 MHz NMR spectroscopy for *p*-methylbenzyl alcohol, a representative case, conversions of the alcohol were 17, 30, and 41% when the oxidations were conducted with Me-IBX, DiMe-IBX, and TetMe-IBX under uniformly identical conditions at room temperature for 10 min. That the tetramethylation brings about a dramatic acceleration of the rate of oxidation when compared with Me-IBX and DiMe-IBX is also strikingly evident from the reaction times for the oxidation of secondary benzylic alcohol and sterically hindered menthol; although the reaction is complete within 2 h (entry 24, Table 1) with TetMe-IBX, the reaction times for Me-IBX and DiMe-IBX are significantly longer (24 h, entries 22 and 23, Table 1). We attribute the origin of enhanced reactivity of TetMe-IBX to the accelerated hypervalent twisting[12] promoted by sterics, vide infra, and increased solubility due to weaker intermolecular interactions; the solubilities determined for Me-IBX, DiMe-IBX, and TetMe-IBX are 0.12, 0.24, and 1.37 g/L, respectively. In all of these oxidations, the reduction product was found to be the iodosobenzoic acid (IBA).

Table 1. Oxidation of Alcohols with Me-IBX, DiMe-IBX, and TetMe-IBX at rt[a]

entry	substrate	reagent[b]	time (h)	product	yield[c] (%)
1		Me-IBX	1.5		94
2		DiMe-IBX	1.5		95
3		**TetMe-IBX**	**0.2**		**93**
4		Me-IBX	2.5		93
5		DiMe-IBX	2.5		95
6		**TetMe-IBX**	**0.1**		**94**
7		Me-IBX	1.5		78[d]
8		DiMe-IBX	0.7		81[d]
9		**TetMe-IBX**	**0.3**		**79**[d]
10		Me-IBX	3.7		97
11		DiMe-IBX	3.7		97
12		**TetMe-IBX**	**0.2**		**96**
13		Me-IBX	6.2		93
14		DiMe-IBX	6.0		94
15		**TetMe-IBX**	**1.1**		**94**
16		Me-IBX	2.1		81
17		DiMe-IBX	1.5		77
18		**TetMe-IBX**	**0.2**		**82**
19		Me-IBX	5.5		78
20		DiMe-IBX	5.5		79
21		**TetMe-IBX**	**1.0**		**78**
22		Me-IBX[e]	24.0		90
23		DiMe-IBX[e]	24.0		89
24		**TetMe-IBX**[e]	**2.0**		**89**

[a]All oxidations were performed in DCM as a solvent at rt. [b]1.2 equiv of the reagent was employed. [c]Isolated yields. [d]The reactions were run for 10 min in CD_2Cl_2 at rt and monitored directly by 500 MHz NMR. [e]1.5 equiv of IBX of the reagent was employed.

Theoretical Calculations. To gauge how the steric interactions between methyl, C═O, and I−OH groups in TetMe-IBX influence the planar nature of IBX, DFT calculations were performed initially on the parent IBX. The metrics of the energy-minimized structure were found to be in complete agreement with those of the X-ray determined structure.[5a,c] Similar calculations on Me-IBX and TetMe-IBX (Chart 1) revealed notable differences in the structures. The sterically induced deformation can be readily deciphered from the angles between the mean plane of the benzene ring and that constituted by the atoms C_2, I_1, O_2, and O_3 in Figure 1. The angles between the plane of the benzene ring and that of the selected atoms of the heteroaryl ring for IBX, Me-IBX, and TetMe-IBX are 1.72, 1.74, and 10.7°, respectively.

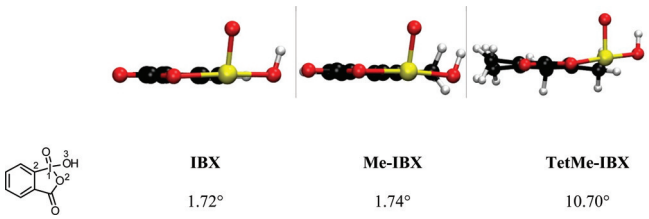
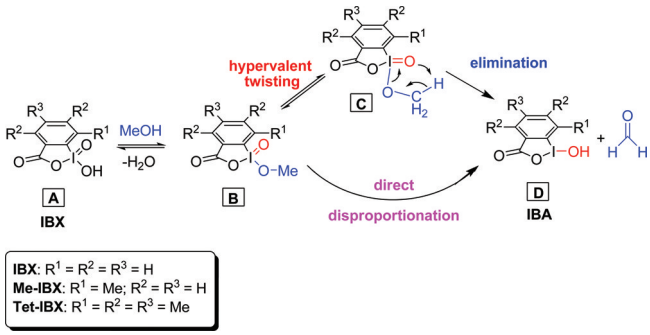


Figure 1. The DFT optimized structures of IBX, Me-IBX, and TetMe-IBX; notice the puckering induced in the latter by tetramethylation. The values refer to the angles between the plane of the Ph ring and that constituted by the atoms C_2, I_1, O_2, and O_3.

Insofar as alcohol oxidations are concerned, it was established by Santagostino et al.[19] on the basis of ^{1}NMR analysis and inverse dependence of the rate of oxidation of alcohols on $[H_2O]$ that disproportionation of the alkoxyperiodinane (**B**, Scheme 2), formed via initial equilibrium exchange of the alcohol, to the carbonyl compound and reduced IBA (**D**) is rate-determining. Subsequently, Goddard et al.[12] showed from DFT calculations that the disproportionation of alkoxyperiodinane **B** is indeed a two-step process and is accompanied by a rate-determining so-called *hypervalent twisting* that leads to isomeric periodinane intermediate **C**, which eliminates **D** and the carbonyl compound; hypervalent twisting is a coordinated motion of the ligands attached to iodine driven by the necessity of generating a stable and planar form of IBA (**D**). They further showed that the energy barrier for the rate-determining hypervalent twisting of I═O bond in alkoxyperiodinane gets lowered when a methyl group is located at the ortho position with respect to iodine as in Me-IBX (Scheme 2);[12] the lowering in the activation energy when *o*-methyl group is present as in Me-IBX is a result of relief of strain induced by the steric effect. The subsequent proton transfer step, i.e., **C** → **D**, was shown to require less energy from theoretical calculations. Recently, Ishihara et al. have performed analogous calculations and found that the twisting is indeed rate-limiting;[9] they showed that the

Scheme 2. Mechanism of Oxidation of Alcohols Using IBX and Its Modified Analogues



dx.doi.org/10.1021/jo201491q | J. Org. Chem. 2011, 76, 9593–9601

stiochiometric oxidation reactivities of substituted IBX and IBS can be rationalized from hypervalent twisting barriers. In general, the rotations about the bonds involved in hypervalent twisting are very different from the usual torsional motions as, for example, the rotation about the C−C bond in ethane. The hypervalent twisting involves major reorganization of the electronic structure at iodine. In particular, the iodine−oxygen dative bond that lies perpendicular to the plane in structure **B** transforms to a conventional covalent bond after twisting (Scheme 2). Therefore, the potential energy changes involved in twisting at the hypervalent iodine are appreciable. It was logical for us to expect that considerable strain built into the structure of TetMe-IBX via sterics between successive methyl groups and the substituents of hypervalent iodine as well as the carbonyl oxygen of the iodoxolone moiety should manifest in further acceleration of hypervalent twisting in pursuit of steric relief.

We performed DFT calculations[13] to ascertain the steric effect on the twisting barrier for reagents IBX, Me-IBX, and TetMe-IBX using methanol as the reactant; the initial equilibrium exchange of the alcohol (**A** → **B**) was assumed to be favored under nonaqueous conditions, as was presumed by Ishihara et al.[9] This step was thus ignored from the calculations. The transition state structure in each case was obtained from the saddle point along the optimized reaction pathway connecting reactant and product. The saddle point featured one negative frequency along a particular vibrational mode, which takes the system from reactant to products. Vibrational contributions to the free energies and zero point energies were accounted while computing the free energy barriers. Figure 2 also shows the results of DFT calculations, cf.

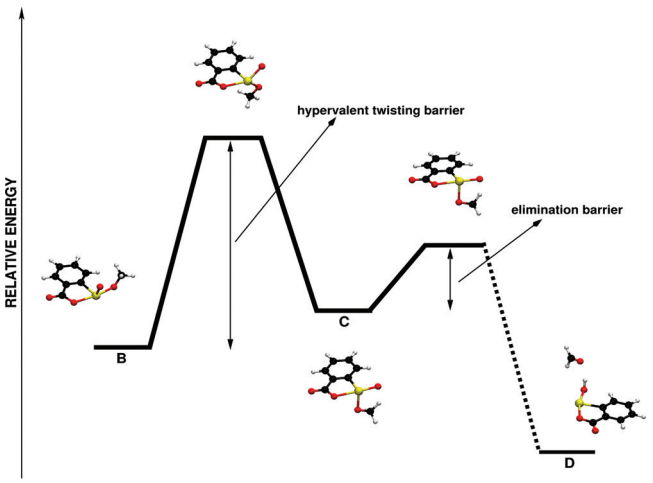


Figure 2. The activation barriers for hypervalent twisting of methoxyperiodinanes derived from IBX, Me-IBX, and TetMe-IBX and subsequent elimination to IBA. The dotted line is meant to indicate that energy levels are not drawn to a scale.

Supporting Information for details. Whereas the monomethyl-substitution at ortho position of the iodine in Me-IBX was found to lower the twisting barrier by 6.06 kcal/mol in close agreement with Goddard's calculations[12] under conditions that exclude solvent effects, the tetramethyl substitution in TetMe-IBX was found to further amplify the lowering by 1.56 kcal/mol, suggesting that the oxidations of alcohols should occur at much more enhanced rates. Evidently, tetramethylation has a much lesser effect than what one observes with monomethylation as in Me-IBX. The fact that the activation barriers calculated for methanol oxidation with IBX, Me-IBX, and TetMe-IBX apply equally well to the alcohols examined in Table 1 was established by computing energies for *p*-methylbenzyl alcohol as a representative case, cf. Supporting Information. Similar energy barriers as those calculated for methanol were in fact observed. Experimentally, it was established that *p*-methylbenzyl alcohol undergoes faster oxidation with TetMe-IBX than others, i.e., Me-IBX and DiMe-IBX, under uniformly identical experimental conditions, cf. Table 1. Thus, when the oxidation of *p*-methylbenzyl alcohol was performed for 10 min in CD_2Cl_2 with IBX, Me-IBX, and TetMe-IBX at rt, the conversions, as determined from 500 MHz ^1H NMR spectral analyses, were 0, 17, and 41%, respectively. Clearly, the observed rapid oxidation of a variety of alcohols at rt in Table 1 using TetMe-IBX are consistent with sterically accelarated rate-determing hypervalent twisting barriers calculated by DFT calculations; of course, the solubility of the reagent is another factor that contributes to the overall reactivity.

Be this as it may, the mechanism of alcohol oxidations using IBX was revisited in a more detail at the behest of a very insightful anonymous referee, who suggested that we probe the kinetic isotope effect in the oxidation of MeOH and MeOH-d_4. A careful literature survey revealed that Corey et al.[20] indeed performed kinetic analysis to establish the fact that the disproportionation is indeed rate-determining. Under conditions that involve a large excess of IBX in DMSO, they found that the oxidation of $C_6H_5CH_2CD_2OH$ is subject a strong primary kinetic isotope effect (k_H/k_D ca. 6.3). In an analogous manner, we have carried out the oxidation of MeOH and MeOH-d_4 in DCM in the presence of excess TetMe-IBX at 20 °C. Monitoring of the disappearance of the alcohol by GC analysis with an internal standard led to good pseudo-first-order kinetics up to 60−75% conversion of the methanol, cf. Supporting Information. Thus, rates of disappearance for MeOH and MeOH-d_4 were determined to be 18.4 and 5.56 × 10^{-5} s^{-1}, respectively, leading to a kinetic isotope effect, i.e., k_H/k_D, of ca. 3.3.

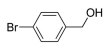
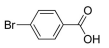
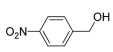
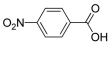
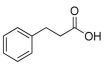
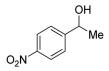
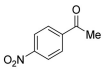
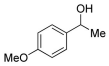
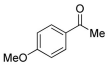
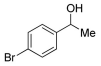
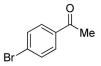
The observation of kinetic isotope by Corey et al. for oxidation of $C_6H_5CH_2CD_2OH/C_6H_5CH_2CD_2OH$ with IBX and that by us for oxidation of MeOH/MeOH-d_4 with TetMe-IBX is inconsistent with a two-step mechanism of oxidation, which involves hypervalent twisting of **B** as the rate-determining step followed by disproportionation of the isomeric alkoxyperiodinane **C** to the products, cf. Scheme 2. As the hypervalent twist involves a simple motion of I═O group and the alkoxy moiety, the isotope effect should not be expected. What then should be the mechanism that accounts for (i) acceleration of reactivity with an *o*-methyl group and (ii) kinetic isotope effect for α-protons of the alcohol? We suspected that the hypervalent twisting of **B** presumably occurs in concert with disproportionation in a direct single step, cf. Scheme 2. To verify this possibility, molecular dynamics simulations for the conversion of **B** → **D** were performed for the oxidation of MeOH with TetMe-IBX, which might offer better insights than static calculations. In several simulations, both two-step and direct disproportionation pathways (Scheme 2) were observed, but with a very marginal (ca. 1.0 kcal/mol)

dx.doi.org/10.1021/jo201491q | *J. Org. Chem.* 2011, 76, 9593−9601

difference in free energy barriers, cf. Supporting Information for details. This shows that there exists a finite probability for certain reactive trajectories that bypass the species **C** and lead directly to the products. It should be mentioned that the accuracy of the present level of calculations is of the order of the differences that we observe.

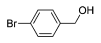
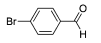
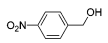
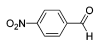
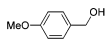
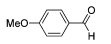
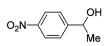
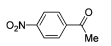
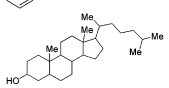
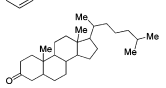
Catalytic Oxidations in the Presence of Oxone. Buoyed by the facile room temperature oxidation of alcohols and sulfides, catalytic oxidation of alcohols with the precursor 3,4,5,6-tetramethyl-2-iodobenzoic acid (TetMe-BA) in the presence of oxone was investigated. The catalytic oxidation of alcohols with IBX that is generated in situ by the oxidation of precursor *o*-iodobenzoic acid with oxone in acetonitrile–water (1:1) at 70 °C was reported for the first time by Vinod et al.;[21] as the oxone is known to convert aldehydes to acids,[22] primary alcohols are oxidized to carboxylic acids under the employed conditions. As mentioned at the outset, Ishihara et al. showed that *o*-iodosulfonic acid can be employed in catalytic amounts in the presence of oxone in nitromethane for oxidation of alcohols to the corresponding carbonyl compounds at 70 °C in short durations.[9] We found that the tetramethyl iodo-acid (10 mol %), the precursor of TetMe-IBX, in the presence of oxone co-oxidant acetonitrile–water (1:1) ratio works very nicely for oxidation of a variety of alcohols at room temperature. The results are summarized in Table 2 together with those using 3,5-dimethyl-2-iodobenzoic (DiMe-BA) acid as the catalyst. Of course, the primary alcohols were converted to their corresponding carboxylic acids. As revealed by the results in Table 2, oxidations with DiMe-BA as the catalyst are rather sluggish, which underscores the importance of tetramethylation. Selective oxidation of primary alcohols to aldehydes was also accomplished by employing the conditions of Ishihara et al.[9] Thus, primary benzylic alcohols were oxidized selectively to their corresponding aldehydes at *room temperature* by employing 10 mol % of TetMe-BA with 1.0 equiv of oxone in nitromethane and anhydrous Na_2SO_4, cf. Table 3. The reason why the oxidation occurs selectively, leading to aldehydes in nitromethane but to acids in acetonitrile–water, can be rationalized on the basis of the solubility of oxone in the two media and the absence of water in the former medium. The oxidation of aldehydes in NO_2Me is slow, whereas that in acetonitrile–water is faster. This is because the co-oxidant, viz., oxone, is more soluble in the latter solvent system as mentioned earlier. As a result, selective oxidation is observed when the oxidation of alcohols is carried out in NO_2Me. To establish if the overoxidation to acids is indeed slow or does not occur at all, the reaction of *p*-bromobenzyl alcohol, a representative case, was conducted in NO_2Me for ca. 36 h on a preparative scale. The acid was isolated in only 12% yield, which attests to the fact that the rate of oxidation of the aldehyde formed to the corresponding acid is very slow. Further, given that the very preparation of the IBX/modified IBX involves reaction of the precursor iodo-acid at 60–70 °C, the question that arises is as to how the IBX formation occurs at room temperature. The point to note here is that that the co-oxidant, i.e., oxone, is present in 10-fold excess with respect to the iodo-acid, when catalytic oxidations are carried out at rt. The concentration effect must take care of the temperature influence. Further, it has been shown by Ishihara and co-workers that electron-donating substituents facilitate generation of the I(V) catalyst;[9] that is, oxone oxidation of *o*-iodobenzoic acid is faster when the latter contains electron-donating substituents. Thus, tetramethylation may render oxidation of the precursor *o*-iodobenzoic acid with oxone more facile. To verify if one does observe the formation of IBX at room temperature when oxone is present in 10-fold excess (mol %),

Table 2. Catalytic Oxidation of a Variety of Alcohols using 3,5-Dimethyl-2-iodobenzoic Acid (DiMe-BA) and 3,4,5,6-Tetramethyl-2-iodobenzoic Acid (TetMe-BA) as a Catalyst (10 mol %) in the Presence of Oxone in CH_3CN/H_2O (1:1) at rt[a]

entry	substrate	catalyst	time (h)	product	yield[b] (%)
1.		DiMe-BA	16.0		92
2.		**TetMe-BA**	15.0		**95**
3.		DiMe-BA	8.5		94
4.		**TetMe-BA**	5.5		**96**
5.		DiMe-BA	16.0		94
6.		**TetMe-BA**	5.5		**94**
7.		DiMe-BA	9.5		83
8.		**TetMe-BA**	3.2		**84**
9.		DiMe-BA	18.3		96
10.		**TetMe-BA**	5.0		**94**
11.		DiMe-BA	11.0		82
12.		**TetMe-BA**	3.5		**85**
13.		DiMe-BA	23.0		91
14.		**TetMe-BA**	5.4		**93**
15.		DiMe-BA	8.1		94
16.		**TetMe-BA**	2.8		**95**
17.		DiMe-BA	8.5		60[c]
18.		**TetMe-BA**	3.0		**63**[c]
19.		DiMe-BA	8.5		60[c]
20.		**TetMe-BA**	3.0		**62**[c]

[a]All oxidations were performed in (1:1) $MeCN/H_2O$ by employing oxone at rt, see text. [b]Isolated yields. [c]Benzoic acid formation (ca. 30%) was observed as a side product.

Table 3. Catalytic Oxidation of a Variety of Alcohols using 3,4,5,6-Tetramethyl-2-iodobenzoic Acid (TetMe-BA, 10 mol %) as a Catalyst in the Presence of Oxone in $MeNO_2$ at rt[a]

entry	substrate	time (h)	product	yield[b] (%)
1		6.0		93
2		8.0		95
3		12.0		46[c]
4		8.0		95
5		8.0		74
6		18.0		92

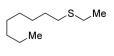
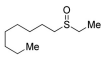
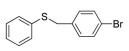
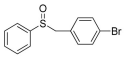
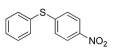
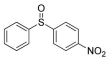
[a]All oxidations were performed by employing 1.0 equiv of oxone in nitromethane at rt. [b]Isolated yields. [c]Bis(4-methoxybenzyl)ether formed as a side product in 35% isolated yield.

dx.doi.org/10.1021/jo201491q | *J. Org. Chem.* 2011, 76, 9593–9601

we have carried out the oxidation of the tetramethyl-*o*-iodobenzoic acid to TetMe-IBX. Indeed, the latter was isolated in 84% yield when the reaction was conducted in a preparative scale at rt for 8 h. Thus, enhanced reactivity due to sterically-accelerated hypervalent twisting and ease of catalyst generation from tetramethyl *o*-iodobenzoic acid permit a facile catalytic approach; of course, the rate of oxidation under catalytic conditions is likely to be limited by catalyst regeneration with oxone unlike that in stoichiometric oxidations. Otherwise, the unique advantage of catalytic oxidation reported by Ishihara et al. with *o*-iodobenzene sulfonic acid is very low catalyst loading (0.5 mol %). The present protocol is appealing from the point of view of low acidity of tetramethyl-substituted benzoic acid (pK_a > 4.5 vis-à-vis ca. −6.5 for benezensulfonic acid) and room temperature for conducting the oxidations.

Oxidation of Sulfides to Sulfoxides at Room Temperature and Mechanistic Considerations. The facile oxidation of alcohols observed with TetMe-IBX spurred us to explore the oxidation of sulfides to sulfoxides; notably, the latter process is heretofore unknown to occur at rt with any of the IBX reagents reported thus far. Remarkably, all the three modified IBXs were found to oxidize the sulfides to sulfoxides selectively in DCM at rt. Dialkyl sulfides were found to undergo oxidation rapidly at rt with all the three reagents. The oxidation of alkyl phenyl sulfide such as ethyl phenyl sulfide was found to be rather slow (16−24 h, entries 4 and 5, Table 4) with Me-

Table 4. Oxidation of Sulfides to Sulfoxides with Me-IBX, DiMe-IBX, and TetMe-IBX at rt[a]

entry	substrate	reagent[b]	time (h)	product	yield[c] (%)
1		Me-IBX	0.6		90
2		DiMe-IBX	0.5		89
3		**TetMe-IBX**	**0.2**		**91**
4		Me-IBX	24.0		86
5		DiMe-IBX	16.0		87
6		**TetMe-IBX**	**1.0**		**92**
7		Me-IBX	6.0		86
8		DiMe-IBX	2.5		87
9		**TetMe-IBX**	**2.0**		**92**
10		Me-IBX	1.5		84
11		DiMe-IBX	0.5		85
12		**TetMe-IBX**	**0.5**		**83**
13		Me-IBX	2.2		87[d]
14		DiMe-IBX	0.8		85[d]
15		**TetMe-IBX**	**2.0**		**86**[d]

[a]All oxidations were performed in DCM as solvent at rt. [b]1.1 equiv of the reagent was employed. [c]Isolated yields. [d]Reactions were performed at reflux in DCE.

IBX and DiMe-IBX, whereas it occurred smoothly with TetMe-IBX within 1 h (entry 6, Table 4). A similar trend in the rates of oxidation was observed for the three IBX reagents for oxidation of diphenyl sulfide and phenyl *p*-bromobenzyl sulfide, as reflected from the durations of the reactions. Intriguingly, the oxidation of *p*-nitrophenyl phenyl sulfide was found to be sluggish at room temperature, but occurred smoothly in DCE at reflux (entries 13−15, Table 4).

DFT computations were undertaken to gain insights into the mechanism of oxidation. The theoretical calculations revealed a single-step mechanism involving the attack of IBX on dimethyl sulfide leading to the formation of O−S bond with concomitant cleavage of the I═O double bond; in the transition state, one observes partial breaking of the double bond of the IBX oxygen with concomitant formation of the bond between iodine and sulfur of the sulfide (Figure 3). We believe that the attack of the

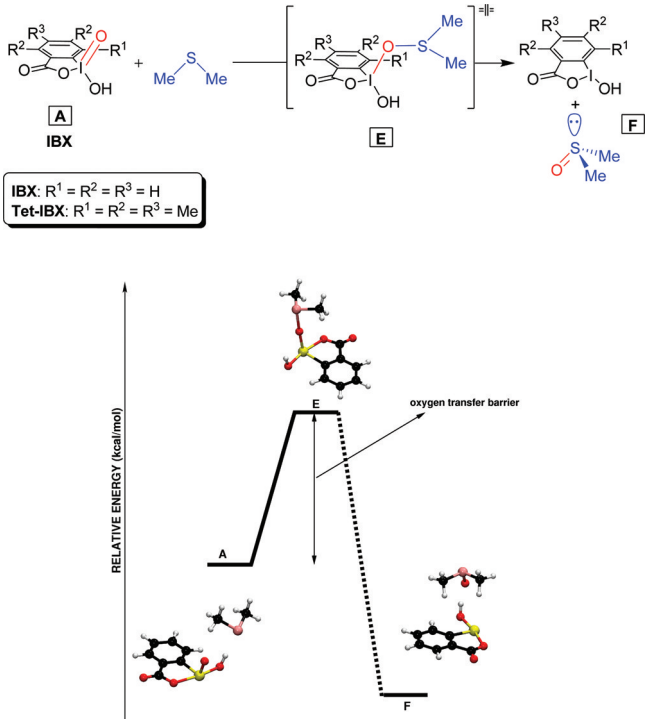


Figure 3. The mechanism of oxidation of dimethyl sulfide with IBX (top) and the activation barriers for the oxygen-transfer process for IBX and TetMe-IBX (bottom). The dotted line is meant to indicate that the energy levels are not drawn to scale.

oxygen of I═O on the sulfur should be assisted by a partial charge transfer initially. The Mulliken charge density analyses of the reactants, transition state species, and products confirmed this trend, cf. Supporting Information; the initial charge transfer between IBX and the sulfide explains the reason as to why *p*-nitrophenyl phenyl sulfide undergoes oxidation at higher temperatures requiring some activation (entries 13−15, Table 4). The mechanism involving initial attack of the sulfur atom of the disulfide on iodine atom is ruled out on the basis of the steep increase of the energy. Indeed, the one-step oxygen-transfer mechanism that is deduced from DFT theoretical calculations herein agrees precisely with the one reported recently by Ruff et al.[23] for oxidation of sulfides with a variety of periodates. The calculations for the oxidation of dimethyl sulfide with IBX and TetMe-IBX reveal that the activation barriers are not influenced much by the modification of IBX structure, Figure 3. Why, then, one observes oxidation at room temperature with TetMe-IBX should be traceable to the considerable solubility of the reagent in DCM. In other words, the differences in the rates of the reactions as reflected by the durations of oxidations in Table 4 for different sulfides with the three reagents are largely a consequence of the differences in the solubilities of the IBX reagents in DCM.

■ CONCLUSIONS

The sterics built via tetramethylation of IBX are shown to lead to considerable twisting of the structure, which manifests in considerable solubility. The DFT calculations reveal that the twisting of the structure with tetramethylation brings about further reduction in the activation energy corresponding to the rate determining *hypervalent twisting*. The increase in solubility via twisting in conjunction with enhancement of reactivity as a result of tetramethylation permit room temperature oxidation

dx.doi.org/10.1021/jo201491q | *J. Org. Chem.* 2011, 76, 9593−9601

of diverse alcohols to the corresponding carbonyl compounds. Indeed, oxidation of sulfides to sulfoxides is found to occur at room temperature, which is reasoned on the basis of the increase in the solubility of TetMe-IBX in DCM. The DFT calculations reveal a single-step mechanism for the oxidation of sulfides, the activation barrier for which is not much influenced by the structural modifications of IBX. The composite effect of solubility and enhanced reactivity of TetMe-IBX was exploited to develop a heretofore unprecedented *room-temperature* catalytic protocol for convenient oxidation of alcohols to the corresponding aldehydes and acids using its precursor *o*-iodo acid, i.e., TetMe-BA, and oxone; the oxidation of primary alcohols to aldehydes selectively can be accomplished when the reactions are run in nitromethane, whereas carboxylic acids are the end products when the solvent system is acetonitrile−water (1:1). We are endeavoring to exploit the very high reactivity of TetMe-IBX to unravel novel synthetic methodologies that surpass the existing ones.

EXPERIMENTAL SECTION

General Aspects. Column chromatography was conducted with silica gel of 100−200 μm particle size. NMR spectra were recorded with 400 and 500 MHz spectrometers. IR spectra were recorded on an FT-IR spectrophotometer. Mass spectral analyses were carried out with an ESI-Q^{TOF} instrument.

Preparation of 2,3,5,6-Tetramethylacetophenone.[24] To a suspension of $AlCl_3$ (16.5 g, 123.1 mmol) in 45 mL of CCl_4 cooled to 5 °C was added acetyl chloride (7.9 mL, 111.9 mmol) slowly. The resulting solution was allowed to stir for 1 h. Subsequently, durene (15.0 g, 111.9 mmol) dissolved in 45 mL of CCl_4 was slowly introduced into the above solution, while the temperature was maintained below 5 °C. The resultant reaction mixture was allowed to stir for 2 h at 0−10 °C and then for another 2 h at room temperature. At the end of this period, it was poured into crushed ice, and 13 mL of concentrated HCl was added. The organic matter was extracted with $CHCl_3$, washed with $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to obtain the crude product, which was purified by silica-gel column chromatography to isolate 2,3,5,6-tetramethylacetophenone as pure colorless solid in 80% yield (15.76 g, 89.5 mmol): mp 69−71 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.09 (s, 6H), 2.20 (s, 6H), 2.46 (s, 3H), 6.95 (s, 1H).

Procedure for the Preparation of 2,3,4,5-Tetramethylacetopheone.[25] A round-bottom flask was charged with 2,3,5,6-tetramethylacetophenone (15.0 g, 85.2 mmol), $AlCl_3$ (31.9 g, 224.1 mmol), NaCl (2.1 g, 34.1 mmol), and H_2O (12 mol %), and the contents were heated at 100 °C for 2 h. Later, the reaction mixture was quenched by adding water. The organic matter was extracted with $CHCl_3$, washed with $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to obtain the crude product, which was purified by column chromatography to isolate 2,3,4,5-tetramethylacetopheone as a pure colorless liquid in 75% yield (11.3 g, 63.9 mmol): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.23 (s, 6H), 2.30 (s, 3H), 2.34 (s, 3H), 2.54 (s, 3H), 7.20 (s, 1H).

Procedure for the Preparation of 2,3,4,5-Tetramethylbenzoic Acid.[26] A round-bottom flask containing 80 mL of water was charged with potassium hydroxide (35.0 g, 625.0 mmol) and bromine (9.7 mL, 187.5 mmol) one after the other at 0 °C. The resulting mixture was allowed to stir for 15−20 min. This solution was slowly added to the solution of 2,3,4,5-tetramethylacetopheone (11.0 g 62.5 mmol) in 160 mL of dioxane, and the mixture was allowed to stir for another 1 h at rt. The resultant mixture was heated at reflux for 1 h. Subsequently, the reaction mixture was acidified with dilute HCl and extracted with EtOAc, washed with brine and $Na_2S_2O_3$ solution, and dried over anhydrous Na_2SO_4. The combined extract was concentrated in vacuo, and the residue was subjected to silica gel chromatography to isolate 2,3,4,5-tetramethylbenzoic acid as a colorless solid in 75% yield (8.4 g, 46.9 mmol): mp 165−167 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.26 (s, 6H), 2.31 (s, 3H), 2.54 (s, 3H), 7.64 (s, 1H).

Preparation of 2-Iodo-3,4,5,6-tetramethylbenzoic Acid. To a solution of 2,3,4,5-tetramethylbenzoic acid (5.5 g, 30.9 mmol) in 50 mL of acetonitrile, *N*-iodosuccinimide (7.7 g, 34.0 mmol) was added. Subsequently, 0.5 mL of concentrated H_2SO_4 and TFA (0.7 mL, 9.3 mmol) were introduced at rt. The resulting reaction mixture was allowed to stir at rt overnight. It was subsequently quenched by adding crushed ice. Filtration of the solid by washing with a small amount of H_2O and petroleum ether, followed by drying under vacuum, led to the pure product in 92% yield (8.6 g, 28.3 mmol): mp 204−207 °C; IR (KBr) cm^{-1} 2919, 2513, 1663; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.20 (s, 3H), 2.32 (s, 3H), 2.33 (s, 3H), 2.51 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.3, 18.4, 18.5, 26.7, 95.5, 131.1, 136.0, 137.0, 137.3, 138.5, 174.8; ESI-MS$^+$ *m*/*z* Calcd for $C_{11}H_{13}IO_2$ 305.0038 [M + H], found 305.0034.

Preparation of 3,4,5,6-Tetramethyl-2-iodoxybenzoic Acid, TetMe-IBX. To a solution of oxone (8.1 g, 13.16 mmol) dissolved in 50 mL of water and 10 mL of acetonitrile was added 2-iodo-3,4,5,6-tetramethylbenzoic acid (2.0 g, 6.58 mmol), and the resultant suspension was heated at 70 °C for 3.5 h with vigorous stirring. The white precipitate that formed was collected by filtration. The precipitate was washed with water and acetone and dried under vacuum to obtain 3,4,5,6-tetramethyl-2-iodoxybenzoic acid as a colorless solid in 82% yield (1.81 g, 5.4 mmol): mp 138−140 °C; IR (KBr) cm^{-1} 3447, 1662, 727; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.28 (s, 6H), 2.62 (s, 3H), 2.67 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 15.9, 16.8, 16.9, 17.4, 127.5, 134.5, 138.6, 141.0, 142.0, 149.6, 168.9; ESI-MS$^+$ *m*/*z* [M − H] Calcd for $C_{11}H_{13}IO_4$ 334.9780, found 334.9786.

3,4,5,6-Tetramethyl-2-iodosobenzoic Acid. Colorless solid: mp 148−150 °C; IR (KBr) cm^{-1} 3427, 1660; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.26 (s, 3H), 2.27 (s, 3H), 2.45 (s, 3H), 2.64 (s, 3H), 8.08 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 15.6, 16.4, 17.3, 19.6, 122.5, 127.7, 135.1, 139.8, 149.0, 169.1; ESI-MS$^+$ *m*/*z* Calcd for $C_{11}H_{13}IO_3$ 318.9831 [M − H], found 318.9833.

Preparation of 3,5-Dimethyl-2-nitrobenzoic Acid.[27] To a solution of 3,5-dimethylbenzoic acid (7.9 g, 52.5 mmol) in 41.0 mL of AcOH, 8.8 mL of HNO_3 was introduced. The resultant mixture was stirred at 80 °C, and 7.9 mL of H_2SO_4 was added at this temperature dropwise to the reaction mixture. The resultant mixture was stirred at the same temperature for 30 min. Subsequently, it was cooled and poured into ice cold water. The solid precipitate was collected by filtration. The colorless solid thus obtained was dried under vacuum to afford 3,5-dimethyl-2-nitrobenzoic acid in 93% yield (9.5 g, 48.9 mmol): mp 186−188 °C; ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 400 MHz) δ 2.15 (s, 3H), 2.25 (s, 3H), 7.13 (s, 1H), 7.51 (s, 1H), 11.01 (brs, 1H).

Preparation of 2-Amino-3,5-dimethylbenzoic Acid.[28] To a solution of 3,5-dimethyl-2-nitrobenzoic acid (9.4 g, 47.9 mmol) in 37.0 mL of EtOH, Sn powder (17.1 g, 143.7 mmol)

dx.doi.org/10.1021/jo201491q | J. Org. Chem. 2011, 76, 9593−9601

was added. The resultant mixture was stirred at 50−60 °C. To this solution was added 93 mL of concentrated HCl dropwise, and the mixture was heated at 70 °C for 1.5 h. Subsequently, the reaction mixture was made alkaline with aqueous NH_3, and the inorganic salts that precipitated out were filtered off. The filtrate was concentrated and acidified with AcOH. The precipitate was collected by filtration, washed with water, and dried under vacuum. 2-Amino-3,5-dimethylbenzoic acid was obtained as a colorless solid in 91% yield (7.2 g, 43.6 mmol): mp 188−190 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.24 (s, 3H), 2.27 (s, 3H), 7.13 (s, 1H), 7.64 (s, 1H).

Preparation of 3,5-Dimethyl-2-iodobenzoic Acid. A solution of 2-amino-3,5-dimethylbenzoic acid (6.8 g, 41.3 mmol) in H_2SO_4−H_2O (25 mL in 50 mL of water) was stirred for 0.2 h at rt and cooled to 0 °C. To this suspension, a solution of $NaNO_2$ (3.7 g, 53.6 mmol) in 7 mL of H_2O was added dropwise to the reaction mixture at 0 °C. The temperature of the reaction was maintained at 0 °C for 1.5 h. To this solution were added a catalytic amount of Cu powder and a solution of KI (34.3 g, 206.5 mmol) in 35 mL of H_2O slowly. The brown-colored mixture was vigorously stirred at room temperature for 3.0 h and allowed to stand overnight. Subsequently, the reaction mixture was diluted with water and extracted with EtOAc, washed with brine and $Na_2S_2O_3$ solution, and dried over anhydrous Na_2SO_4. The combined extract was concentrated in vacuo, and the residue was subjected to silica-gel chromatography to isolate 3,5-dimethyl-2-iodobenzoic acid as a colorless solid in 50% yield (5.7 g, 20.6 mmol): mp 158−160 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.31 (s, 3H), 2.50 (s, 3H), 7.23 (d, J = 1.5 Hz, 1H), 7.44 (d, J = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.6, 29.8, 96.5, 129.2, 133.9, 135.8, 137.8, 143.6, 173.0; ESI-MS$^+$ m/z Calcd for $C_9H_9IO_2$ 274.9569 [M − H], found 274.9569.

Preparation of 3,5-Dimethyl-2-iodoxybenzoic Acid. To a solution of oxone (15.6 g, 25.4 mmol) in 60 mL of distilled water, 3,5-dimethyl-2-iodobenzoic acid (3.5 g, 12.7 mmol) was added over a period of 30 min. The resultant mixture was stirred at 70 °C for 5 h. The reaction mixture was cooled to 5−10 °C. The solid precipitate was filtered and dried under vacuum to afford 3,5-dimethyl-2-iodoxybenzoic acid as a colorless solid in 82% yield (3.2 g, 10.4 mmol): mp 151−152 °C (201−203); IR (KBr) cm^{-1} 3462, 1665, 733; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.39 (s, 3H), 2.74 (s, 3H), 7.43 (s, 1H), 7.71 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 19.6, 20.3, 129.2, 133.0, 138.5, 139.0, 142.5, 144.5, 167.9; ESI-MS$^+$ m/z Calcd for $C_9H_9IO_4$ 306.9467 [M − H], found 306.9464.

3,5-Dimethyl-2-iodosobenzoic Acid. Colorless solid: mp 155−156 °C; IR (KBr) cm^{-1} 3186, 1607; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.37 (s, 3H), 2.57 (s, 3H), 7.40 (s, 1H), 7.66 (s, 1H), 8.24 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 19.8, 20.3, 115.0, 130.5, 132.6, 139.6, 140.3, 140.6, 168.0; ESI-MS$^+$ m/z Calcd for $C_9H_9IO_3$ 290.9518 [M − H], found 290.9519.

Preparation of 2-Amino-3-methylbenzoic Acid.[29] To a solution of 3-methyl-2-nitrobenzoic acid (5.0 g, 27.6 mmol) in 70 mL of EtOH, 10% Pd−C (0.4 g) was added, and the mixture was stirred under H_2 atm for overnight. After completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was evaporated under reduced pressure to yield 2-amino-3-methylbenzoic acid in 98% yield (4.1 g, 27.0 mmol): mp 170−172 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.19 (s, 3H), 6.62 (t, J = 7.6 Hz, 1H), 7.24 (d, J = 7.1 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H).

Preparation of 2-Iodo-3-methylbenzoic Acid.[29] A solution of 2-amino-3-methylbenzoic acid (4.0 g, 26.5 mmol) was stirred in H_2SO_4−H_2O (15 mL of H_2SO_4 in 30 mL of water) for 0.2 h. The resultant suspension was cooled to 0 °C, and a solution of $NaNO_2$ (2.4 g, 34.4 mmol) in 5 mL of H_2O was added dropwise to the reaction mixture at 0 °C. The temperature of the reaction mixture was maintained at 0 °C for 1.5 h. To this reaction mixture, a solution of KI (22.0 g, 132.4 mmol) in 25 mL of H_2O was added slowly. The brown-colored mixture was vigorously stirred at room temperature overnight. Subsequently, the reaction mixture was diluted with water and extracted with EtOAc. The combined extract was washed with brine and $Na_2S_2O_3$ solution followed by water and dried over anhydrous Na_2SO_4. Solvent was removed in vacuo, and the residue was subjected to silica-gel chromatography to isolate 2-iodo-3-methylbenzoic acid as a colorless solid in 86% yield (6.0 g, 22.8 mmol): mp 142−145 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.57 (s, 3H), 7.31 (t, J = 7.6 Hz, 1H), 7.40(d, J = 7.6 Hz, 1H), 7.63(d, J = 7.6 Hz, 1H).

Preparation of 3-Methyl-2-iodoxybenzoic Acid, Me-IBX. To a solution of oxone (14.1 g, 22.9 mmol) in 50 mL of distilled water, 2-iodo-3-methylbenzoic acid (3.0 g, 11.5 mmol) was added over a period of 5 min. The resultant mixture was stirred at 70 °C for 4 h. Subsequently, the reaction mixture was cooled to 5−10 °C, and the solid precipitate was filtered, washed with cold acetone, and dried under vacuum to afford Me-IBX as a colorless solid in 78% isolated yield (2.6 g, 8.9 mmol): mp 146−148 °C (190−192); IR (KBr) cm $^{-1}$ 3450, 1671, 751,728; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.78 (s, 3H), 7.61 (d, J = 5.5 Hz, 1H), 7.65 (d, J = 5.8 Hz, 1H), 7.88 (d, J = 5.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 19.8, 128.9, 132.2, 132.9, 138.1, 139.3, 147.6, 168.1; ESI-MS$^+$ m/z Calcd for $C_8H_7IO_4$ 292.9310 [M − H], found 292.9315.

3-Methyl-2-iodosobenzoic Acid. Colorless solid: mp 168−170 °C; IR (KBr) cm $^{-1}$3449, 1642; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.63 (s, 3H), 7.55−7.56 (m, 2H), 7.84 (d, J = 6.55 Hz, 1H), 8.30 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 20.5, 118.7, 130.1, 130.3, 132.6, 138.8, 141.1, 168.0; ESI-MS$^+$ m/z Calcd for $C_8H_7IO_3$ 276.9361 [M − H], found 276.9360.

Procedure for Oxidation of Alcohols and Sulfides with Modified IBXs. In a typical experiment, 0.5−1.0 mmol of the alcohol/sulfide was taken in 10.0 mL of DCM, and to it, 1.2/1.1 equiv of modified methyl-IBX was introduced. The reaction mixture was stirred for the durations mentioned in Tables 1 and 2 at rt (25−30 °C). The progress of the reaction was monitored by TLC analysis. After completion of the reaction, the solid material from the reaction mixture was filtered in vacuo. Concentration of the filtrate afforded the product, which was subjected to silica-gel column chromatography to isolate the pure product.

Procedure for Catalytic Oxidation of Alcohols with 3,5-Dimethyl-2-iodobenzoic Acid and 2-Iodo-3,4,5,6-tetramethylbenzoic Acid in the Presence of Oxone in CH_3CN/H_2O (1:1). In a typical experiment, to a solution of 0.5−1.05 mmol of the alcohol in 9 mL of 1:1 acetonitrile and water mixture was added powdered oxone (1 equiv for secondary alcohols and 2 equiv for primary alcohols). To this reaction mixture was introduced 10 mol % of 3,5-dimethyl-2-iodobenzoic acid/2-iodo-3,4,5,6-tetramethylbenzoic acid, and the mixture was stirred at rt for the durations given in Table 3. After completion of the reaction as monitored by TLC analysis, a small amount of water was added to dissolve the inorganic salts. Acetonitrile solvent was removed in vacuo, and the

dx.doi.org/10.1021/jo201491q | J. Org. Chem. 2011, 76, 9593−9601

organic matter was extracted with ethyl acetate. The combined extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was subjected to column chromatography to isolate the pure oxidation product.

Procedure for Catalytic and Selective Oxidation of Primary Alcohols with 2-Iodo-3,4,5,6-tetramethylbenzoic Acid in the Presence of Oxone in CH_3NO_2. The same procedure as above was employed, and the reactions were run at room temperature when CH_3NO_2 was used as a solvent.

■ ASSOCIATED CONTENT

Supporting Information

Details of theoretical calculations and ^1H and ^{13}C NMR spectral reproductions of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENTS

We thank the Department of Science and Technology (DST), India for financial support. K.S. and K.N.P. are grateful to UGC and CSIR for their research fellowships. All computations were carried out at the ChemFIST Computer Lab, Department of Chemistry, IIT Kanpur. We thankfully acknowledge the invaluable suggestions and criticisms of the anonymous referees.

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