JOC Note
pubs.acs.org/joc

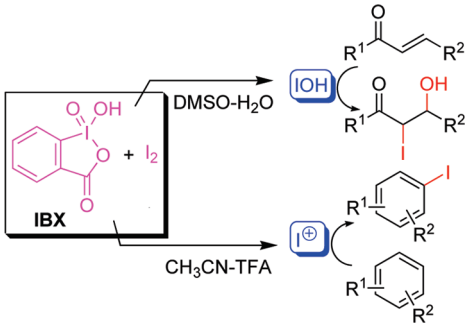
IBX−I_2 Redox Couple for Facile Generation of IOH and I^+: Expedient Protocol for Iodohydroxylation of Olefins and Iodination of Aromatics

Jarugu Narasimha Moorthy,* Kalyan Senapati, and Sarvesh Kumar

Department of Chemistry, Indian Institute of Technology, Kanpur 208 016, India

moorthy@iitk.ac.in

Received April 16, 2009



IBX is readily reduced to IBA in the presence of molecular iodine in DMSO to generate hypoiodous acid (IOH), which reacts with a variety of olefins as well as α,β-unsaturated ketones leading to their respective iodohydrins with anti stereochemistry. The same redox chemistry in acetonitrile containing TFA produces iodonium ions for facile iodination of a variety of aromatic compounds in respectable isolated yields.

There is a surge of interest in hypervalent organic compounds at present due to their nontoxic nature, ready availability, and environmentally benign attributes. In particular, the pentavalent iodine compound,[1] namely *o*-iodoxybenzoic acid (1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide), referred to popularly as IBX, has assumed significant prominence as a fantastic oxidation reagent since the demonstration in 1994 by Frigerio and co-workers.[2] In addition to the ease with which it is readily prepared starting from cheap *o*-iodobenzoic acid, the stability and advantages associated with obviating the use of copious amounts of metal-based reagents render IBX an indispensable and sought-after reagent in oxidation chemistry. Because of its mild nature and ability to accomplish a variety of transformations that are unknown for other oxidation reagents, the interest in IBX chemistry continues unabated.[3]

We have been interested in understanding the reactivity of IBX and exploiting the same to unravel new synthetic transformations.[4] In continuation of our studies, we have inquired into the redox chemistry of IBX with molecular iodine. The latter and metal iodides have been oxidized by a number of reagents to produce hypoiodous (IOH) acid and iodonium (I^+) ions. Although periodic acid ($HIO_4 \cdot 2H_2O$),[5] periodate ($NaIO_4$),[6] *m*-iodosylbenzoic acid,[7] etc. have all been employed to oxidize molecular iodine or metal iodides, IBX has surprisingly not been employed as an oxidant. Herein, we report that the redox chemistry between IBX and I_2 in DMSO leads supposedly to IOH, which can be conveniently exploited to convert a variety of e-rich olefins as well as e-deficient α,β-unsaturated carbonyl compounds to their corresponding iodohydrins with anti stereochemistry in good-to-excellent isolated yields; indeed, the treatment of iodohydrin in the same pot with NaOH leads to α,β-epoxyketones in respectable isolated yields. Further, it is shown that the redox chemistry between the IBX−I_2 couple in the presence of TFA permits facile iodination of a number of e-rich as well as e-poor aromatic compounds via generation of reactive iodonium ions.

To begin with, the reduction of IBX with added molecular iodine in DMSO-d_6 was examined by ^{1}H NMR (500 MHz) spectroscopy. As shown in Figure 1, the signals corresponding to IBX completely disappeared within 0.5 h of the addition of 2.2 equiv of iodine leading to concomitant appearance of the signals that could be assigned to *o*-iodosobenzoic acid (IBA), the 2-e reduction product. Further standing of the reaction mixture for 1−2 h at rt led to the formation of *o*-iodobenzoic acid (BA) in small amounts, as monitored by ^{1}H NMR spectroscopy, cf. Figure 1.[8] A similar spectral monitoring in CD_3CN containing TFA (9:1) proved difficult, as IBX was found to be virtually insoluble. Nonetheless, the addition of I_2 to the suspension of IBX in CD_3CN−TFA led to noticeable dissolution. The ^{1}H NMR monitoring of the

(1) (a) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. (b) Ladziata, U.; Zhdankin, V. V. *ARKIVOC* **2006**, *108*, 26.
(2) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019.
(3) (a) Uyanik, M.; Akakura, M.; Ishihara, K. *J. Am. Chem. Soc.* **2009**, *131*, 251. (b) Fontaine, P.; Masson, G.; Zhu, J. *Org. Lett.* **2009**, *11*, 1556. (c) Richardson, R. D.; Zayed, J. M.; Altermann, S.; Smith, D.; Wirth, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 6529. (d) Studer, A.; Janza, B. *J. Org. Chem.* **2005**, *70*, 6991. (e) Bhalerao, D. S.; Mahajan, U. S.; Chaudhari, K. H.; Akamanchi, K. G. *J. Org. Chem.* **2007**, *72*, 662. (f) Nicolaou, K. C.; Baran, P. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2678. (g) Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 4077. (h) Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *J. Am. Chem. Soc.* **2004**, *126*, 5192.
(4) (a) Moorthy, J. N.; Singhal, N.; Mal, P. *Tetrahedron Lett.* **2004**, *45*, 309. (b) Moorthy, J. N.; Singhal, N.; Venkatakrishnan, P. *Tetrahedron Lett.* **2004**, *45*, 5419. (c) Moorthy, J. N.; Singhal, N.; Senapati, K. *Tetrahedron Lett.* **2006**, *47*, 1757. (d) Moorthy, J. N.; Singhal, N.; Senapati, K. *Org. Biomol. Chem.* **2007**, *5*, 767. (e) Moorthy, J. N.; Singhal, N.; Senapati, K. *Tetrahedron Lett.* **2008**, *49*, 80. (f) Moorthy, J. N.; Senapati, K.; Singhal, N. *Tetrahedron Lett.* **2009**, *50*, 2493.
(5) Masuda, H.; Takase, K.; Nishio, M.; Hasegawa, A.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* **1994**, *59*, 5550.
(6) (a) Kraszkiewicz, L.; Sosnowski, M.; Skulski, L. *Synthesis* **2006**, 1195. (b) Emmanuvel, L.; Shukla, R. K.; Sudalai, A.; Gurunath, S.; Sivaram, S. *Tetrahedron Lett.* **2006**, *47*, 4793.
(7) Yusubov, M. S.; Yusubova, R. Y.; Kirschning, A.; Park, J. Y.; Chi, K.-W. *Tetrahedron Lett.* **2008**, *49*, 1506.
(8) The doublet that appears at ca. δ 8.3 when I_2 is added to IBX (and not to IBA) is presumably due to the formation of 1-benziodoxole hypoiodide.

DOI: 10.1021/jo9007892 Published on Web 07/10/2009

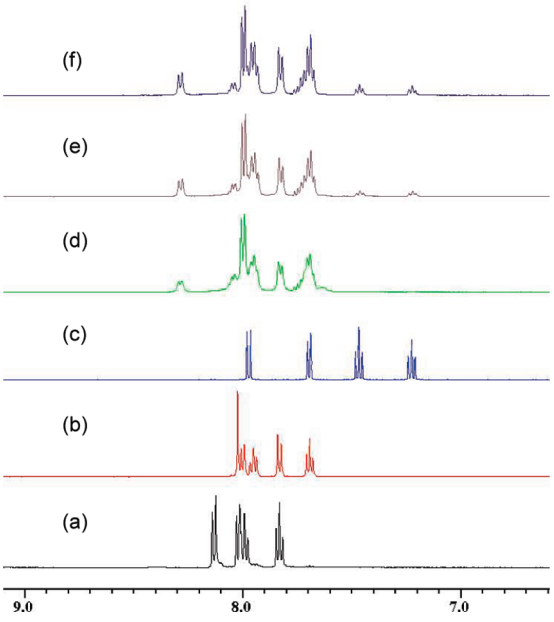


FIGURE 1. ^{1}H NMR spectra in DMSO-d_6 of (a) IBX, (b) IBA, (c) *o*-iodobenzoic acid (BA), and (d−f) IBX + I_2, after 0.5, 1.0, and 2.0 h following the addition of I_2. Notice that IBX is reduced to IBA within 0.5 h (d), while further reduction to BA occurs only in small amounts as reflected by the signals in the region of δ 7.0−7.5 in the spectrum (c).

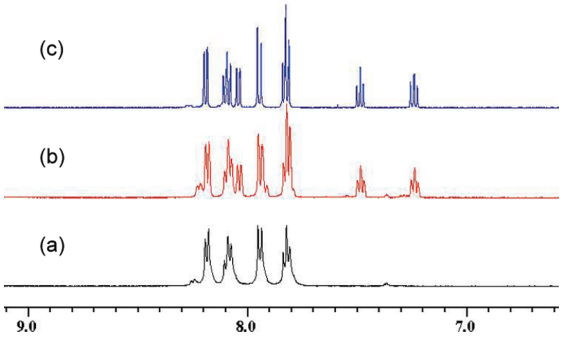
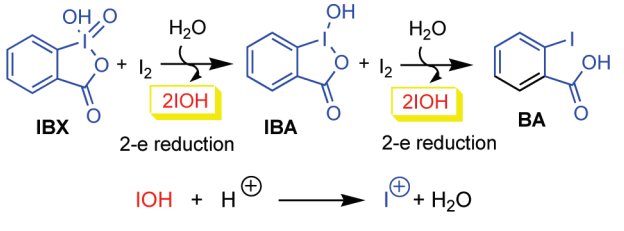


FIGURE 2. ^{1}H NMR spectra of (a) IBA in CD_3CN−TFA (9:1), (b) IBA + I_2 in CD_3CN−TFA after 1 h following the addition of I_2, and (c) IBX + I_2 after 0.5 h following the addition of I_2.

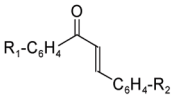
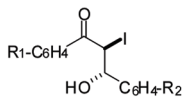
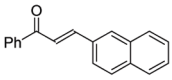
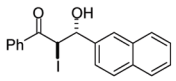
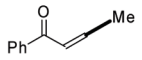
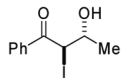
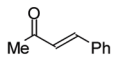
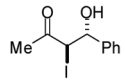
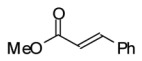
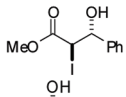
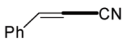
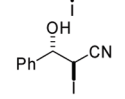
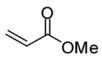
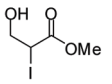
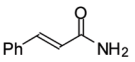
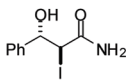
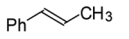
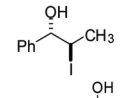
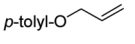
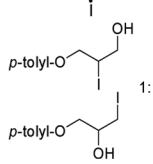
SCHEME 1. The Redox Chemistry between IBX and I_2 and the Species Generated



sample after 0.5 h revealed the signals corresponding to IBA. After 1 h, IBA was found to be further reduced to *o*-iodobenzoic acid, cf. Figure 2. Thus, it was concluded that IBX undergoes facile 2-e reduction in the presence of I_2 in DMSO leading to I(III) species, while further 2-e reduction to I(I) occurs in acetonitrile containing TFA (Scheme 1).

As the species generated in DMSO was presumed to be IOH, the redox reaction between IBX and I_2 was conducted in the presence of added olefins to explore the extent to which the latter undergo iodohydroxylations.[9] While e-rich olefins were found to react readily to afford the corresponding

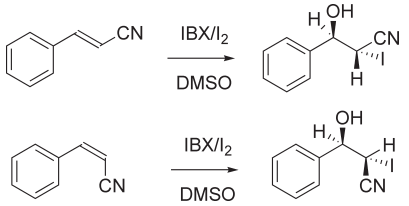
TABLE 1. Results of Iodohydroxylation of Olefins with IBX−I_2 in DMSO[a]

entry	substrate	IBX : I_2 (time, h)	product	yield (%)
				
	R_1 R_2			
1	H H	0.6 : 1.5 (15.0)		83
2	H H	1.0 : 2.2 (1.1)		81
3	H 4-F	1.0 : 2.2 (1.3)		89
4	H 4-OMe	1.0 : 2.2 (0.3)		75
5	4-OMe H	1.0 : 2.2 (0.9)		78
6	H 4-Br	1.0 : 2.2 (4.0)		86
7	4-NO_2 H	1.0 : 2.2 (10.0)		75
8	H 4-NO_2	1.0 : 2.2 (14.0)		78
9		1.0 : 2.2 (1.0)		80
10		1.0 : 2.2 (1.0)		72[b]
11		1.0 : 2.2 (1.0)		84
12		1.0 : 2.2 (4.0)		88
13		1.0 : 2.2 (35.0)		84[b,c]
14		1.0 : 2.2 (0.3)		86
15		1.0 : 2.2 (1.8)		54
16		0.5 : 1.1 (0.2)		91
17		0.5 : 1.1 (0.1)		63[d]
18		0.5 : 1.1 (0.8)	 1:1	97

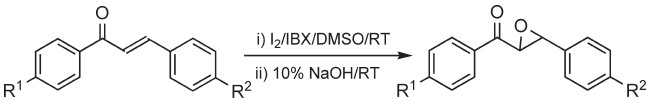
[a]All reactions were conducted on 0.5−1.5 mmol of the olefin. [b]A mixture of syn and anti diastereomers. [c]Conversion ca. 90%. [d]Formation of epoxide was observed in ca. 20% yield.

(9) The IBX−I_2 reagent system in water has been reported to convert olefins to α-iodoketones, see: Yadav, J. S.; Reddy, B. V. S.; Singh, A. P.; Basak, A. K. *Tetrahedron Lett.* **2008**, *49*, 5880.

SCHEME 2. Highly Stereoselective *Anti* Addition of IOH



SCHEME 3. One-Pot Conversion of α,β-Unsaturated Ketones to α,β-Epoxyketones



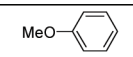
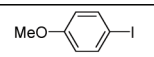
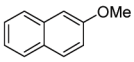
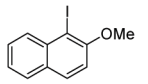
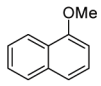
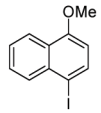
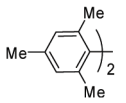
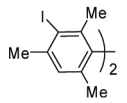
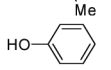
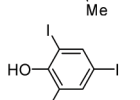
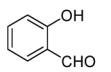
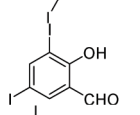
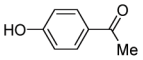
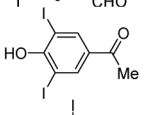
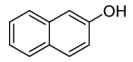
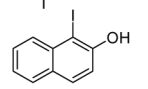
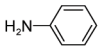
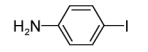
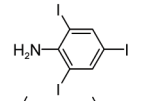
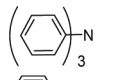
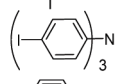
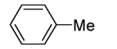
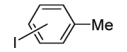
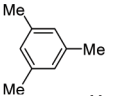
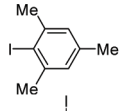
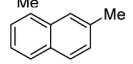
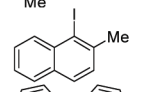
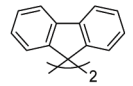
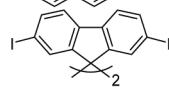
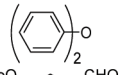
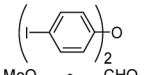
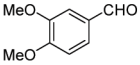
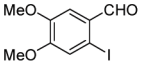
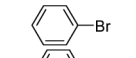
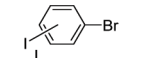
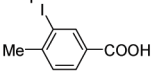
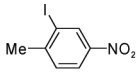
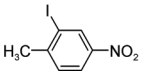
		duration (h)	yield (%)
R^1 = H	R^2 = H	1.0 + 0.1	81
R^1 = H	R^2 = F	1.0 + 0.1	71
R^1 = H	R^2 = OMe	0.25 + 0.1	68
R^1 = OMe	R^2 = H	0.7 + 0.1	80
R^1 = H	R^2 = Br	4.0 + 0.1	82
R^1 = NO_2	R^2 = H	10.0 + 0.3	79
R^1 = H	R^2 = NO_2	14.0 + 0.5	86

iodohydrins in near-quantitative yields, e-deficient α,β-unsaturated ketones were found to react rather slowly. The employment of excess reagent (IBX and I_2 in 1:2.2 equiv) was found to offset the slow reaction times (entries 1 and 2, Table 1). Thus, a variety of olefins shown in Table1 were conveniently converted to their respective iodohydrins in moderate durations. While the olefins such as styrene reacted within 0.1−0.8 h (entries 16−18), the α,β-unsaturated carbonyl compounds reacted in 0.3−4.0 h with the notable exceptions being nitro-substituted chalcones (entires 7 and 8) and cinnamonitrile (entry 13), which reacted rather slowly over a period of 10−35 h. For all olefins with the exception of *p*-tolyl allyl ether (entry 18), no regioisomeric iodohydrins were observed as revealed by ^{1}H NMR analyses of crude reaction mixtures. Further, the fact that the addition occurs with a very high anti stereoselectivity was established by subjecting the pure cis and trans isomers of cinnamonitrile to iodohydroxylations, Scheme 2; the stereochemistry of the products was deduced based on a comparison with the literature-reported spectral data and X-ray structure determination of one of the products, cf. the SI. ^{1}H NMR spectroscopic monitoring of the reactions of both pure isomers with IBX−I_2 independently revealed the formation of corresponding iodohydrins derived via anti addition almost exclusively at conversions as high as 80%, cf. the SI. The formation of the diastereomeric iodohydrin derived via syn addition was barely evident (< 2−3%) from ^{1}H NMR analysis in each case.

We also examined the viability of one-pot conversion of α-iodo-β-hydroxyketones to the corresponding α,β-epoxyketones by treatment with a base. Indeed, addition of 10% NaOH solution to the reaction mixture after the disappearance of α,β-unsaturated ketone, as judged by the TLC analyses, led to the desired epoxides in respectable yields as shown in Scheme 3.

As shown in Scheme 1, the hypoiodous acid generated in acidic medium should liberate iodonium ions, which can be

TABLE 2. Results of Iodination of Aromatics with IBX−I_2

entry	substrate	IBX:I_2/Solvent temp/time (h)	product	yield (%)
1		1.0 : 1.5/DMSO rt/5.00		96
2		0.5:1.25/MeCN[a] rt/2.00		91
3		1.0:1.5/DMSO rt/1.0		96
4		0.5:1.25/MeCN[a] rt/0.5		96
5		1.0:1.5/DMSO rt/ 0.40		95
6		0.5:1.25/MeCN[a] rt/0.25		95
7		2.0:3.0/DMSO 50°C/0.50		82
8		1.0:2.5/MeCN[a] rt/3.50		85
9		1.32:2.0/DMSO rt /0.5		85
10		1.0:1.5/DMSO rt/0.75		87
11		1.0:1.5/DMSO rt/ 2.0		91
12		0.33:0.5/DMSO rt/0.10		87
13		0.33:0.5/DMSO rt/ 0.10		88
14		2.0:3.0/DMSO rt/1.50		64
15		1.0:1.5/DMSO rt/ 1.75		97
17		0.5:1.25/MeCN[a] rt/7.00		85
18		0.5:1.25/MeCN[a] rt/0.75		96
19		0.5:1.25/MeCN[a] rt/0.75		92
20		2.0:5.0/MeCN[a] reflux/16.0		71
21		1.0:2.5/MeCN[a] 50°C/1.50		95
22		0.5:1.25/MeCN[a] rt/9.50		70[b]
23		0.5:1.25/TFA 50°C/1.25		81
24		0.5:1.25/TFA 50°C /6.00		89
25		0.5:1.25/AcOH[c] 50°C /29.00		88

[a]TFA (10%). [b]8% diiodo compound was isolated. [c]98% H_2SO_4 (5 equiv).

trapped for aromatic electrophilic substitutions. As revealed by ^{1}H NMR analysis in Figure 1, 4 mol equiv of IOH should in principle be generated for each mole of IBX. In line with this expectation, the 4-e reduction product, namely *o*-iodobenzoic acid, was isolated in near-quantitative yields, when the reactions were run with mesitylene as a representative case in CH_3CN containing TFA. Thus, iodination of a variety of aromatic compounds was explored with IBX−I_2 in DMSO as well as in CH_3CN−TFA. While the iodination was found to occur with IBX−I_2 in DMSO, the reaction was found to be more efficient when carried out in CH_3CN−TFA (entries 1−6, Table 2). However, for less activated aromatics, excess reagent was found to expedite the reactions leading to excellent yields of iodinated aromatic products in reasonable reaction durations as shown in Table 2. A perusal of the results in Table 2 shows that a variety of aromatic compounds can be iodinated in either of the two conditions involving the use of DMSO or CH_3CN−TFA. Most remarkable is the fact that e-deficient aromatics could also be subjected to iodination, albeit at a relatively higher temperature with/without added H_2SO_4 (entries 23−25).

A variety of reagents are known for direct iodination of aromatics based on oxidation of molecular iodine.[10] It is evident from the results described herein that IBX can be reduced from its higher oxidation state to *o*-iodobenzoic acid (BA) with concomitant formation of 4 equiv of iodonium ions. This in conjunction with the use of CH_3CN or DMSO in which most aromatics that can be reacted should make the reagent system based on IBX−I_2 convenient for iodination of aromatic compounds in general. It is needless to emphasize the utility of aryl iodides in medicinal and biochemistry, as radioactive markers[11] and as valuable intermediates in metal-catalyzed cross-coupling reactions.[12]

In conclusion, we have shown that the redox chemistry between IBX and molecular iodine leads to facile generation of hypoiodous acid, which in the presence of olefins reacts to afford the corresponding halohydrins with a very high anti stereoselectivity conveniently. It should be pointed out that iodohydroxylations are largely reported for e-rich olefins,[13] and one observes only scattered and scant examples involving e-deficient olefins.[14] In the present investigation, we have found that a variety of α,β-unsaturated carbonyl compounds undergo conversion to the corresponding iodohydrins. Presumably, the solvation effects involving DMSO render IOH remarkably reactive for addition to e-deficeint olefins. Further, it is shown that tandem halohydroxylation−dehydroiodocyclization of olefins to epoxides can be conveniently carried out in one pot. That the redox chemistry in acidic medium leads to abundant iodonium ions for aromatic iodination is demonstrated with diverse aromatic compounds. A variety of e-rich as well as poor aromatics are shown to be iodinated with the IBX−I_2 reagent system in very good isolated yields.

(10) For a recent review on iodinations with iodine or iodides, see: Stavber, S.; Jereb, M.; Zupan, M. *Synthesis* **2008**, 1487.
(11) *Handbook of Radiopharmaceuticals: Radiochemistry and Applications*; Welch, M. J., Redvanly, C. S., Eds.; Wiley: Chichester, UK, 2003.
(12) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
(13) (a) Barluenga, J.; Marco-Arias, M.; González-Bobes, F.; Ballesteros, A.; Gozález, J. M. *Chem.—Eur. J.* **2004**, *10*, 1677. (b) Corso, A. R. D.; Panunzi, B.; Tingoli, M. *Tetrahedron Lett.* **2001**, *42*, 7245. (c) Iranpoor, N.; Shekarriz, M. *Tetrahedron* **2000**, *56*, 5209. (d) Asensio, G.; Andreu, C.; Boix-Bernardini, C.; Mello, R.; Gonzlez-Nuez, M. E. *Org. Lett.* **1999**, *1*, 2125. (e) Stavber, G.; Iskra, J.; Zupan, M.; Stavber, S. *Adv. Synth. Catal.* **2008**, *350*, 2921. (f) Ribeiro, R. S.; Esteves, P. M.; Mattos, M. C. S. *Tetrahedron Lett.* **2007**, *48*, 8747. (g) Das, B.; Venkateswarlu, K.; Damodar, K.; Suneel, K. *J. Mol. Catal. A: Chem.* **2007**, *269*, 17. (h) Barluenga, J. *Pure Appl. Chem.* **1999**, *71*, 431.
(14) (a) Urankar, D.; Rutar, I.; Modec, B.; Dolenc, D. *Eur. J. Org. Chem.* **2005**, 2349. (b) Hajra, S.; Bhowmick, M.; Karamakar, A. *Tetrahedron Lett.* **2005**, *46*, 3073.

Experimental Section

General Procedure for Iodohydroxylation of Olefins. In a typical procedure, 1.0−1.5 mmol of chalcone, 1.0 equiv of I_2, and 2.2 equiv of IBX in 2−3 mL of DMSO were stirred at room temperature. For e-rich olefins, IBX (0.5 equiv) and I_2 (1.1 equiv) were stirred in DMSO for 0.5 h first and then the olefin was introduced. The progress of the reaction was monitored by TLC analysis. After completion of the reaction, the reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic extracts were washed with 10% aq sodium thiosulfate solution followed by water and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the crude product was purified by column chromatography over silica gel (100−200 μm). While the duration of reaction was typically 10−45 min for e-rich olefins, it varied from 0.3 to 14 h for e-deficient olefins such as α,β-unsaturated carbonyl compounds.

General Procedure for One-Pot Epoxidation of Olefins. After the disappearance of the olefin in the iodohydroxylation reaction described above, 1.5 equiv of 10% aq NaOH solution was added to the reaction mixture in the same pot at room temperature. The progress of the reaction was monitored by TLC analysis. Subsequent to the disappearance of iodohydrin, the reaction mixture was quenched with water. Regular workup followed by silica gel chromatography led to the epoxides, which were characterized by spectroscopic data, cf. the SI.

General Procedure for Iodination of Aromatics. In a representative reaction, IBX, I_2, and the substrate, according to the composition shown in Table 2, were taken in 2.0−3.0 mL of DMSO or CH_3CN−TFA (9:1) and stirred at the indicated temperature. The progress of the reaction was monitored by TLC analysis. For iodination of phenol and aniline derivatives, the reagent was prepared first by stirring I_2 and IBX in DMSO at room temperature for 30 min and the substrate was added later. After completion of the reaction as judged by TLC analysis, the reaction mixture was quenched with 10% aq sodium thiosulfate solution and extracted with ethyl acetate. The combined organic extracts were washed with water and brine, then dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the crude product was purified by column chromatography, using silica gel (100−200 μm). For phenols, the aqueous reaction mixture was neutralized with NH_4Cl before extraction.

Acknowledgment. J.N.M. and S.K. are thankful to DST (the Department of Science and Technology), India for financial support. K.S. is grateful to UGC (the University Grants Commision) for a senior research fellowship.

Supporting Information Available: Characterization data, ^{1}H and ^{13}C spectral reproductions for halohydrins and aryl iodides, and crystal data for 3-hydroxy-2-iodo-1-(4-methoxyphenyl)-3-phenylpropan-1-one. This material is available free of charge via the Internet at http://pubs.acs.org.