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Safe oxidation of sulfides into sulfoxides using SIBX

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Abstract—SIBX is a stabilized (i.e., nonexplosive) formulation of the λ^5-iodane 2-iodoxybenzoic acid IBX that can be used as a suspension in various organic solvents to oxidize safely sulfides into sulfoxides. Most yields are comparable to those obtained using IBX or other iodanes such as PhIO and $PhIO_2$. An asymmetric version of this SIBX-mediated sulfoxidation was performed in high chemical yield and moderate enantioselectivity by simple addition of an external chiral source.

Hypervalent iodine-based reagents are today commonly used in organic synthesis to perform a wide variety of transformations thanks to their high chemoselectivity with various types of polyfunctionalized substrates, low toxicity and ease of handling.[1–3] For example, the utility of hypervalent iodine compounds of both λ^3- and λ^5-iodane types has been evidenced in demonstrations of their selectivity in oxidation reactions of sulfides into sulfoxides without overoxidation to sulfones.[4] Sulfoxidation is one of the key reactions used by medicinal chemists in drug development and its stereoselective versions constitute a valuable means of introducing and controlling chirality in asymmetric synthesis.[5,6] In this context, the λ^5-iodane 2-iodoxybenzoic acid (i.e., 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide, referred to as IBX) has been revealed as a particularly useful source of oxygen atom,[7] but the standard use of this reagent by industrial process chemists has been thwarted by two major drawbacks. The first one is due to the fact that IBX violently decomposes under impact and/or heating,[8] and the second one is the lack of stereochemical control in the oxygenation of the sulfur atom. Modified IBX-like reagents have been introduced to solve the safety issue, but their preparation requires additional steps.[9] It thus became desirable to find other means of stabilizing IBX in order to allow its safe utilization in process chemistry. Research conducted at Simafex led to the development of a nonexplosive white-powder formulation of IBX referred to as SIBX for 'Stabilized IBX', and composed of IBX (49%), benzoic acid (22%), and isophthalic acid (29%).[10] We previously reported on the use of SIBX as an effective oxidant of phenols, alcohols, and anilines.[11–13] In this letter, we wish to highlight the performances of SIBX in sulfoxidation reactions and to report on our first attempts to control the stereochemistry of such a transformation by using chiral additives.

We first examined a variety of reaction conditions using thioanisole (**1**) as a model substrate (Table 1). In a preliminary experiment, sulfide **1** was submitted to SIBX (1 equiv) as a suspension in toluene, but no reaction was observed even after three days (Table 1, entry 1). The presence of carboxylic acids in the SIBX formulation led us to include a small amount of water in the solvent system in the hope of promoting an acid catalysis of the reaction via protonation of IBX. Surprisingly, this addition of water had no effect on the outcome of the reaction (Table 1, entry 2). This lack of reactivity then led us to consider the addition of a quaternary ammonium salt that has previously been shown to be critical for the success of iodane-mediated sulfoxidation reactions.[7,14,15] Indeed, in the presence of such a salt (i.e., cetyltrimethylammonium bromide, CTAB), sulfoxidation of **1** was effective. In anhydrous toluene, **1** was converted into the sulfoxide **2** in 72% after 40 h in the presence of 20 mol % of CTAB (Table 1, entry 3). In this case, CTAB probably acts as an IBX activator by polarizing its I=O (2c–4e) hypervalent bond.[7] However, the

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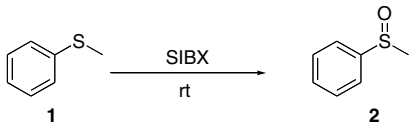
Table 1. Optimization of SIBX-mediated sulfoxidation[a]



1 **2**

Entry	SIBX (equiv)	Solvent	CTAB (mol %)	Time (h)	Yield[b] (%)
1	1	Toluene	0	72	No reaction
2	1	Toluene/H_2O (50:1)	0	72	No reaction
3	1	Toluene	20	40	72
4	1	Toluene/H_2O (50:1)	20	2	93
5	1	CH_2Cl_2/H_2O (50:1)	20	0.5	89
6	1	EtOAc/H_2O (50:1)	20	2.5	86
7	5	CH_2Cl_2/H_2O (50:1)	20	24	91[c]
8	0.5	CH_2Cl_2/H_2O (50:1)	20	96	50[d]

[a] All reactions were run at rt using 0.2 mmol of **1** in ca. 5 mL of solvent and 1 equiv of SIBX, unless otherwise noted.
[b] Isolated yields.
[c] Reaction completed in 30 min; yield evaluated from NMR analysis of the reaction mixture.
[d] Reaction not completed after 96 h.

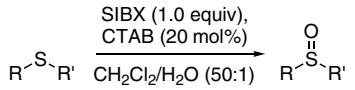
addition of a small amount of water was here found to be highly beneficial for accelerating the reaction, which presumably then takes place at the interior of reversed micelles formed by CTAB acting as a surfactant.[14–16] Thus, in a 50:1 toluene–water plus 20 mol % CTAB reversed micellar medium, the same reaction led to **2** in 93% yield after only 2 h (Table 1, entry 4). Sulfoxidation of **1** is even faster and completed in 30 min in dichloromethane–water (50:1), but slows down in a more polar solvent system such as ethyl acetate–water (50:1) (Table 1, entries 5 and 6).

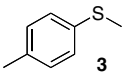
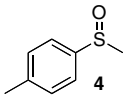
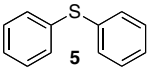
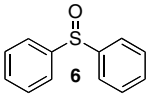
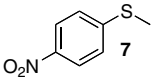
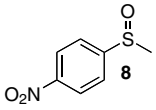
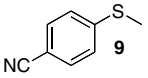
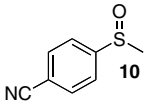
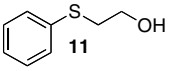
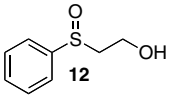
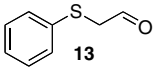
The selectivity of this oxygenation reaction was then put to the test by adding an excess of SIBX, up to 5 equiv, and by letting the reaction go for 24 h in the 50:1 dichloromethane–water solvent system, still in the presence of 20 mol % of CTAB. Under such reaction conditions, **1** was cleanly converted into **2** in 91% yield (Table 1, entry 7). The only additional product was the corresponding sulfone (not shown) that was observed in only 9% yield. Both the presence of water and the acidity of the SIBX formulation certainly help preventing overoxidation of the sulfoxide into a sulfone. Indeed, both solvation by water and protonation of the sulfoxide will decrease the nucleophilicity of its sulfur atom, thereby lowering its susceptibility to further oxygenation.[17] Once the reaction is completed, the insoluble white powder is removed by filtration. It contains the λ^3-iodane iodosobenzoic acid (IBA) generated as a result of the concomitant reduction of IBX during the oxidation process. Since IBA is also capable of oxidizing sulfides into sulfoxides,[15] we then wanted to verify if less than stoichiometric amounts of SIBX could be enough to lead the reaction to completion. The sulfoxidation of **1** using 0.5 equiv of SIBX proceeded initially quite rapidly but then seemed to stop. After four days, **2** was obtained in only 50% yield (Table 1, entry 8). Consequently, all subsequent reactions were run using 1 equiv of SIBX.

Several other sulfides were then oxidized under our optimized CTAB-induced reversed micellar conditions in dichloromethane–water (50:1) (Table 2). Methyl *p*-tolylsulfide (**3**) and diphenylsulfide (**5**) were rapidly converted into sulfoxides **4** and **6** in 82% and 84% yields (Table 2, entries 1 and 2). Oxidation of electron-poor sulfides such as **7** and **9** furnished sulfoxides **8** and **10** in 74% and 76% yields, but these reactions were much slower (Table 2, entries 3 and 4). Diphenyldisulfide (not shown) was refractory to any oxygenation. Also, SIBX expressed the same shift of chemoselectivity than that previously observed with IBX in the presence of catalytic amounts of $Et_4N^+Br^-$ in either dimethylsulfoxide–acetone or chloroform–water.[7] In our case, phenylthioethanol (**11**) was converted into the corresponding sulfoxide **12** in 91% yield in the reversed micellar system (Table 2, entry 5), whereas it furnished aldehyde **13** in quantitative yield in refluxing ethyl acetate (Table 2, entry 6).[11]

Asymmetric sulfoxidation has previously been accomplished by Kita and co-workers with moderate to good enantioselectivity (up to 72% ee) using the λ^5-iodane $PhIO_2$ (0.5 equiv) in a reversed micellar medium (i.e., toluene–water (50:1) plus 20 mol % CTAB) in the presence of 10 mol % of a chiral additive.[15] We were therefore curious to examine the ability of SIBX to perform such an asymmetric reaction under similar conditions. Thus, we first evaluated the potential of various chiral species to induce enantioselective oxidation of sulfide **3** (Table 3). Although the use of dichloromethane was shown to increase the sulfoxidation rate of **1** (Table 1, entry 4 vs 5), we chose to use the same solvent system as the one used by Kita and co-workers (i.e., toluene–water (50:1)) in this evaluation of chiral additives. The best one thus tested was the tartaric acid derivative **14** (i.e., di(2-methoxybenzoyl)-L-tartaric acid) that led to sulfoxide **4** in quantitative yield with a 28% ee in favor of the *S* enantiomer (Table 3, entry 7). This tartaric acid was also shown by Kita and co-workers as the most efficient inductor of asymmetry among the chiral species they used in concert with $PhIO_2$ as the oxygen source.[15] Interestingly, these authors postulated the in situ generation of some stereochemically-defined intermediate from $PhIO_2$ and **14** as the reactive species responsible for the observed asymmetric oxygenation event.[15] Such an intermediate could indeed conceivably be formed via nucleophilic addition of the carboxylic acid

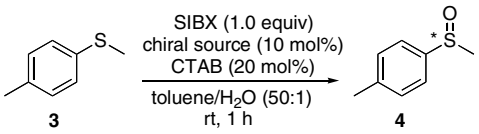
Table 2. SIBX-mediated sulfoxidation of various sulfides[a]



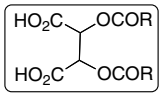
Entry	Substrate	Product	Time (h)	Yield[b] (%)
1	 **3**	 **4**	1	82
2	 **5**	 **6**	4	84
3	 **7**	 **8**	12	74
4	 **9**	 **10**	12	76
5	 **11**	 **12**	2	91
6		 **13**	8[c]	Quant.

[a] All reactions were run at rt using 1 mmol of sulfide in ca. 5 mL of solvent, unless otherwise noted.[18]
[b] Isolated yields.
[c] Reaction performed in refluxing EtOAc without CTAB.

Table 3. SIBX-mediated asymmetric sulfoxidation[a]

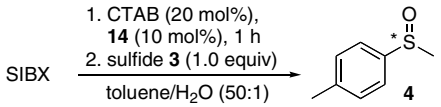


3 **4**

Entry	Chiral source	Yield[b] (%)	ee[c] (%)
1	(+)-10-Camphorsulfonic acid	90	0
2	*N*-FMOC-L-proline	Quant.	0
3	(+)-*cis*-Pinan-2-ol	Quant.	0
4	(*S*)-(+)-α-Methoxyphenyl-acetic acid	83	5 (*S*)
			
5	L-(−) R = 2,3,4-$(MeO)_3$Ph	Quant.	0
6	L-(−) R = 2,6-$(MeO)_2$Ph	Quant.	24 (*S*)
7	L-(−) R = 2-MeOPh (**14**)	Quant.	28 (*S*) 32 (*S*)[d]
8	D-(+) R = 2-MeOPh (**15**)	Quant.	22 (*R*) 19 (*R*)[e]

[a] All reactions were run at rt using 0.2 mmol of **3** in ca. 5 mL of solvent and 1 equiv of SIBX.
[b] Isolated yields.
[c] Enantiomeric excess determined by chiral HPLC using a Chiralcel ASH column, eluting with hexane–isopropanol (1:1) at a flow rate of 0.5 mL/min; t_R (*R*) = 21 min and t_R (*S*) = 30 min (UV detection at $\lambda = 254$ nm).
[d] Reaction performed using 1 equiv of IBX.
[e] Reaction performed using 1 equiv of **15**.

Table 4. Variation of the reaction temperature[a]



Entry	$T_{step\ 1}$ (°C)	$T_{step\ 2}$ (°C)	Time (h) step 2	Yield[b] (%)	ee[c] (%)
1	0	0	30	Quant.	5
2	−20	−20	48	Quant.	10
3	50	50	1	81	15
4	50	50→rt	1	Quant.	23
5	rt	rt	1	Quant.	28
6	rt	0	40	87	28
7	rt	10	20	97	37
8	0	0→rt	1	Quant.	40
9	10	10	24	Quant.	46
10	10	10[d]	24	81	50

[a] All reactions were run using 0.2 mmol of **3** in ca. 5 mL of solvent and 1 equiv of SIBX.
[b] Isolated yields.
[c] See Table 3.
[d] Sulfide **3** added as a solution in toluene (1 mL).

functions of **14** onto the electrophilic iodine(V) center of $PhIO_2$. The methoxy group of **14** might as well be engaged in an additional interaction with the highly coordinating iodine center, as proposed by Kita and co-workers,[15] but our attempts to exploit this possibility using di- or trimethoxylated analogues of **14** did not provide any stereochemical control improvements (Table 3, entries 5 and 6). Although such a coordination effect hence remains speculative, we still wondered if the aromatic carboxylic acids present in significant quantities in the SIBX formulation (vide supra)[10,11] could interfere with the formation of any stereochemically-defined reactive intermediate from IBX and **14**. This issue was addressed simply by repeating the reaction using standard IBX. No significant change of the enantiomeric excess of the sulfoxide product **4** was observed (Table 3, entry 7[d]). At this stage, it is thus not clear how the chiral source **14** manage to induce asymmetry in this SIBX-mediated sulfoxidation reaction, but what is certain is that the SIBX stabilizers do not cause any inconvenience and that a catalytic amount (10 mol %) of the chiral source is indeed sufficient. This was herein confirmed during reactions performed using di-(2-methoxybenzoyl)-D-tartaric acid (**15**). Adding a stoichiometric amount of this optical antipode of **14** did not improve the expected excess of the *R* enantiomer of **4** (Table 3, entry 8[e]).

A last series of experiments was then carried out with the aim of improving the enantioselectivity of the reaction, notably by examining the influence of the reaction temperature (Table 4). Furthermore, the fact that a substoichiometric amount of the chiral source is enough to induce some asymmetry gives credit to the possibility of an in situ formation of a key reacting intermediate generated from IBX and the acid tartaric-based chiral source. This additive would be released and recycled as the reaction progresses with the concomitant reduction of IBX into IBA and then eventually to 2-iodobenzoic acid. Hence, we decided to let systematically SIBX and the chiral source **14** mix for 1 h in the reversed micellar solvent system to allow the formation of any stereochemically-relevant species (step 1) before adding the starting sulfide **3** (step 2). The results gathered in Table 4 show that performing both steps at or below 0 °C slows down considerably the reaction without any increase of its enantioselectivity (entries 1 and 2). Increasing the temperature to 50 °C was also detrimental to the stereoselectivity of the reaction (entries 3 and 4). The best experimental conditions were obtained by carrying out both steps of the reaction at 10 °C, and by letting the sulfoxidation run for 24 h. Excellent chemical yields and enantiomeric excesses up to 50% were thus achieved (entries 9 and 10).

In conclusion, IBX can be replaced by SIBX to oxidize rapidly and safely sulfides into sulfoxides in reversed micellar solvent systems without any overoxidation into sulfones. Asymmetric sulfoxidation can also be performed under such conditions with moderate enantioselectivity (up to 50% ee) in the presence of catalytic amounts of a tartaric acid-based chiral source. A detailed mechanistic description of the reaction and its stereochemical control cannot be provided at this time, because of the difficulty to obtain sound structural data on the SIBX-derived species reacting in this micellar system. Nevertheless, the reaction described herein is operational and constitutes a safe and efficient method for selective oxidation of sulfides into sulfoxides.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.06.072.

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18. *Typical procedure for the SIBX-mediated oxidation of sulfides.* To a stirred yellow suspension of SIBX (600 mg, 49% IBX by weight, that is, 1.05 mmol of IBX) and CTAB (0.2 mmol, 20 mol %) in CH_2Cl_2 (5 mL) and H_2O (0.1 mL) was added the starting sulfide (1 mmol). This reaction mixture was stirred at rt for the indicated time (see Table 2), and then poured over EtOAc (20 mL), washed by an aqueous saturated solution of $NaHCO_3$ (3×5 mL) and brine (5 mL), dried over Na_2SO_4, filtered, and evaporated to furnish the corresponding sulfoxide (see Table 2).