An effective and catalytic oxidation using recyclable fluorous IBX†

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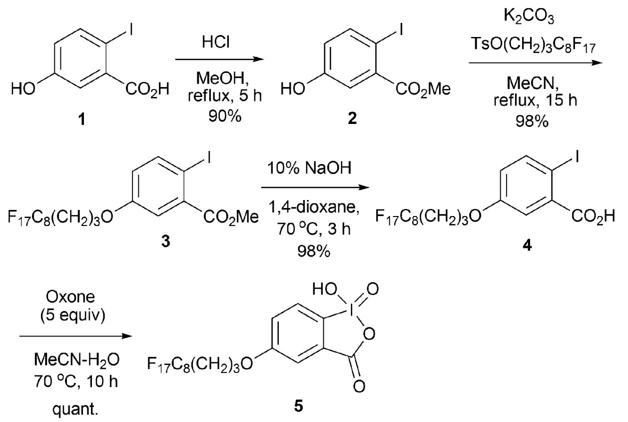
Oxidation of alcohols in the presence of a catalytic amount of fluorous IBX and Oxone as a co-oxidant resulted in the corresponding carbonyl compounds in good to high yields. The fluorous IBX is readily recovered as insoluble fluorous IBA from the reaction mixture by simple filtration, and can be reused without significant loss of the catalytic activity.

o-Iodoxybenzoic acid (IBX) as a hypervalent iodine compound has attracted a great deal of attention in organic synthesis since its synthetic utility as an oxidant was reported by Frigerio and Santagostino in 1994,[1] because IBX is a mild, selective, metal-free, and non-toxic oxidation reagent.[2] However, IBX is a potentially shock- or heat-sensitive explosive compound,[3] and must be used in DMSO due to its insolubility in common organic solvents.[1] Also, 2-iodosobenzoic acid (IBA), a waste product from the oxidations of IBX, often makes it difficult to separate the desired products from the reaction mixture. To resolve these issues, modified IBX,[4] with reduced explosive property that can be used in common solvents, and polymer support IBX,[5] which can be easily separated from the desired products, have been reported. In addition, oxidation with catalytic IBX and 2-iodoxybenzenesulfonic acid (IBS), that are generated *in situ* from 2-iodobenzoic acid and 2-iodobenzenesulfonic acid in the presence of Oxone, has also been reported.[6,7] Oxone also is an environmentally safe reagent, and offers several significant advantages such as stability, easy of transport, simple handling, controllable addition, and nontoxic nature.[6a,7]

From a view point of green chemistry, development of a metal-free process has been focused and a variety of organocatalysts, including IBX, have been developed.[8] Along with this, recovery of organocatalysts from the reaction mixture and its recycling are highly desired, as most organocatalysts are expensive and require more steps for synthesis. The fluorous tag technique by fluorous solid-phase or fluorous–organic solvent extraction is one of a recycling method, and many groups have attempted recyclable reactions.[9,10] Oxidation of alcohols and phenols with fluorous hypervalent iodines also have been reported.[11] Furthermore, several groups have reported recovery of catalyst with a fluorous tag only by filtration due to its insolubility.[12] This method is a better protocol, which can recover without using expensive fluorous solvents and fluorous silica gel.

With these perspectives, in order to recover and reuse IBA as a waste, we have attempted the development of a novel hypervalent iodine organocatalyst with a fluorous tag, fluorous IBX. We describe a catalytic oxidation using reusable fluorous IBX in the presence of Oxone as a co-oxidant and Bu_4NHSO_4 as a phase-transfer catalyst in this report.



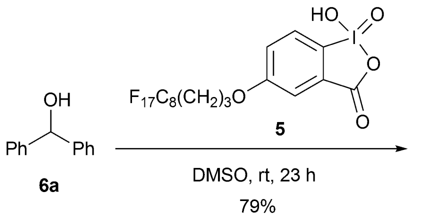
Scheme 1 Preparation of fluorous 2-iodobenzoic acid and fluorous IBX.

The fluorous iodobenzoic acid **4** and fluorous IBX **5** we designed are prepared as shown in Scheme 1. Treatment of 5-hydroxy-2-iodobenzoic acid (**1**) with hydrochloric acid in methanol affords methyl ester **2** in 90% yield. Ester **2** is coupled with the fluorous tosylate in the presence of potassium carbonate in acetonitrile to give the fluorous benzoate **3** in 98% yield. Fluorous IBX **5** is obtained in quantitative yield by treatment of **4** with Oxone after hydrolysis of **3**.

First, we examined the activity of **5** for oxidation of alcohol, and found that it smoothly oxidized alcohol **6a** to the corresponding ketone **7a** in 79% yield (Scheme 2).

Next, we studied the catalytic oxidation with **5** generated *in situ* from fluorous iodobenzoic acid **4** as a pre-catalyst in the presence of Oxone. We optimized the reaction conditions for the oxidation, and found that a better result was obtained with a catalytic amount of Bu_4NHSO_4 in the nitromethane/water solvent system (Table 1).[6b]

Table 2 shows the scope and limitation of the oxidation with various alcohols (**6a–6k**) under the optimized reaction



Scheme 2 Oxidation using fluorous IBX.

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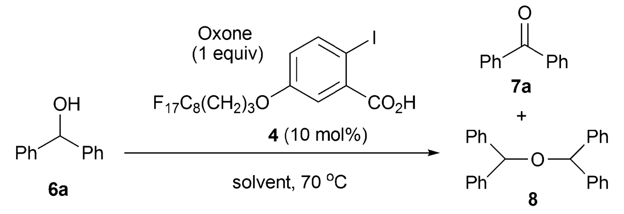
Table 1 Optimization of reaction conditions



Entry	Solvent	Time/h	Yield[a] (%) 7a	8	6a[b]
1	DMSO	60	5[c]	8[c]	70[c]
2	H_2O	78	23[c]	16[c]	38[c]
3	EtOAc	60	30[c]	20[c]	36[c]
4	1,4-Dioxane	71	38	0	60
5	MeCN	34	44	35	0
6	$MeNO_2$	81	59	37	4
7[d]	$MeNO_2$–H_2O	8	88	0	0
8[d,e]	$MeNO_2$–H_2O	12	99	0	0

[a] Isolated yield. [b] Recovered yields of starting material **6a**. [c] Determined by ^1H NMR. [d] Bu_4NHSO_4 (0.1 equiv.) was added. [e] Fluorous IBX **5** was used as the catalyst instead of **4**.

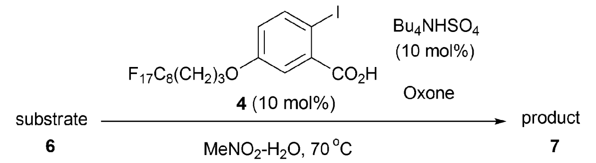
condition as mentioned above.[13] Secondary alcohols are smoothly oxidized by the catalytic oxidative system to afford the corresponding ketones in good to high yields (entries 1–5). Aliphatic primary alcohols also are oxidized to the corresponding carboxylic acids in high yields (entries 6–8). On the other hand, a variety of benzylic alcohols are converted to the corresponding aldehydes in moderate to high yields (entries 9–11).[6b]

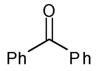
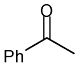
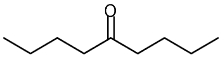
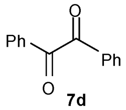
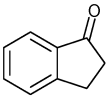
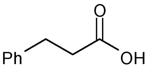
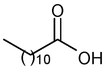
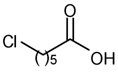
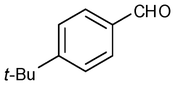
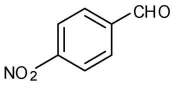
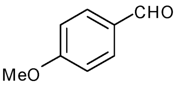
The second objective of our project is recovery of fluorous IBA **9**, a precursor of **5**. Fortunately, the recovery of **9**[14] could be carried out only by filtration (65–100%) from the reaction mixture, not by the fluorous solid phase and fluorous–organic solvent extraction technique, due to its insolubility. In each reuse, the recovered **5**, without further purification, retains its catalytic activity for five cycles (Table 3).

Although the structure of **9** could not be identified by NMR measurement due to its insolubility in any organic solvents and water, we could detect **9** by high resolution mass spectra. Therefore, we assume that this reaction with **5** proceeds in a similar manner to those of the catalytic IBX oxidations (Scheme 3).[6,7] Fluorous iodobenzoic acid **4** is converted to **5**, active species of oxidizing alcohol, by oxidation with tetra-*n*-butylammonium oxone through **9**. Fluorous IBX **5** is regenerated by re-oxidation with tetra-*n*-butylammonium oxone.

In conclusion, novel fluorous IBX **5**, generated *in situ* from pre-catalyst **4**, efficiently works as a catalyst for oxidation of various alcohols to the corresponding carbonyl compounds in good to high yields. The organocatalyst **5** can be regenerated *in situ* from fluorous IBA **9**, which is readily recovered only by simple filtration, in the presence of Oxone. The catalytic activity of **5**, regenerated from recovered **9**, does not change significantly up to five times. Further application to the other oxidation is currently in progress in our laboratory.

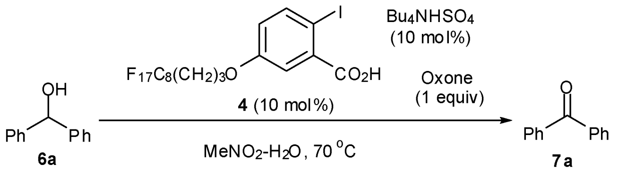
Table 2 Oxidation of alcohols using fluorous organocatalyst



Entry	Product	Oxone (equiv.)	Time/h	Yield[a] (%)
1	 **7a**	1	8	88
2	 **7b**	1	10	75
3	 **7c**	1	24	78
4[b]	 **7d**	2	20	84
5	 **7e**	1	12	70[c]
6	 **7f**	1.5	8	92
7[b]	 **7g**	1.5	12	91
8	 **7h**	1.5	12	92
9[d,e]	 **7i**	1	20	77
10[d]	 **7j**	1	12	86
11[d]	 **7k**	1	4	49[f]

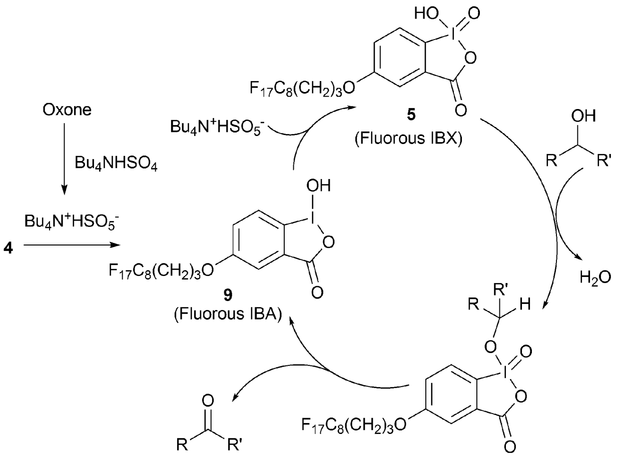
[a] Isolated yield. [b] 0.2 equiv. of catalyst **4** was used. [c] Determined by ^1H NMR. [d] $MeNO_2$ was used as the reaction solvent. [e] Bu_4NHSO_4 was not added. [f] *p*-Methoxybenzyl alcohol (**6k**) was recovered in 36% yield.

Table 3 Recycling and reuse of the fluorous catalyst by filtration



Entry	Time/h	Yield[a] (%)	Cat. recovery[b]
Initial	9	83	100
First reuse	9	82	100
Second reuse	9	91	100
Third reuse	9	95	84
Fourth reuse	10	94	91
Fifth reuse	10	88	65

[a] Isolated yield. [b] Determined by weight of recovered fluorous IBA (**9**).



Scheme 3 Plausible mechanism of catalytic oxidation using fluorous IBX.

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13 A typical procedure of oxidation using fluorous organocatalyst **4** is as follows: to a colorless solution of diphenylmethanol (**6a**, 100 mg, 0.543 mmol) and the organocatalyst **4** (39.3 mg, 0.054 mmol) in $MeNO_2$ (1.6 mL) and H_2O (0.6 mL) were added Oxone (334 mg, 0.543 mmol) and Bu_4NHSO_4 (18.4 mg, 0.054 mmol) at room temperature. The reaction mixture was stirred at 70 °C for 8 h, and then cooled to room temperature. The precipitated fluorous IBA (**9**) was filtered, and washed with water and ether. The collected **9** was dried *in vacuo*, and was used in the next step without further purification. The filtrate was extracted three times with EtOAc. The EtOAc layers were combined, washed with brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by flash column chromatography on silica gel with a 5 : 1 mixture of hexane and EtOAc to afford pure benzophenone (**7a**, 86.4 mg, 87%).

14 Fluorous IBA (**9**) did not have the oxidative activity. Only 5% of benzophenone (**7a**) was given when using a stoichiometric amount of **9** in the presence of Bu_4NHSO_4 (0.1 equiv.) in $MeNO_2$–H_2O at 70 °C for 8 h.