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Hypervalent iodine(III)/$Et_4N^+Br^-$ combination in water for green and racemization-free aqueous oxidation of alcohols

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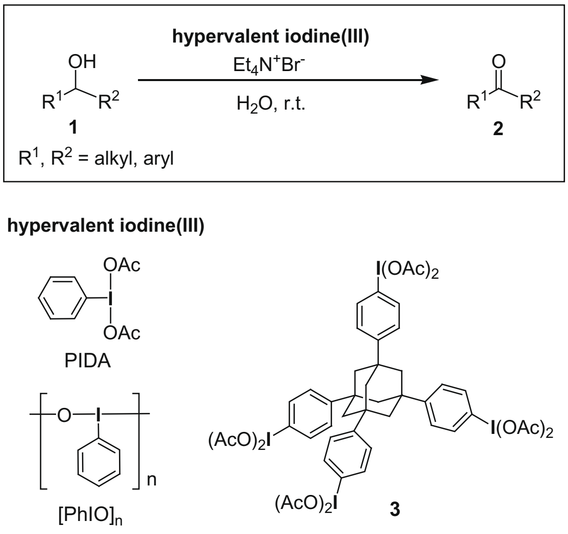
ABSTRACT

We have found that the use of the $PhI(OAc)_2/Et_4N^+Br^-$ combination *in water* can significantly enhance its oxidation ability and oxidize a wide range of alcohols **1** to carbonyl compounds **2** in good to excellent yields. This clean aqueous oxidation method shows no detectable racemization processes, and even an enolizable ketone **2m** could be obtained in an optically pure form from the corresponding chiral alcohol **1m**. Utilization of the recyclable reagent **3** as a more practical alternative to $PhI(OAc)_2$ is also successful in these reactions.

The oxidation of alcohols to carbonyl compounds is one of the pivotal transformations in the area of organic synthesis.[1] In view of the recent strong demand for establishing greener synthetic processes,[2] the aqueous-phase oxidation of alcohols has been extensively studied these days,[3] as it surely reduces environmental and economical issues caused by the use of organic solvents as the reaction media.

Hypervalent iodine reagents are now widely accepted as a promising synthetic tool for the development of environmentally benign oxidations due to their mild reactivities, low toxicity, safety, ready availability, easy handling, etc.[4] Both iodine(V) and iodine(III) compounds have been successfully utilized for alcohol oxidations in organic solvents such as DMSO, CH_2Cl_2, and acetone, and have already been applied in the key synthetic steps of natural products and other related complex molecules.[5] However, examples of the effective oxidation of alcohols *in water* are rather limited[6–8] because the solubilities and reactivities of the organoiodine compounds are quite low in water. To overcome this problem, we have previously reported that the activation of iodosobenzene ($[PhIO]_n$) or phenyliodine diacetate ($PhI(OAc)_2$, PIDA) by metal bromides, that is, potassium bromide (KBr), in water is a solution that enhances the solubilities and reactivities of the hypervalent iodine reagents in aqueous alcohol oxidations.[6] As part of our study, we now report the practical metal-free aqueous oxidation of alcohols with the combination of the trivalent iodine reagents and tetraethylammonium bromide ($Et_4N^+Br^-$) (Scheme 1). The selection of $Et_4N^+Br^-$ would suppress the undesired racemization processes caused by the metal bromides, and would allow the efficient utilization of the recyclable iodine reagent **3**[9] during the aqueous reaction.

The PIDA/tetraalkylammonium bromides combination is known to induce the oxidation of benzyl alcohols in CH_2Cl_2, but the method is not broadly applicable for the oxidation of aliphatic alcohols such as cyclohexanol **1a**.[10]



Scheme 1. Aqueous alcohol oxidation with the combination of hypervalent iodine(III) and $Et_4N^+Br^-$.

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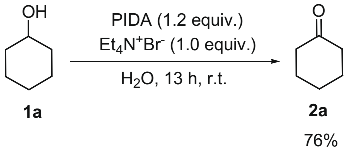
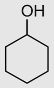
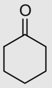
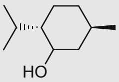
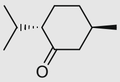
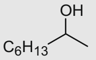
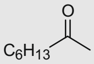
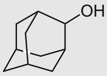
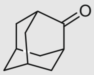
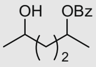
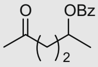
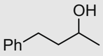
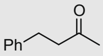
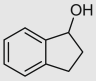
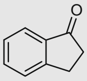
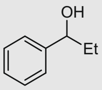
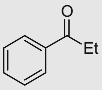
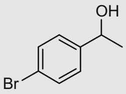
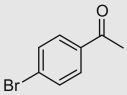
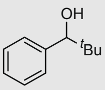
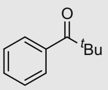
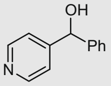
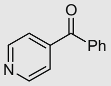
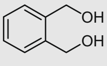
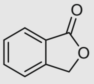


(1)

We have now determined that the reactivity of the PIDA/ammonium bromides is significantly enhanced in water, and the aqueous oxidation of an aliphatic alcohol **1a** to the corresponding ketone **2a** could smoothly occur at room temperature (Eq. 1). In this oxidation, the effect of water is remarkable, and the oxidation of **1a** did not effectively proceed in organic solvents.

Table 1
Aqueous oxidation with the combination of PIDA and $Et_4N^+Br^-$[a]

Entry	Substrate	Product	Yield[b] (%), time (h)
1	 **1a**	 **2a**	76, 13
2	 **1b**	 **2b**	72, 4
3	 **1c**	 **2c**	90, 4
4	 **1d**	 **2d**	90, 6
5	 **1e**	 **2e**	89,[c] 5
6	 **1f**	 **2f**	81, 6
7	 **1g**	 **2g**	77,[c] 4
8	 **1h**	 **2h**	84, 4
9	 **1i**	 **2i**	78, 8 75,[c] 8
10	 **1j**	 **2j**	88, 3
11	 **1k**	 **2k**	75, 12
12[d]	 **1l**	 **2l**	66,[c] 9

[a] Reactions were performed using PIDA (1.2 equiv) and $Et_4N^+Br^-$ (1.0 equiv) in H_2O (0.1 M) at room temperature unless otherwise noted.
[b] GC yield.
[c] Isolated yield after purification.
[d] 2.5 equiv of PIDA was used.

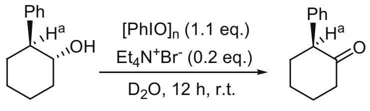
As the ammonium bromides, we chose $Et_4N^+Br^-$ because of the several following reasons: it is not only readily available and low-cost, but also easily removable from the product mixture after the reactions. Indeed, the separation of $Et_4N^+Br^-$ from the product **2a** could be easily attained by a simple workup (AcOEt or CH_2Cl_2 extraction),[11] taking advantages of the unique high partition coefficient of $Et_4N^+Br^-$ to water at ambient temperature.[12]

To confirm the scope of the aqueous system, we next examined the reactions using several types of alcohols, and the results are summarized in Table 1. The aliphatic secondary alcohols **1a**–**f** generally afforded the corresponding ketones **2a**–**f** in good to excellent yields (entries 1–6). The yields of **2c**–**f** were higher than the results in cyclohexanol **1a** and a sterically hindered alcohol **1b**. In an ester **1e**, no hydrolysis of **1e** and the product **2e** was observed (entry 5). Furthermore, benzyl alcohols **1g**–**k** also gave the aryl ketones **2g**–**k** in good yields (entries 7–11). Due to the mild reaction nature of the present system, a nitrogen atom containing substrate **1k** was applicable for the reactions (entry 11). Unfortunately, when we tried to perform the oxidation of primary alcohols under the same reaction conditions, the formation of small amounts of ester products was detected by GC analysis as a result of the oxidative condensation between two molecules of the starting primary alcohols.[13] An intramolecular fashion of this type of condensation rapidly occurred in the diol **1l** to exclusively produce the corresponding five-membered lactone **2l** in a good yield (entry 12).

The important synthetic merit of the present method is featured in the case of the oxidation of an optically active alcohol **1m** (Scheme 2). The chiral alcohol **1m** is a challenging substrate, which produces an enolizable α-aryl ketone **2m** as a result of the oxidation. With the $[PhIO]_n/Et_4N^+Br^-$ combination,[14] the oxidation of an alcohol **1m** could proceed in a good yield and notably, the optical activity of the ketone **2** was well maintained throughout the reaction. We have clarified the racemization-free evidence by confirming the no in situ H/D exchange of deuterium at the acidic α-position of the resulting α-aryl ketone **2m** based on ^1H NMR and GC–Mass analyses. In contrast, the use of KBr[6] instead of $Et_4N^+Br^-$ was found to somewhat reduce the ee value of **2m** (85% yield and 73% ee), indicating that even the weak Lewis acidity of the potassium ion is enough to cause the undesired enolization process of the α-aryl ketone **2m** in water. The racemization-free oxidation of **1m** to **2m** was also difficult using the metal-catalyzed aqueous oxidation strategy such as $Na_2WO_4/[(C_8H_{17})_3NMe]^+HSO_4^-$ in 30% H_2O_2 aq.[3a,3b]

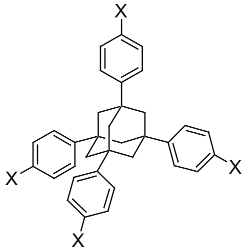
In the present iodine(III)-mediated oxidation method, iodobenzene (PhI) was typically co-produced together with the desired oxidation products **2**. This forces the removal of the organic contaminant from the products **2** by tedious chromatographic workup. To make the purification step simpler, we therefore planned to apply a recyclable hypervalent iodine(III) reagent as a useful alternative to PIDA or $[PhIO]_n$. The use of 1,3,5,7-tetrakis[4-(diacetoxyiodo)phenyl]adamantane **3** (Fig. 1), a recyclable iodine(III) reagent developed by us,[9] met this purpose, and ketones **2** were obtained by a simpler experimental operation (see below). Typically, the recyclable reagent **3** could afford the ketones **2** in better yields than PIDA, except for the alcohols **1c** and **1j** (Table 2).

In all the experiments listed in Table 2, the reagent **3** could easily be removed from the reaction mixtures by simple filtration,



1m **2m**
83%, >98% ee
($H^a/D \geqq 100$)

Scheme 2. Recemization-free oxidation of an optically active alcohol **1m**.



3 : X = I(OAc)$_2$
4 : X = I

Figure 1. Adamantane-type recyclable hypervalent iodine(III) reagent.

Table 2
Reactions using a recyclable iodine(III) reagent **3**[a]

Entry	Substrate	Product	Yield (%), time (h)
1	**1a**	**2a**	99, 4
2	**1c**	**2c**	88, 18
3[b]	**1e**	**2e**	99, 2
4	**1g**	**2g**	99, 4
5	**1h**	**2h**	91, 5
6	**1j**	**2j**	82, 3
7[c,d]	**1l**	**2l**	97, 24

[a] Reactions were performed using **3** (1.1 × 1/4 equiv) and $Et_4N^+Br^-$ (0.5 equiv) in H_2O (0.1 M) at room temperature. The reagent **3** was recovered as its reduced form **4** in over 95% yields by filtration.

[b] 0.2 equiv of $Et_4N^+Br^-$ was used.

[c] 2.0 × 1/4 equiv of **3** was used.

[d] 1.0 equiv of $Et_4N^+Br^-$ was used.

utilizing the insolubility of the co-produced tetraiodide **4** in water and methanol. Thus, after completion of the reactions, saturated $NaHCO_3$ aq and methanol were added to the reaction mixtures. The resulting precipitates involving **4** were collected by filtration and the residues were washed several times with small portions of methanol. With this operation, the reagent **4** could be removed from the mixtures in at least 95% recovered yields, which could be reoxidized to the initial form **3** in nearly quantitative yields by the treatment with *m*-chloroperbenzoic acid (*m*CPBA).[9] On the other hand, the crude products **2** could be obtained from the filtrates by extraction with AcOEt or CH_2Cl_2 and by evaporation of the solvents. Isolation of the pure **2** could be easily achieved by short column chromatography on silica gel.

Another merit of choosing $Et_4N^+Br^-$ instead of KBr[6] is the fact that the former bromide source exhibits superior performance when using the recyclable reagent **3**. $Et_4N^+Br^-$ is not only an effective bromide source, but also works as a phase transfer catalyst permitting the high reactivity of the water-insoluble reagent **3** in water. For example, the oxidation of **1a** with the recyclable reagent **3** and KBr (0.5 equiv) required a longer reaction time to reach the high conversion of the alcohol **1a** (24 h, 76% yield) compared to that using the same amount of $Et_4N^+Br^-$ (Table 2, entry 1). This result also implies that the use of $Et_4N^+Br^-$ enables the utilization of a variety of alternative reagents, and will potentially contribute to the development of new and green aqueous-phase oxidations.

In summary, we have demonstrated the facile and green aqueous oxidation of alcohols **1** to ketones **2** using the combination of hypervalent iodine(III) reagents and $Et_4N^+Br^-$. The present system showed a broad generality of the substrates **1** including the aliphatic alcohols. The choice of $Et_4N^+Br^-$ is indispensable for the successful reaction progress and suppression of the undesired racemization process of the enolizable α-aryl ketone product **2m**. In addition, effective utilization of the recyclable hypervalent iodine(III) reagent **3** is possible when using $Et_4N^+Br^-$ as the bromide source, enhancing the practicability of the aqueous method. Further investigations on the scope of the functional group compatibility and availability of chiral compounds will lead to application of the method to more complex molecules such as natural products.

Acknowledgments

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11. *Typical experimental procedure in* Table 1: To a suspension of **1e** (33.3 mg, 0.150 mmol) in H_2O (1.50 mL) were added PIDA (58.0 mg, 0.180 mmol) and $Et_4N^+Br^-$ (31.5 mg, 0.150 mmol). The mixture was then stirred for 5 h at room temperature. AcOEt and solid sodium thiosulfate were successively added to the reaction mixture. After stirring for 5 min, the organic layer was separated, dried with Na_2SO_4, and evaporated to remove the solvent. Purification of the residue by column chromatography on silica gel gave **2e** (29.5 mg, 0.134 mmol) in 89% yield.
12. It is known that the concentration of $Et_4N^+Br^-$ in the same volume of CH_2Cl_2 and water is in the ratio of 1/10,000: Pradines, V.; Despoux, S.; Claparols, C.; Martins, N.; Micheau, J.-C.; Lavabre, D.; Pimienta, V. *J. Phys. Org. Chem.* **2006**, *19*, 350.
13. Direct oxidative esterification of alcohols, see: Tohma, H.; Maegawa, T.; Kita, Y. *Synlett* **2003**, 723. and references cited therein.
14. The use of PIDA caused partial racemization of **2m** (3 h, 85% yield and 83% ee), probably due to the in situ released acetic acid.