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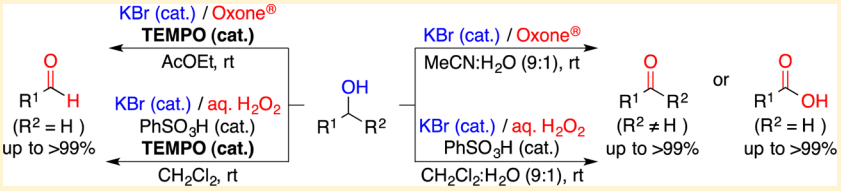
Selective Oxidation of Alcohols with Alkali Metal Bromides as Bromide Catalysts: Experimental Study of the Reaction Mechanism

Katsuhiko Moriyama,* Misato Takemura, and Hideo Togo*

Department of Chemistry, Graduate School of Science, Chiba University, 1-33 Yayoi-cho, Inage-ku, Chiba 263-8522, Japan

Supporting Information



ABSTRACT: A bromide-catalyzed oxidation of alcohols was developed which proceeded in the presence of an alkali metal bromide and an oxidant under mild conditions. The reaction involved an organic-molecule-free oxidation using KBr and Oxone and a Brønsted acid assisted oxidation using KBr and aqueous H_2O_2 solution to provide a broad range of carbonyl compounds in high yields. Moreover, the bromide-catalyzed oxidation of primary alcohols enabled the divergent synthesis of carboxylic acids and aldehydes under both reaction conditions in the presence of TEMPO. A possible catalytic mechanism was suggested on the basis of various mechanistic studies.

INTRODUCTION

The umpolung-based oxidative transformation of halides (I^-, Br^-, and Cl^-) into halonium ions (X^+) by oxidants is a very important tool for the biosynthesis of natural products[1] and has attracted much attention as a green sustainable method that is expected to replace heavy metal reactions in modern organic synthesis.[2] As the oxidation of halides is catalyzed by haloperoxidases in many organisms,[3] the potential of oxidative transformation through the oxidation of halides should be examined to develop biomimetic processes. As one of the most abundant natural resources on earth, alkali metal halides are stable in air, easy to handle, neutral, and nontoxic, and elaboration of the products does not pollute the environment. We have developed ingenious transformations involving the oxidation of alkali metal halides.[4] Nevertheless, alkali metal halide catalyzed oxidative transformation has not been established and remains a daunting challenge in organic chemistry. On the other hand, the catalytic oxidation of alcohols is one of the economically important transformations that provide corresponding carbonyl compounds.[5]

Recently, the catalytic oxidation of alcohols was accomplished by using numerous transition metal catalysts[6] and organocatalysts.[7,8] The halogen reagent catalyzed oxidation of alcohols typically requires toxic reagents, such as Br_2 and HBr.[9] Moreover, the use of alkali metal halides for oxidation has also been reported.[10,11] However, this method requires organic oxidants such as hypervalent iodines, which produce a stoichiometric amount of the corresponding organic waste, or shows a limitation of substrate versatility and lower chemoselectivity. In addition, oxidations with halogen reagents and alkali metal halides cannot be used for the divergent synthesis of carboxylic acids and aldehydes from primary alcohols. We report herein a halide-catalyzed selective oxidation of alcohols, which involves the oxidation of an alkali metal halide with an oxidant under mild conditions, as a biomimetic method for the realization of a green sustainable process (Figure 1).

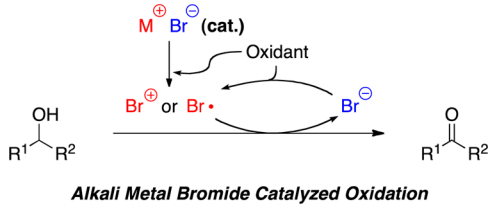


Figure 1. Alkali metal bromide catalyzed oxidation of alcohols with aqueous hydrogen peroxide.

RESULTS AND DISCUSSION

First, we screened for solvents, metal bromides, and oxidants for the bromide-catalyzed oxidation of 5-nonanol (**1a**) (Table 1).

Treatment of **1a** with KBr (10 mol %) and Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) (1.0 equiv) in MeCN at room temperature gave **2a** in 89% yield (entry 1). Whereas the reaction in AcOEt showed reactivity similar to that in MeCN, the reactions in THF, $MeNO_2$, and CH_2Cl_2 gave low yields of **2a** (entries 2−5). NaBr was an effective bromo source for the oxidation of **1a**, whereas $CaBr_2$ was much less effective than alkali metal bromides (entries 6 and 7). Other oxidants, such as H_2O_2, *t*-BuOOH (TBHP), and *t*-BuOCl, were much less effective than

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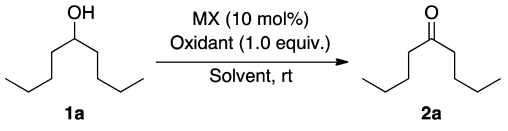
Table 1. Screening for Metal Halides, Oxidants, and Solvent for Alkali Metal Halide Catalyzed Oxidation of 1a



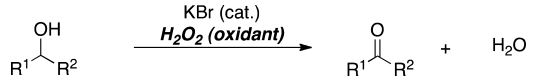
entry	MX	oxidant	solvent	time (h)	yield (%)[a]
1	KBr	Oxone	MeCN	5	89
2	KBr	Oxone	AcOEt	7	86
3	KBr	Oxone	THF	24	25 (51)
4	KBr	Oxone	$MeNO_2$	5	68
5	KBr	Oxone	CH_2Cl_2	10	70
6	NaBr	Oxone	MeCN	7	80
7	$CaBr_2$	Oxone	MeCN	5	69
8	KBr	H_2O_2	MeCN	24	0 (>99)
9	KBr	TBHP	MeCN	24	5 (93)
10	KBr	*t*-BuOCl	MeCN	24	45 (33)
11	KCl	Oxone	MeCN	24	53 (36)
12	KI	Oxone	MeCN	24	0 (>99)
13	KBr	Oxone	MeCN/H_2O (9/1)	2	>99
14	-	Oxone	MeCN	24	0 (>99)

[a]Values in parentheses indicate the recovery of **1a**.

Oxone (entries 8−10). Use of KCl and KI instead of KBr decreased the yields of **2a** (entries 11 and 12). The addition of H_2O to MeCN promoted the oxidation of **1a** to give **2a** in a quantitative yield (entry 13). The oxidation of **1a** did not proceed in the absence of KBr (entry 14).

On the other hand, the use of aqueous hydrogen peroxide as an oxidant is the most attractive for various oxidations because it has higher atom economy and is milder than the other oxidants, producing only water as the byproduct of an organic reaction. Thus, we attempted to perform an atom-economical bromide-catalyzed oxidation of alcohols by using aqueous hydrogen peroxide as the oxidant (Scheme 1).

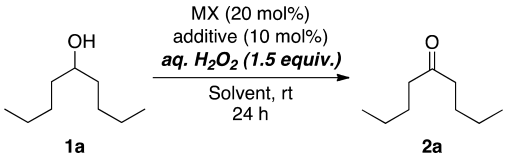
Scheme 1. Alkali Metal Bromide Catalyzed Oxidation of Alcohols with Aqueous H_2O_2 as Oxidant



In our previous work, we showed that hydrogen peroxide was ineffective for alkali metal bromide based oxidations (Table 1, entry 8).[4] Therefore, the bromide-catalyzed oxidation of 5-nonanol (**1a**) in the presence of an additive, such as a Brønsted acid, was examined by using aqueous hydrogen peroxide as the oxidant (Table 2).

The addition of a catalytic amount of $PhSO_3H$ (10 mol %) to a mixture of KBr (20 mol %) and aqueous H_2O_2 (1.5 equiv) in MeCN and H_2O (9/1) at room temperature furnished 5-nonanone (**2a**) in 23% yield (entry 1). The reaction in CH_2Cl_2 instead of MeCN provided **2a** in 97% yield (entry 3), whereas the reaction in AcOEt showed reactivity similar to that in MeCN (entry 2). Both an increase and a decrease in the amount of H_2O in CH_2Cl_2 reduced the yield of **2a** (entries 4 and 5). LiBr, NaBr, and $CaBr_2$ were effective bromo sources for the oxidation of **1a**, whereas the use of KCl and KI did not give any product (entries 6−10). Other Brønsted acids, such as $MeSO_3H$, $(PhO)_2P(O)OH$, *p*-NO_2-$C_6H_4SO_3H$, CF_3CO_2H, and $PhCO_2H$, were much less effective than $PhSO_3H$ (entries

Table 2. Screening for Metal Bromides, Additives, and Solvents for Alkali Metal Halide Catalyzed Oxidation of 1a with Aqueous H_2O_2 as Oxidant



entry	MX	additive	solvent	yield (%)[a]
1	KBr	$PhSO_3H$	MeCN/H_2O (9/1)	23 (70)
2	KBr	$PhSO_3H$	AcOEt/H_2O (9/1)	35 (64)
3	KBr	$PhSO_3H$	CH_2Cl_2:H_2O (9/1)	97
4	KBr	$PhSO_3H$	CH_2Cl_2/H_2O (4/1)	64 (27)
5	KBr	$PhSO_3H$	CH_2Cl_2/H_2O (19/1)	81
6	LiBr	$PhSO_3H$	CH_2Cl_2/H_2O (9/1)	92
7	NaBr	$PhSO_3H$	CH_2Cl_2/H_2O (9/1)	93
8[b]	$CaBr_2$	$PhSO_3H$	CH_2Cl_2/H_2O (9/1)	89
9	KCl	$PhSO_3H$	CH_2Cl_2/H_2O (9/1)	0 (>99)
10	KI	$PhSO_3H$	CH_2Cl_2/H_2O (9/1)	0 (97)
11	KBr	$MeSO_3H$	CH_2Cl_2/H_2O (9/1)	89
12	KBr	$(PhO)_2P(O)OH$	CH_2Cl_2/H_2O (9:1)	3 (87)
13	KBr	*p*-NO_2-$C_6H_4SO_3H$	CH_2Cl_2:H_2O (9/1)	80
14	KBr	CF_3CO_2H	CH_2Cl_2/H_2O (9/1)	82
15	KBr	$PhCO_2H$	CH_2Cl_2/H_2O (9/1)	1 (94)
16[c]	KBr	$PhSO_3H$	CH_2Cl_2/H_2O (9/1)	59 (41)
17		$PhSO_3H$	CH_2Cl_2/H_2O (9/1)	0 (>99)
18	KBr		CH_2Cl_2/H_2O (9/1)	0 (>99)

[a]Values in parentheses indicate the recovery of **1a**. [b]$CaBr_2$ (10 mol %) was used. [c]KBr (10 mol %) was used.

11−15). Decreasing the amount of KBr (10 mol %) did not promote the oxidation of **1a** (entry 16). The oxidation did not proceed in the absence of KBr or $PhSO_3H$ (entries 17 and 18).

To explore the scope of the alkali metal bromide catalyzed oxidation of alcohols, various secondary alcohols **1** and primary alcohols **3** were examined under the optimum conditions for the organic-molecule-free oxidation using Oxone (method A) and the catalytic Brønsted acid assisted oxidation using hydrogen peroxide (method B), respectively (Table 3). When 1-arylethanols bearing 4-Me (**1b**), 4-Cl (**1c**), 4-NO_2 (**1d**), 3-Cl (**1e**), and 2-Cl (**1f**) groups on the aromatic ring were used under both conditions, aryl methyl ketones **2b−f** were obtained in excellent yields (86 to >99%) (entries 1−5). The reaction of benzyl alcohols bearing various alkyl or aryl groups at the α position, such as Et (**1g**), *i*-Pr (**1h**), *t*-Bu (**1i**), and Ph (**1j**), also gave the corresponding ketones **2g−j** in excellent yields (96 to >99%) (entries 6−9). In contrast to the organic-molecule-free oxidation using Oxone (method A) of 1-tetralol (**1k**) that provided 1-tetralone (**2k**) in 89% yield, the Brønsted acid-assisted oxidation using aqueous H_2O_2 (method B) did not proceed at all (entry 10). The reaction of aliphatic alcohols, such as 2-octanol (**1l**), cyclododecanol (**1m**), 4-*tert*-butylcyclohexanol (**1n**), (−)-menthol (**1o**), and β-cholestanol (**1p**), under method A conditions also occurred to give the corresponding ketones **2l−p** in high yields (62 to >99%) (entries 11−15, method A). However, method B conditions were much less effective than method A conditions for the transformation of **1** into **2** (entries 13−15, method B). Bulky aliphatic alcohols **1q,r** were also oxidized under both conditions to give the desired ketones **2q,r** in high yields (78−98%), respectively (entries 16 and 17). Furthermore, the same treatment of various alcohols bearing such functional groups

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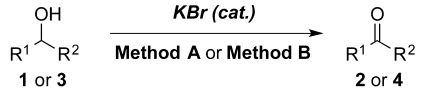
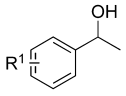
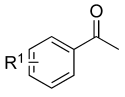
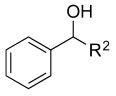
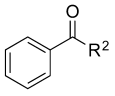
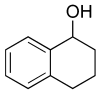
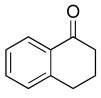
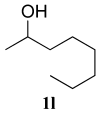
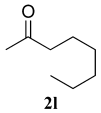
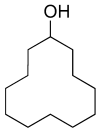
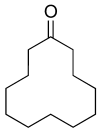
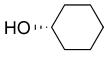
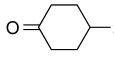
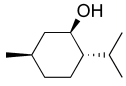
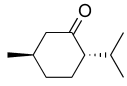
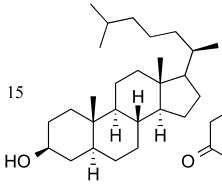
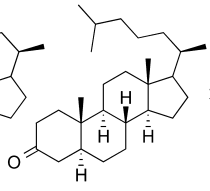
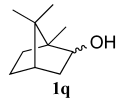
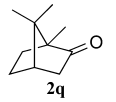
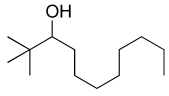
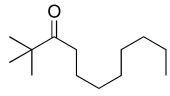
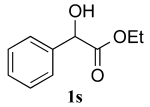
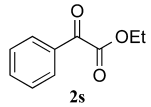
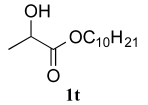
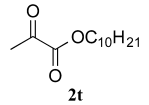
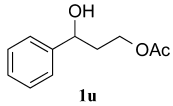
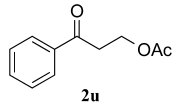
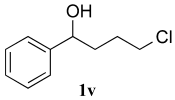
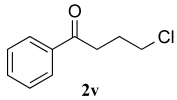
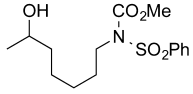
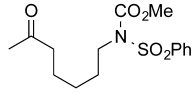
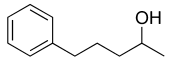
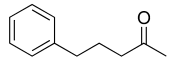
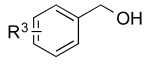
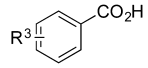
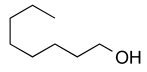
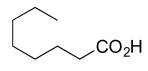
Table 3. Screening for Substrates and Optimum Conditions for Alkali Metal Bromide Catalyzed Oxidation of 1a



Method A: KBr (10 mol%), Oxone® (1.0 equiv.) in MeCN:H_2O (9:1) at room temperature.
Method B: KBr (20 mol%), aq. H_2O_2 (1.5 equiv.), $PhSO_3H$ (10 mol%) in CH_2Cl_2:H_2O (9:1) at room temperature.

Entry	Alcohol	Product	Time (h), Yield (%) Method A	Method B (24 h)
				
1	**1b**: R^1 = 4-Me	**2b**	1, 86	94
2	**1c**: R^1 = 4-Cl	**2c**	3, 95	97
3	**1d**: R^1 = 4-NO_2	**2d**	3, >99	>99
4	**1e**: R^1 = 3-Cl	**2e**	1, 98	>99
5	**1f**: R^1 = 2-Cl	**2f**	3, 99	>99
				
6	**1g**: R^2 = Et	**2g**	1, >99	>99
7	**1h**: R^2 = *i*-Pr	**2h**	4, 96	94
8	**1i**: R^2 = *t*-Bu	**2i**	4, >99	>99
9	**1j**: R^2 = Ph	**2j**	8, >99	>99
10	 **1k**	 **2k**	3, 89	0 (74)[a]
11	 **1l**	 **2l**	1, >99	85
12	 **1m**	 **2m**	1, >99	>99
13	 **1n**	 **2n**	7, 87[b]	54 (33)[a]
14	 **1o**	 **2o**	24, 62 (15)[a]	0 (71)[a]
15	 **1p**	 **2p**	24, 90[c]	73

Entry	Alcohol	Product	Time (h), Yield (%) Method A	Method B (24 h)
16	 **1q**	 **2q**	8, 78	87
17	 **1r**	 **2r**	8, 98	87[d]
18	 **1s**	 **2s**	5, 93	>99
19	 **1t**	 **2t**	5, 96	>99
20	 **1u**	 **2u**	6, 89[e]	89
21	 **1v**	 **2v**	6, >99	90
22	 **1w**	 **2w**	24, 99	96
23	 **1x**	 **2x**	24, 78 (10)[a]	20 (60)[a]
				
24	**3a**: R^3 = 4-Me	**4a**	24, 67[e,f]	69[d,g]
25	**3b**: R^3 = 4-F	**4b**	24, 91[f]	91[d,g]
26	**3c**: R^3 = 4-Cl	**4c**	24, >99[f]	96[d,g]
27	**3d**: R^3 = 3-Cl	**4d**	24, >99[f]	96[g,h]
28	**3e**: R^3 = 2-Cl	**4e**	24, >99[i]	>99[d,g]
29	 **3f**	 **4f**	24, 85[j]	20[d] (80)[k]

[a]Values in parentheses indicate the recovery of **1**. [b]Cs_2CO_3 (1.0 equiv) was added. [c]The reaction was carried out in a mixture of AcOEt and H_2O (9/1) (2 mL). [d]KBr (20 mol %), aqueous H_2O_2 (3.0 equiv), and $PhSO_3H$ (20 mol %) were used. [e]The reaction was carried out in MeCN. [f]KBr (20 mol %) and Oxone (2.0 equiv) were used. [g]The reaction was carried out under fluorescent light irradiation. [h]KBr (30 mol %), aqueous H_2O_2 (3.0 equiv), and $PhSO_3H$ (30 mol %) were used. [i]KBr (20 mol %) and Oxone (2.5 equiv) were used. [j]The reaction was carried out in a mixture of MeCN and H_2O (9/1) (2 mL). [k]The value in parentheses indicates the yield of octyl octanoate.

as esters (**1s–u**), chloro (**1v**), and amide (**1w**) provided the corresponding products **2s–w** in high yields (89 to >99%), respectively (entries 18–22). In the present oxidation with KBr and oxidant, a benzylic hydrogen atom could be abstracted by a bromo radical to provide various benzylic substitution products.[4b] Fortunately, 4-phenyl-2-butanol (**1x**) was efficiently and selectively oxidized under method A conditions to give 4-phenyl-2-butanone (**2x**) in 78% yield (entry 23). The oxidation of benzyl alcohols bearing 4-Me (**3a**), 4-F (**3b**), 4-Cl (**3c**), 3-Cl (**3d**), and 2-Cl (**3e**) groups on the aromatic ring with twice the amount of oxidant under both conditions provided carboxylic acids in high yields (67 to >99%), respectively (entries 24–28).

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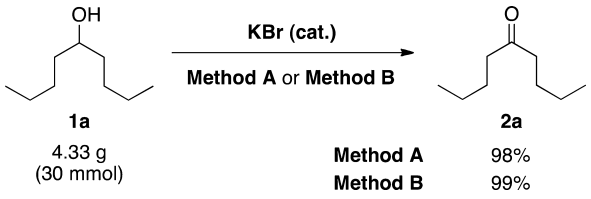
Whereas method A conditions for the oxidation of 1-octanol (**3f**) at a concentration of 0.25 M provided caprylic acid (**4f**) in 85% yield, method B conditions gave a lower yield of the same transformation product (entry 29). From the results in Table 3, the organic-molecule-free oxidation using Oxone (method A) is much more effective than the Brønsted acid assisted oxidation using aqueous H_2O_2 (method B) for the alkali metal bromide catalyzed oxidation of alcohols. Moreover, when the reaction was conducted on a 30 mmol scale of **1a** (4.33 g) under both conditions (methods A and B), KBr showed high catalytic activity and **2a** was obtained in 98% and 99% yields, respectively (Scheme 2).

Scheme 2. Catalytic Gram-Scale Oxidation of 1a[a]



[a]Method A: KBr (10 mol %) and Oxone (1.0 equiv) in MeCN/H_2O (9/1) at room temperature. Method B: KBr (20 mol %), aqueous H_2O_2 (1.5 equiv), and $PhSO_3H$ (10 mol %) in CH_2Cl_2/H_2O (9/1) at room temperature.

Next, we investigated the divergent transformation of primary alcohols **3** into carboxylic acids **4** and aldehydes **5** by the alkali metal bromide catalyzed oxidation. To this end, the alkali metal bromide catalyzed chemoselective oxidation of 4-chlorobenzyl alcohol (**3c**) into 4-chlorobenzaldehyde (**5c**) was examinded (Table 4). The use of method A conditions for secondary alcohol oxidation provided carboxylic acid **4c** as the major product (entries 1 and 2). Whereas the oxidation by method A in the presence of TEMPO[7] (5 mol %) in a mixture of MeCN and H_2O showed reactivity similar to that in the absence of TEMPO (entry 1 vs 3), the oxidation in MeCN increased the yield of desired aldehyde **5c** in the bromide catalyzed oxidation (entry 2 vs 4). Optimization experiments of the solvent and the amount of TEMPO demonstrated that the use of TEMPO (10 mol %) in AcOEt gave the best conditions for the bromide catalyzed transformation into aldehyde **5c** with KBr/Oxone (entries 5−8). On the other hand, those reactions conducted under method B conditions also provided **4c** as the major product (entries 10−12). The addition of TEMPO and the removal of water in the chemoselective oxidation with KBr/H_2O_2/$PhSO_3H$ improved the yields (entries 13 and 14), and the oxidation with KBr (20 mol %), aqueous H_2O_2 (2.0 equiv), $PhSO_3H$ (20 mol %), and consequently TEMPO (10 mol %) in CH_2Cl_2 generated the desired product **5c** in a quantitative yield (entry 15). The oxidation of **3c** into **5c** did not proceed in the absence of KBr under both conditions (entries 9 and 16).

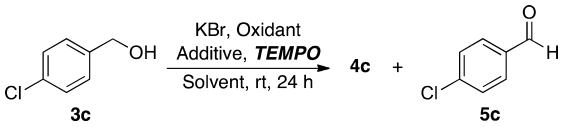
To explore the scope of the alkali metal bromide catalyzed oxidative transformation of alcohols into aldehydes, various primary alcohols **3** were examined under the optimum conditions of methods C and D (Scheme 3).

The oxidation of benzyl alcohols **3a−e** bearing a substituent on the aromatic ring produced the corresponding aldehydes **5a−e** in high yields under both conditions (methods C and D) (77 to >99%), respectively. The oxidation of aliphatic alcohol **3f** provided the desired aldehyde **5f** in low yields (40% and 32%) under both conditions due to side reactions (i.e., formation of octyl octanoate via oxidative dimerization).

In order to elucidate the mechanism of the present reactions, we investigated the bromide catalyzed oxidation of **1a** in the presence of a galvinoxyl free radical under each set of reaction conditions (methods A−D) (Scheme 4).

The reaction using method A in MeCN/H_2O (9/1) provided the desired product **2a** in 58% yield together with 38% recovery of **1a**, whereas that in CH_2Cl_2/H_2O (9/1) gave

Table 4. Screening for Optimum Conditions for Alkali Metal Bromide Catalyzed Selective Oxidation of 3c into Aldehyde 5c



entry	KBr (mol %)	oxidant (equiv)	$PhSO_3H$ (mol %)	TEMPO (mol %)	solvent	yield (%)[a] 4c	yield (%)[a] 5c
1	10	Oxone (1.0)			MeCN/H_2O(9/1)	63	22
2	10	Oxone (1.0)			MeCN	91	9
3	10	Oxone (1.0)		5	MeCN/H_2O(9/1)	58	22
4	10	Oxone (1.0)		5	MeCN	14	67
5	10	Oxone (1.0)		5	AcOEt	0	83
6	10	Oxone (1.0)		5	CH_2Cl_2	0	82
7	10	Oxone (1.0)		10	AcOEt	0	91
8	10	Oxone (1.0)		10	CH_2Cl_2	0	85
9		Oxone (1.0)		10	AcOEt	0 (94)	4
10	20	aq H_2O_2 (2.0)	10		CH_2Cl_2/H_2O(9/1)	75	10
11	20	aq H_2O_2 (2.0)	20		CH_2Cl_2/H_2O(9/1)	68	27
12	20	aq H_2O_2 (2.0)	20		CH_2Cl_2	73	14
13	20	aq H_2O_2 (2.0)	20	5	CH_2Cl_2/H_2O(9/1)	4	81
14	20	aq H_2O_2 (2.0)	20	10	CH_2Cl_2/H_2O(9/1)	0 (21)	79
15	20	aq H_2O_2 (2.0)	20	10	CH_2Cl_2		>99
16		aq H_2O_2 (2.0)	20	10	CH_2Cl_2	0 (92)	3

[a]Values in parentheses indicate the recovery of **3c**.

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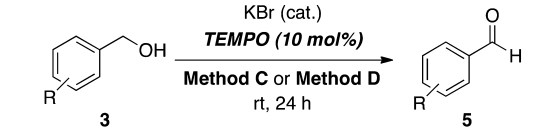
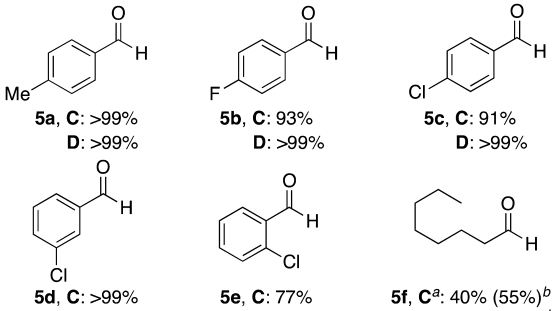
Scheme 3. Divergent Transformation of 3 into 4 and 5 by Alkali Metal Bromide Catalyzed Oxidation



Method C: KBr (10 mol%), Oxone® (1.0 equiv.), TEMPO (10 mol%) in AcOEt.

Method D: KBr (20 mol%), aq. H_2O_2 (2.0 equiv.), TEMPO (10 mol%) $PhSO_3H$ (20 mol%) in CH_2Cl_2.

Product (**5**), Method, and Yield



5a, **C**: >99% **D**: >99%

5b, **C**: 93% **D**: >99%

5c, **C**: 91% **D**: >99%

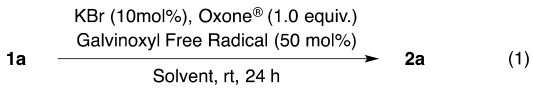
5d, **C**: >99% **D**: >99%

5e, **C**: 77% **D**: 97%

5f, **C**[a]: 40% (55%)[b] **D**[c]: 32% (10%)[d] (10%)[b] (31%)[e]

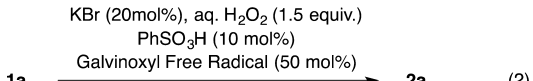
[a]The reaction was carried out in CH_2Cl_2 (2 mL). [b]Values in parentheses indicate the yield of octyl octanoate. KBr (30 mol %), aqueous H_2O_2 (3.0 equiv), and $PhSO_3H$ (30 mol %) were used. [d]Value in parentheses indicates the yield of **4f**. [e]Value in parentheses indicates the recovery of **3f**.

Scheme 4. Bromide-Catalyzed Oxidation of Alcohols by Galvinoxyl Free Radical



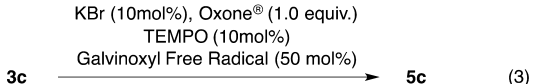
(1)

Solvent	Yield of **2**
MeCN:H_2O (9:1)	58% (38%)[a]
CH_2Cl_2:H_2O (9:1)	0% (91%)[a]



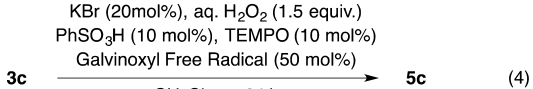
(2)

Solvent	Yield of **2**
MeCN:H_2O (9:1)	0% (93%)[a]
CH_2Cl_2:H_2O (9:1)	0% (>99%)[a]



(3)

68% (22%)[a] (10%)[b]



(4)

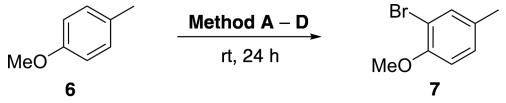
16% (82%)[a]

[a]Value in parentheses indicates the recovery of **1**. [b]Value in parentheses indicates the yield of **4c**.

no product (eq 1). The reaction using method B did not generate any oxidized products under both solvent conditions (eq 2). The difference in reactivity may mainly come from the oxidizability of the oxidant in addition to the solvent effect (eq 1 vs eq 2). In addition, the reactions with TEMPO (methods C and D) in the presence of galvinoxyl free radical gave the oxidative products under both reaction conditions (eq 3 and eq 4). In those cases, the oxidation with Oxone is more effective (**5c** in 68% yield and **4c** in 10% yield) than the oxidation with $H_2O_2/PhSO_3H$ (**5c** in 16% yield) (eq 3 vs eq 4). These observations support that the oxidation with H_2O_2 in a solution of CH_2Cl_2/H_2O mainly proceeds via a radical pathway. In contrast, the oxidation with Oxone in a mixture of MeCN and H_2O (method A) and the addition of TEMPO (methods C and D) involve simultaneous ionic reactions in addition to a radical reaction. Furthermore, the use of TEMPO in the oxidation increases the ionic character of the bromide catalyzed oxidation (eq 1 vs eq 3 and eq 2 vs eq 4).

To evaluate the in situ generation of a cationic bromo ion from an alkali metal bromide, we investigated the bromination of *p*-methoxytoluene (**6**) with KBr under all of the reaction conditions (methods A–D) (Scheme 5).[12] The treatment of **6**

Scheme 5. Bromination of *p*-Methoxytoluene (6) with KBr under Conditions of Methods A–D[a]



Method	Yield of **7**
Method A	85%
Method B	8% (72%)[b]
Method C	0% (88%)[b]
Method D	7% (72%)[b]

[a]Method A: KBr (1.2 equiv) and Oxone (1.0 equiv) in MeCN/H_2O (9/1). Method B: KBr (1.2 equiv), aqueous H_2O_2 (1.5 equiv), and $PhSO_3H$ (10 mol %) in CH_2Cl_2/H_2O (9/1). Method C: KBr (1.2 equiv), Oxone (1.0 equiv), and TEMPO (10 mol %) in AcOEt. Method D: KBr (1.2 equiv), aqueous H_2O_2 (1.5 equiv), $PhSO_3H$ (10 mol %), and TEMPO (10 mol %) in CH_2Cl_2. [b]Values in parentheses indicate the recovery of **6**.

with KBr and Oxone in a mixture of MeCN and H_2O (method A) promoted the bromination on the aromatic ring to give the brominated product **7** in 85% yield, whereas the bromination with H_2O_2 and $PhSO_3H$ in a mixture of CH_2Cl_2 and H_2O (method B) and those systems with TEMPO (method C and D) gave little or no yield of **7**. Above all, those reactions did not produce the benzyl bromide via the radical reaction. The results indicated that using Oxone in polar solvents for the oxidation of bromide promotes the generation of bromonium ion from a bromide.

Hammett plots for the oxidation of various secondary alcohols under the conditions of nethods A and B (Figure 2a,b) and primary alcohols (Figure 2c,d) under the conditions of methods C and D with KBr are drawn.[13] A linear relationship was observed in all cases between $\log(k_X/k_H)$ and substituent constant σ^+, and the reaction constants ρ were −0.66 (method A), −0.56 (method B), −1.29 (method C), and −1.11 (method D). The negative reaction constants denote that a small positive charge is found at the benzylic position of **1** and **3** in the transition state. Moreover, the large absolute values (−1.29 and −1.11) for the oxidation with TEMPO (methods C and D) in comparison to those values (−0.66 and −0.56) for the oxidation without TEMPO (methods A and B) indicate that

dx.doi.org/10.1021/jo5008064 | J. Org. Chem. 2014, 79, 6094–6104

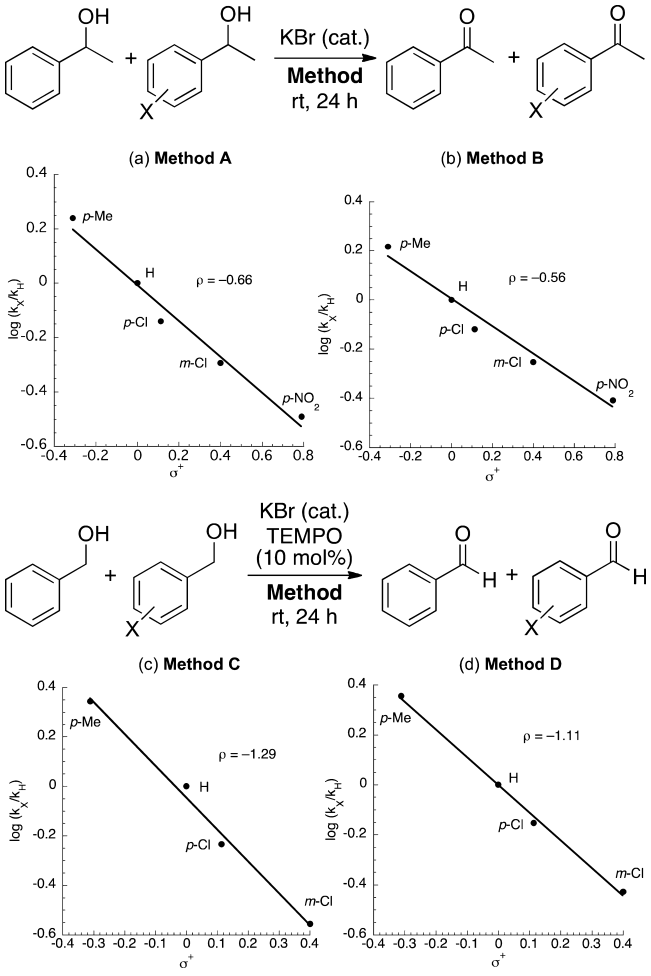
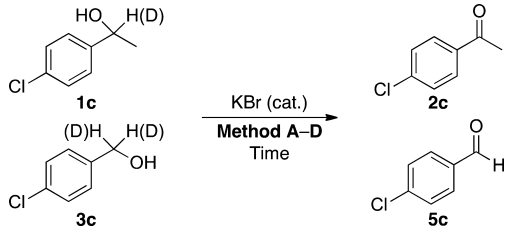


Figure 2. Hammett plots of log (k_X/k_H) versus σ^+ for bromide-catalyzed oxidation of 1° and 2° benzyl alcohols;: (a) method A, KBr (10 mol %) and Oxone (0.5 equiv) in MeCN/H_2O (9/1), log(k_X/k_H) = −0.66, σ^+ = −6.3 × 10^{-3} (r = 0.977); (b) method B, KBr (10 mol %), aqueous H_2O_2 (1.0 equiv), and $PhSO_3H$ (10 mol %) in CH_2Cl_2/H_2O (9/1), log(k_X/k_H) = −0.56, σ^+ = −3.8 × 10^{-3} (r = 0.974); (c) method C, KBr (10 mol %), Oxone (0.5 equiv), and TEMPO (10 mol %) in AcOEt, log(k_X/k_H) = −1.29, σ^+ = −4.6 × 10^{-2} (r = 0.991); (d) method D, KBr (10 mol %), aqueous H_2O_2 (1.0 equiv), $PhSO_3H$ (10 mol %), and TEMPO (10 mol %) in CH_2Cl_2, log(k_X/k_H) = −1.12, σ^+ = −4.4 × 10^{-4} (r = 0.997).

the use of TEMPO increases the positive charge at the benzylic position of **1** and **3** in the transition state.

The deuterium kinetic isotope effect on the alkali metal bromide catalyzed oxidation was evaluated in the competitive reaction of a 1/1 mixture of **1c** and 1-deuterio-1-(4-chlorophenyl)ethanol (**1c**-*d*) or **3c** and dideuterio(4-chlorophenyl)methanol (**3c**-*d*) under each set of reaction conditions (Table 5). The small k_H/k_D values of 1.62 (entries 1 and 2) and 1.43 (entries 3 and 4) indicate a hydrogen atom at the α-carbon of a hypobromite intermediate, which is formed via a substitution of bromide from alcohols in a concerted fashion, not the direct C−H abstraction of alcohol, is the rate-determining step for the oxidation in the absence of TEMPO (methods A and B). In contrast, the large k_H/k_D values of 3.25 (entries 5 and 6) and 3.00 (entries 7 and 8) confirm that oxidation with TEMPO (methods C and D) directly promotes hydrogen transfer from the hydrogen at the α-carbon of the alcohol in the rate-determining step.

Table 5. Kinetic Isotope Effect on 1c and 3c in Alkali Metal Bromide Catalyzed Oxidation



entry	1 or 3	method[a]	time (h)	product	yield (%)[b]	k_H/k_D
1	**1c**	A	1	**2c**	34 (66)	1.62
2	**1c**-*d*	A	1	**2c**-*d*	21 (79)	
3	**1c**	B	3	**2c**	60 (40)	1.43
4	**1c**-*d*	B	3	**2c**-*d*	42 (58)	
5	**3c**	C	5	**5c**	52 (48)	3.25
6	**3c**-*d*	C	5	**5c**-*d*	16 (84)	
7	**3c**	D	3	**5c**	72 (28)	3.00
8	**3c**-*d*	D	3	**5c**-*d*	24 (76)	

[a]Method A: KBr (10 mol %) and Oxone (1.0 equiv) in MeCN/H_2O (9/1). Method B: KBr (20 mol %), aqueous H_2O_2 (1.5 equiv), and $PhSO_3H$ (10 mol %) in CH_2Cl_2/H_2O (9/1). Method C: KBr (10 mol %), Oxone (1.0 equiv), and TEMPO (10 mol %) in AcOEt. Method D: KBr (10 mol %), aqueous H_2O_2 (1.5 equiv), $PhSO_3H$ (10 mol %), and TEMPO (10 mol %) in CH_2Cl_2. [b]Values in parentheses indicate the recovery of substrates.

Then, we investigated the competitive oxidation of secondary alcohol **1c** and primary alcohol **3c** with Oxone (0.5 equiv) or aqueous H_2O_2 (1.0 equiv) under each set of conditions (Table 6). The oxidation of **1c** and **3c** under all the reaction conditions (methods A−D) occurred with comparable selectivity to give the corresponding ketone **2c** and aldehyde **5c** (eqs 7 and 8). For the oxidation in the absence of TEMPO (Methods A and B), the oxidation of secondary alcohol (**1c**) has an advantage over one of primary alcohol (**3c**) because it is likely to be

Table 6. Competitive Reactions of Alcohols 1c and 3c in Bromide-Catalyzed Oxidation[a]

1c + **3c** —KBr (cat.), **Method A** or **Method B**, rt, 24 h→ **2c** + **5c** (7)

Method	Yield			
	1c	**2c**	**3c**	**5c**
Method A	57%	38%	62%	23%
Method B	51%	48%	50%	39%

1c + **3c** —KBr (cat.), TEMPO (10 mol%), **Method C** or **Method D**, rt, 24 h→ **2c** + **5c** (8)

Method	Yield			
	1c	**2c**	**3c**	**5c**
Method C	69%	33%	42%	52%
Method D	41%	54%	56%	42%

[a]Method A: KBr (10 mol %) and Oxone (0.5 equiv) in MeCN/H_2O (9/1). Method B: KBr (10 mol %), aqueous H_2O_2 (1.0 equiv), and $PhSO_3H$ (10 mol %) in CH_2Cl_2/H_2O (9/1). Method C: KBr (10 mol %), Oxone (0.5 equiv), and TEMPO (10 mol %) in AcOEt. Method D: KBr (10 mol %), aqueous H_2O_2 (1.0 equiv), $PhSO_3H$ (10 mol %), and TEMPO (10 mol %) in CH_2Cl_2.

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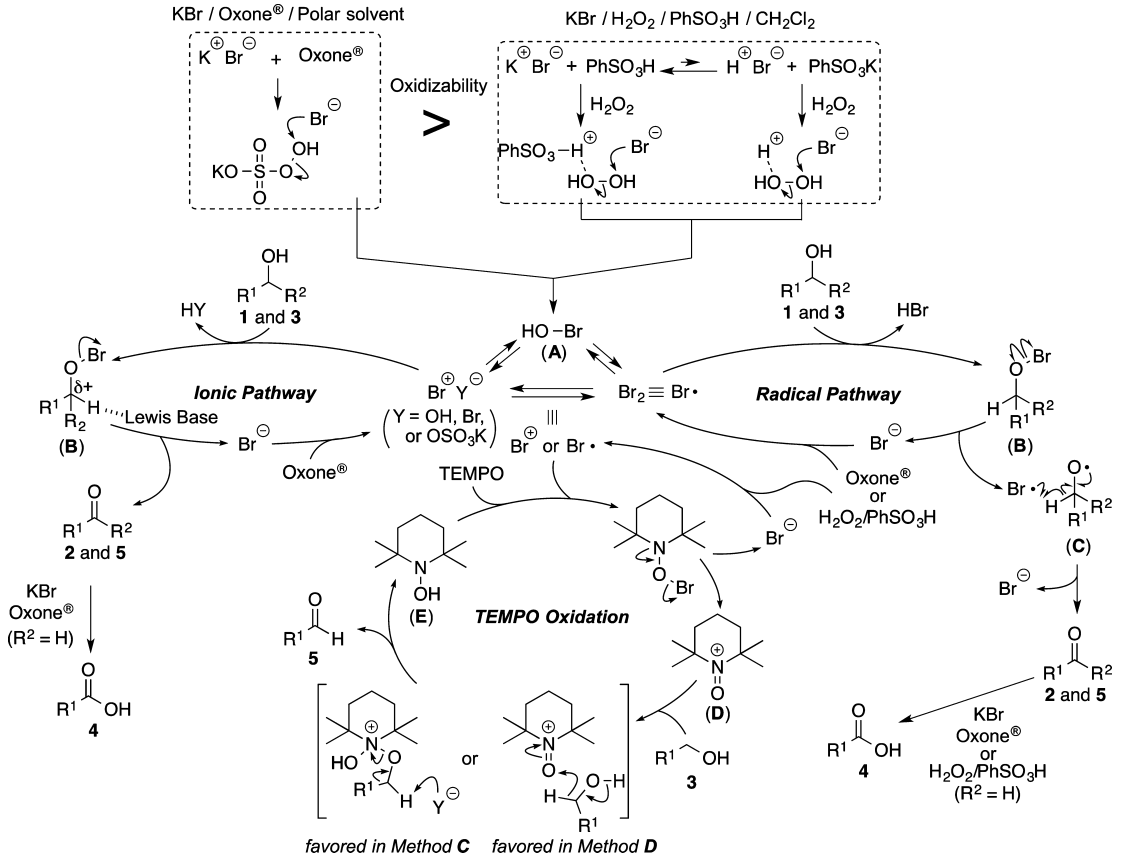

Figure 3. Plausible reaction mechanism.

caused by the stability of positive charge at α-carbon of a hypobromite intermediate (eq 7). In particular, in the oxidation with TEMPO, the primary alcohol is oxidized more rapidly than the secondary alcohol (method C), indicating that the oxidation favors the formation of an acyclic intermediate by the nucleophlic addition of alcohol in the transition state,[14a−c] whereas the secondary alcohol is oxidized more rapidly than the primary alcohol (method D), indicating that the oxidation favors the intermolecular hydride transfer in the transition state (eq 8).[14d]

A plausible mechanism for the alkali metal bromide catalyzed oxidation of alcohols is depicted in Figure 3.

In the first step of all the reaction conditions, the oxidation of KBr with an oxidant generates hypobromous acid (**A**) in situ, the formation of which is promoted by the nucleophilic substitution to potassium peroxymonosulfate bearing the monosulfate as the leaving group with bromide ion (method A) or by hydrogen peroxide activated by Brønsted acid with bromide ion (method B). In method B, KBr in the presence of $PhSO_3H$ is in equilibrium with HBr and $PhSO_3K$, but the equilibrium favors KBr and $PhSO_3H$ over HBr and $PhSO_3K$ (pK_a: 4-Me-$C_6H_4SO_3H$, 8.0; HBr, 5.5; in MeCN).[15] In the bromide-catalyzed oxidation in the absence of TEMPO, hypobromous acid (**A**) is mainly converted into molecular bromine (Br_2), which forms a bromo radical ($Br^{\bullet}$) that expeditiously reacts with alcohols (**1** and **3**) to yield hypobromite intermediate (**B**). Subsequent oxidation of **B** provides the corresponding carbonyl compounds **2** and **5** via the trapping of hydrogen atom at the α carbon of an alkoxy radical intermediate (**C**) by a bromo radical ($Br^{\bullet}$). The reduced bromide is oxidized again by oxidants to form a bromo radical that becomes involved again in the catalytic cycle (right cycle). Aldehydes **5** (R^2 = H) obtained from primary alcohols **3** are rapidly oxidized to the corresponding carboxylic acids **4** by residual oxidants through the formation of their hydrates under acidic conditions. In method A, the bromonium ion competitively reacts with alcohols (**1** and **3**) through an ionic pathway to produce the corresponding carbonyl compounds (left cycle). In contrast, the addition of TEMPO in methods C and D rapidly promotes the formation of oxoammmonium ion (**D**) from TEMPO via oxidation by the bromo radical or the bromonium ion, and the addition of alcohols **3** gives the corresponding aldehydes **5**. In particular, the TEMPO oxidation preferentially occurs via the formation of an acyclic intermediate in method C[14a−c] or the intermolecular hydride transfer from the α-carbon of alcohol to the oxygen of the oxoammonium cation in method D.[14d] Reduced hydroxylamine (**E**) is reoxidized by activated bromine species ($Br^{\bullet}$ or Br^{+}) to promote the catalytic process (bottom cycle).

Finally, the bromide catalyzed oxidation of alcohols (**8**) bearing an unsaturated aliphatic carbon, such as alkene or alkyne, was attempted with alkali metal bromide because it was difficult to oxidize alcohols **8** by the high reactivity of unsaturated aliphatic carbon with activated bromine. Indeed, the bromide-catalyzed oxidation of **8a−c** with KBr under both method A and method B conditions absolutely did not provide the desired ketone (**9a−c**), respectively.[16] Basifying the conditions for oxidation of **8** with TEMPO suppressed undesirable reactions; when alkynyl alcohol **8a**, cinnamyl alcohol **8b**, and terminal alkenyl alcohol **8c** were treated with KBr (20 mol %), Oxone (1.0 equiv), TEMPO (20 mol %), and Na_2CO_3 (3.0 equiv) in CH_2Cl_2, the desired ketones **9a−c** were

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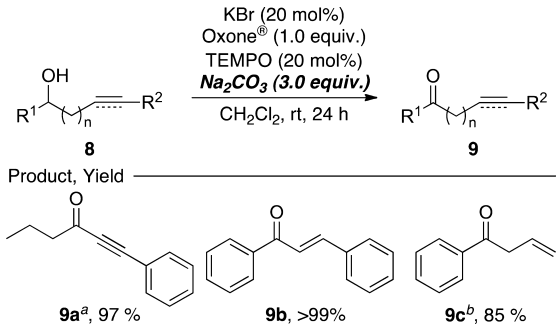
obtained in high yields (78 to >99%) without damaging the unsaturated aliphatic groups (Scheme 6).

Scheme 6. Bromide-Catalyzed Oxidation of Alcohols Bearing Unsaturated Aliphatic Carbon



[a]The reaction was carried out in CH_2Cl_2 (1 mL). [b]The reaction was carried out at 0 °C.

In conclusion, we have developed an alkali metal bromide catalyzed oxidation of alcohols, which proceeds under mild conditions. This bromide catalyzed reaction efficiently proceeded through an organic-molecule-free oxidation using Oxone (method A) and a Brønsted-acid-assisted oxidation using hydrogen peroxide as the oxidant (method B) and by controlling the transformation into aldehydes by the addition of a catalytic amount of TEMPO under both oxidation conditions (methods C and D). The mechanism of the reaction was proposed from the results of experiments with galvinoxyl free radical, Hammett plots, the study of the deuterium kinetic isotope effect, and the competitive reactions of primary and secondary alcohols. These methods developed herein are environmentally sustainable strategies for organic synthesis. We are optimistic that the present catalytic oxidative transformation using alkali metal bromide would be applicable to fine organic synthesis.

EXPERIMENTAL SECTION

General Procedure. ^{1}H NMR spectra were measured on a 400 MHz spectrometer. Chemical shifts were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on a 100 MHz spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuteriochloroform at 77.0 ppm). ^{19}F NMR spectra were measured on a 471 MHz spectrometer. High-resolution mass spectra (HRMS) were obtained by orbitrap mass spectrometers. Characteristic peaks in the infrared (IR) spectra are recorded in wavenumbers (cm^{-1}) using ATR. Melting points are reported as uncorrected. Thin-layer chromatography (TLC) was performed using a 0.25 mm silica gel plate (60F-254). The products were purified by column chromatography on silica gel 60 (63−200 mesh). Visualization was accomplished by UV light (254 nm), anisaldehyde, $KMnO_4$, and phosphomolybdic acid.

General Procedure for Bromide Catalyzed Oxidation of Alcohols 1 and 3 with Metal Bromides (Method A) (Tables 1 and 3). To a solution of **1w** (164.7 mg, 0.50 mmol) and KBr (6.0 mg, 0.05 mmol) in a mixture of MeCN (0.9 mL) and H_2O (0.1 mL) was added Oxone (307.4 mg, 0.50 mmol) at room temperature, and the mixture was stirred for 24 h. Saturated Na_2SO_3 aqueous solution (10 mL) was added to the reaction mixture, and the product was extracted with AcOEt (15 mL × 3). The combined extracts were washed with brine (10 mL) and dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography (eluent hexane/AcOEt 3/1) to give the desired product **2w** (162.1 mg, 99% yield).

General Procedure for Bromide Catalyzed Oxidation of Alcohols 1 and 3 Using Alkali Metal Bromides and Aqueous H_2O_2 (Method B) (Tables 2 and 3). To a solution of **1w** (164.7 mg, 0.50 mmol), KBr (11.9 mg, 0.10 mmol), and $PhSO_3H$ (7.9 mg, 0.05 mmol) in a mixture of CH_2Cl_2 (0.9 mL) and H_2O (0.1 mL) was added 30% aqueous H_2O_2 (85.0 μL, 0.75 mmol) at room temperature, and the mixture was stirred for 24 h. Saturated Na_2SO_3 aqueous solution (10 mL) was added to the reaction mixture, and the product was extracted with AcOEt (15 mL × 3). The combined extracts were washed with brine (10 mL) and dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography (eluent hexane/AcOEt 3/1) to give the desired product **2w** (156.8 mg, 96% yield).

*Methyl (6-oxoheptyl)(phenylsulfonyl)carbamate (**2w**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31−1.41 (m, 2H), 1.63 (quin, J = 7.6 Hz, 2H), 1.77 (quin, J = 7.8 Hz, 2H), 2.15 (s, 3H), 2.46 (t, J = 7.6 Hz, 2H), 3.68 (s, 3H), 3.83 (t, J = 7.8 Hz, 2H), 7.53 (t, J = 7.6 Hz, 2H), 7.63 (t, J = 7.6 Hz, 1H), 7.94 (d, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.1, 26.0, 29.8, 29.9, 43.4, 47.3, 53.7, 128.2 (2C), 128.7 (2C), 133.5, 139.5, 152.8, 208.8. IR (neat): 1732, 1713, 1354, 1275, 1163, 1132 cm^{-1}. MS (ESI) calcd for $C_{15}H_{22}NO_5S$ $[M + H]^+$ 328.1213, found 328.1210.

*5-Nonanone (**2a**; Commercially Available).* Colorless oil (method A, 70.8 mg, >99%; method B, 68.7 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, J = 7.6 Hz, 6H), 1.31 (sext, J = 7.6 Hz, 4H), 1.55 (quin, J = 7.6 Hz, 4H), 2.39 (t, J = 7.6 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8 (2C), 22.3 (2C), 26.0 (2C), 42.5 (2C), 211.7. IR (neat): 2958, 1712, 1465, 1379, 1133, 1043 cm^{-1}.

*4-Methylacetophenone (**2b**; Commercially Available).* Colorless oil (method A, 57.9 mg, 86%; method B, 63.2 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3H), 2.58 (s, 3H), 7.26 (d, J = 8.2 Hz, 2H), 7.86 (d, J = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 26.5, 128.4 (2C), 129.2 (2C), 134.7, 143.8, 197.8. IR (neat): 1679, 1605, 1574, 1265, 1181 cm^{-1}.

*4-Chloroacetophenone (**2c**; Commercially Available).* White solid (method A, 73.6 mg, 95%; method B, 75.3 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.59 (s, 3H), 7.44 (d, J = 8.9 Hz, 2H), 7.90 (d, J = 8.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.6, 128.9 (2C), 129.7 (2C), 135.4, 139.6, 196.8. IR (neat): 1683, 1587, 1357, 1258, 1092 cm^{-1}.

*4-Nitroacetophenone (**2d**; Commercially Available).* White solid (method A, 82.4 mg, >99%; method B, 82.2 mg, >99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.69 (s, 3H), 8.12 (d, J = 8.9 Hz, 2H), 8.32 (d, J = 8.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.0, 123.8 (2C), 129.3 (2C), 141.4, 150.3, 196.3. IR (KBr) 3110, 1693, 1608, 1525, 1345, 1261 cm^{-1}.

*3-Chloroacetophenone (**2e**; Commercially Available).* Colorless oil (method A, 75.6 mg, 98%; method B, 76.9 mg, >99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.60 (s, 3H), 7.41 (t, J = 8.0 Hz, 1H), 7.54 (ddd, J = 8.0, 2.0, 1.2 Hz, 1H), 7.83 (ddd, J = 8.0, 2.0, 1.2 Hz, 1H), 7.93 (t, J = 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.6, 126.4, 128.4, 129.9, 133.0, 134.9, 138.5, 196.7. IR (neat): 1688, 1572, 1422, 1358, 1251 cm^{-1}.

*2-Chloroacetophenone (**2f**; Commercially Available).* White solid (method A, 76.3 mg, 99%; method B, 76.9 mg, >99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.65 (s, 3H), 7.32 (ddd, J = 7.8, 7.1, 1.8 Hz, 1H), 7.36−7.44 (m, 2H), 7.55 (dd, J = 7.8, 1.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.7, 126.9, 129.4, 130.6, 131.3, 132.0, 139.1, 200.5. IR (neat): 1695, 1432, 1357, 1276, 1240, 1095 cm^{-1}.

*Propiophenone (**2g**; Commercially Available).* Colorless oil (method A, 67.0 mg, >99%; method B, 73.7 mg, >99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (t, J = 7.3 Hz, 3H), 3.00 (q, J = 7.3 Hz, 2H), 7.45 (t, J = 7.8 Hz, 2H), 7.55 (t, J = 7.8 Hz, 1H), 7.97 (d, J = 7.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.2, 31.7, 127.9 (2C), 128.5 (2C), 132.8, 136.8, 200.7. IR (neat): 2979, 1685, 1597, 1448, 1351, 1218 cm^{-1}.

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*Isobutyrophenone (**2h**; Commercially Available).* Colorless oil (method A, 70.9 mg, 96%; method B, 69.8 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (d, J = 6.9 Hz, 6H), 3.56 (sept, J = 6.9 Hz, 1H), 7.46 (t, J = 7.3 Hz, 2H), 7.55 (t, J = 7.3 Hz, 1H), 7.96 (d, J = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2 (2C), 35.4, 128.4 (2C), 128.7 (2C), 132.9, 136.3, 204.6. IR (neat): 2972, 1684, 1465, 1383, 1225, 1161 cm^{-1}.

*Pivalophenone (**2i**; Commercially Available).* Colorless oil (method A, 81.0 mg, >99%; method B, 80.7 mg, >99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (s, 9H), 7.39 (tt, J = 7.3, 1.6 Hz, 2H), 7.45 (tt, J = 7.3, 1.6 Hz, 1H), 7.68 (dt, J = 7.3, 1.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.9 (3C), 44.1, 127.8 (2C), 128.0 (2C), 130.7, 138.5, 209.2. IR (neat): 2969, 1674, 1476, 1366, 1277, 1175 cm^{-1}.

*Benzophenone (**2j**; Commercially Available).* White solid (method A, 90.9 mg, >99%; method B, 90.7 mg, >99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (t, J = 7.8 Hz, 4H), 7.60 (t, J = 7.8 Hz, 2H), 7.81 (d, J = 7.8 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 128.2 (4C), 130.0 (4C), 132.2 (2C), 137.6 (2C), 196.7. IR (KBr) 3055, 1652, 1596, 1319, 1278 cm^{-1}.

*α-Tetralone (**2k**; Commercially Available).* Colorless oil (method A, 64.7 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.14 (quin, J = 6.4 Hz, 2H), 2.66 (t, J = 6.4 Hz, 2H), 2.97 (t, J = 6.4 Hz, 2H), 7.25 (d, J = 7.6 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H), 7.47 (td, J = 7.6, 1.4 Hz, 1H), 8.03 (dd, J = 8.0, 1.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.4, 29.7, 39.1, 126.6, 127.1, 128.7, 132.6, 133.4, 144.4, 198.4. IR (neat): 2944, 1679, 1600, 1324, 1284 cm^{-1}.

*2-Octanone (**2l**; Commercially Available).* Colorless oil (method A, 64.0 mg, >99%; method B, 54.3 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, J = 6.9 Hz, 3H), 1.24−1.36 (m, 6H), 1.52−1.62 (m, 2H), 2.13 (s, 3H), 2.42 (t, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.4, 23.8, 28.8, 29.8, 31.5, 43.7, 209.3. IR (neat): 2928, 1715, 1410, 1359, 1226, 1164 cm^{-1}.

*Cyclododecanone (**2m**; Commercially Available).* White solid (method A, 91.0 mg, >99%; method B, 90.7 mg, >99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22−1.37 (m, 14H), 1.67−1.76 (m, 4H), 2.44−2.49 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.3, 22.5 (2C), 24.2 (2C), 24.6 (2C), 24.7 (2C), 40.3 (2C), 212.9. IR (neat): 2927, 1702, 1470, 1362, 1204, 1131 cm^{-1}.

*4-tert-Butylcyclohexanone (**2n**; Commercially Available).* White solid (method A, 67.1 mg, 87%; method B, 41.3 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (s, 9H), 1.38−1.55 (m, 3H), 2.03−2.15 (m, 2H), 2.25−2.36 (m, 2H), 2.36−2.45 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.4 (5C), 32.4, 41.2 (2C), 46.6, 212.5. IR (neat): 2947, 1722, 1419, 1365, 1222, 1161 cm^{-1}.

*(−)-Menthone (**2o**; Commercially Available).* Colorless oil (method A, 47.9 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H), 1.01 (d, J = 6.4 Hz, 3H), 1.28−1.45 (m, 2H), 1.78−1.93 (m, 2H), 1.99 (td, J = 12.8, 1.2 Hz, 1H), 2.01−2.09 (m, 2H), 2.09−2.21 (m, 1H), 2.35 (ddd, J = 12.8, 3.9, 2.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.7, 21.2, 22.3, 25.8, 27.8, 33.9, 35.5, 50.8, 55.9, 212.5. IR (neat): 2955, 1708, 1456, 1366, 1202, 1045 cm^{-1}.

*5α-Cholestan-3-one (**2p**; Commercially Available).* White solid (method A, 174.8 mg, 90%; method B, 141.5 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.68 (s, 3H), 0.67−0.77 (m, 1H), 0.86 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H), 1.01 (s, 3H), 0.93−1.19 (m, 9H), 1.19−1.44 (m, 9H), 1.46−1.62 (m, 4H), 1.69 (dq, J = 13.1, 3.4 Hz, 1H), 1.76−1.89 (m, 1H), 1.95−2.12 (m, 3H), 2.27 (t, J = 14.6 Hz, 2H), 2.27−2.44 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.5, 12.0 18.6, 21.4, 22.5, 22.8, 23.8, 24.2, 28.0, 28.2, 28.9, 31.7, 35.4, 35.6, 35.8, 36.1, 38.2, 38.5, 39.5, 39.9, 42.5, 44.7, 46.7, 53.7, 56.21, 56.24, 212.3. IR (neat): 2930, 1712, 1466, 1383, 1229, 1173 cm^{-1}.

*(−)-Camphor (**2q**; Commercially Available).* White solid (method A, 59.7 mg, 78%; method B, 66.2 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (s, 3H), 0.91 (s, 3H), 0.96 (s, 3H), 1.29−1.46 (m, 2H), 1.69 (td, J = 13.2, 3.9 Hz, 1H), 1.85 (d, J = 18.3 Hz, 1H), 1.90−2.01 (m, 1H), 2.09 (t, J = 4.5 Hz, 1H), 2.35 (dt, J = 18.3, 4.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.2, 19.1, 19.8, 27.0, 29.9, 43.0, 43.3, 46.8, 57.7, 219.7. IR (neat): 2958, 1739, 1448, 1390, 1277, 1045 cm^{-1}.

*2,2-Dimethyl-3-undecanone (**2r**).*[17a] Colorless oil (method A, 97.5 mg, 98%; method B, 86.2 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, J = 7.0 Hz, 3H), 1.13 (s, 9H), 1.20−1.34 (m, 10H), 1.54 (quin, J = 7.3 Hz, 2H), 2.47 (t, J = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.6, 23.9, 26.4 (3C), 29.2, 29.3, 29.5, 31.8, 36.4, 44.1, 216.2. IR (neat): 2925, 1707, 1465, 1365, 1124, 1072 cm^{-1}.

*Ethyl Phenylglyoxylate (**2s**; Commercially Available).* Colorless oil (method A, 83.1 mg, 93%; method B, 88.6 mg, >99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (t, J = 7.3 Hz, 2H), 4.46 (q, J = 7.3 Hz, 2H), 7.51 (t, J = 7.6 Hz, 2H), 7.66 (t, J = 7.6 Hz, 1H), 8.01 (d, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 62.3, 128.8 (2C), 130.0 (2C), 132.4, 134.8, 163.8, 186.4. IR (neat): 1733, 1686, 1300, 1198, 1175, 1013 cm^{-1}.

*Decyl Pyruvate (**2t**).* Colorless oil (method A, 109.5 mg, 96%; method B, 113.9 mg, >99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, J = 6.9 Hz, 3H), 1.23−1.42 (m, 14H), 1.73 (quin, J = 6.9 Hz, 2H), 2.47 (s, 3H), 4.25 (t, J = 6.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.6, 25.7, 26.7, 28.3, 29.1, 29.2, 29.40, 29.43, 31.8, 66.6, 160.8, 192.0. IR (neat): 2925, 1756, 1730, 1467, 1299, 1136 cm^{-1}. MS (ESI) calcd for $C_{13}H_{24}NaO_3$ $[M + Na]^+$ 251.1618, found 251.1617.

*3-Acetoxypropiophenone (**2u**).* Colorless oil (method A, 85.3 mg, 89%; method B, 85.7 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.04 (s, 3H), 3.33 (t, J = 6.4 Hz, 2H), 4.53 (t, J = 6.4 Hz, 2H), 7.49 (t, J = 7.6 Hz, 2H), 7.59 (t, J = 7.6 Hz, 1H), 7.95−7.99 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 37.3, 59.6, 128.0 (2C), 128.6 (2C), 133.4, 136.5, 171.0, 196.9. IR (KBr) 2984, 1731, 1671, 1372, 1255, 1214 cm^{-1}. MS (ESI) calcd for $C_{11}H_{12}NaO_3$ $[M + Na]^+$ 215.0679, found 215.0679.

*4-Chlorobutyrophenone (**2v**; Commercially Available).* Colorless oil (method A, 91.1 mg, >99%; method B, 82.5 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.23 (quin, J = 6.8 Hz, 2H), 3.18 (t, J = 6.8 Hz, 2H), 3.68 (t, J = 6.8 Hz, 2H), 7.44−7.51 (m, 2H), 7.57 (tt, J = 7.4, 1.4 Hz, 1H), 7.98 (dd, J = 8.3, 1.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.7, 35.2, 44.6, 127.9 (2C), 128.6 (2C), 133.2, 136.6, 198.9. IR (neat): 1683, 1448, 1322, 1225, 742, 688 cm^{-1}.

*5-Phenyl-2-pentanone (**2x**).*[17b] White solid (method A, 63.2 mg, 78%; method B, 66.2 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.91 (quin, J = 7.5 Hz, 2H), 2.11 (s, 3H), 2.43 (t, J = 7.5 Hz, 2H), 2.62 (t, J = 7.5 Hz, 2H), 7.14−7.22 (m, 3H), 7.28 (t, J = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.1, 29.9, 34.9, 42.8, 125.9, 128.3 (2C), 128.4 (2C), 141.5, 208.8. IR (neat): 1712, 1496, 1453, 1358, 1159 cm^{-1}.

*4-Methylbenzoic Acid (**4a**; Commercially Available).* White solid (method A, 45.8 mg, 67%; method B, 47.2 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 7.28 (d, J = 8.2 Hz, 2H), 8.01 (d, J = 8.2 Hz, 2H), 12.20 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 126.5, 129.2 (2C), 130.2 (2C), 144.6, 172.4. IR (neat): 2823, 1668, 1610, 1416, 1281, 1181 cm^{-1}.

*4-Fluorobenzoic Acid (**4b**; Commercially Available).* White solid (method A, 63.7 mg, 91%; method B, 63.7 mg, 91%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.34 (brs, 1H), 7.31 (t, J = 9.1 Hz, 2H), 7.99 (dd, J = 9.1, 5.6 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 115.6 (d, J = 22.0 Hz, 2C), 127.4 (d, J = 2.9 Hz), 132.1 (d, J = 9.6 Hz, 2C), 164.9 (d, J = 252.0 Hz), 166.4. ^{19}F NMR (471 MHz, DMSO-d_6) d −106.8. IR (neat): 2828, 1672, 1603, 1425, 1291, 1157 cm^{-1}.

*4-Chlorobenzoic Acid (**4c**; Commercially Available).* White solid (method A, 78.1 mg, >99%; method B, 75.4 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.35 (brs, 1H), 7.58 (d, J = 8.6 Hz, 2H), 7.94 (d, J = 8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 128.8 (2C), 129.6, 131.2 (2C), 137.8, 166.5. IR (KBr) 2839, 1685, 1592, 1425, 1324, 1092 cm^{-1}.

*3-Chlorobenzoic Acid (**4d**; Commercially Available).* White solid (method A, 78.1 mg, >99%; method B, 75.2 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (t, J = 8.0 Hz, 1H), 7.60 (ddd, J = 8.0, 2.0, 1.2 Hz, 1H), 8.01 (dt, J = 8.0, 1.2 Hz, 1H), 8.10 (t, J = 8.0, 2.0 Hz, 1H), 11.20 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 128.3, 129.9, 130.3, 130.9, 133.9, 134.7, 170.7. IR (neat): 2882, 1682, 1415, 1299, 1260, 1074 cm^{-1}.

*2-Chlorobenzoic Acid (**4e**; Commercially Available).* White solid (method A, 78.1 mg, >99%; method B, 77.9 mg, >99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (ddd, J = 7.8, 6.2, 2.5 Hz, 1H), 7.46−7.53

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(m, 2H), 8.04 (dd, J = 7.8, 1.2 Hz, 1H), 10.97 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 126.7, 128.3, 131.5, 132.5, 133.6, 134.8, 170.5. IR (neat): 2816, 1681, 1408, 1311, 1265, 1042 cm^{-1}.

*Octanoic Acid (**4f**; Commercially Available).* Colorless oil (method A, 61.7 mg, 85%; method B, 14.7 mg, 20%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, J = 7.0 Hz, 3H), 1.21−1.39 (m, 8H), 1.65 (quin, J = 7.5 Hz, 2H), 2.35 (t, J = 7.5 Hz, 2H), 11.5 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.6, 24.6, 28.9, 29.0, 31.6, 34.1, 180.5. IR (neat): 2925, 1707, 1413, 1276, 1231 cm^{-1}.

General Procedure for Bromide Catalyzed Transformation of Alcohols 3 into Aldehydes 5 with Metal Bromides and TEMPO (Method C) (Table 4 and Scheme 3). To a solution of **3c** (71.3 mg, 0.50 mmol), KBr (6.0 mg, 0.05 mmol), and TEMPO (7.8 mg, 0.05 mmol) in AcOEt (1 mL) was added Oxone (307.4 mg, 0.50 mmol) at room temperature, and the mixture was stirred for 24 h. Saturated Na_2SO_3 aqueous solution (10 mL) was added to the reaction mixture, and the product was extracted with ether (15 mL × 3). The combined extracts were washed with brine (10 mL) and dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography (eluent hexane/AcOEt 50/1), to give the desired product **5c** (63.8 mg, 91% yield).

General Procedure for Bromide Catalyzed Transformation of Alcohols 3 into Aldehydes 5 with Metal Bromides and TEMPO (Method D) (Table 4 and Scheme 3). To a solution of **3c** (71.3 mg, 0.50 mmol), KBr (11.9 mg, 0.10 mmol), $PhSO_3H$ (15.8 mg, 0.10 mmol), and TEMPO (7.8 mg, 0.05 mmol) in CH_2Cl_2 (1 mL) was added 30% aqueous H_2O_2 (113.4 mL, 1.00 mmol) at room temperature, and the mixture was stirred for 24 h. Saturated Na_2SO_3 aqueous solution (10 mL) was added to the reaction mixture, and the product was extracted with ether (15 mL × 3). The combined extracts were washed with brine (10 mL) and dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography (eluent hexane/AcOEt 50/1), to give the desired product **5c** (69.9 mg, >99% yield).

*4-Chlorobenzaldehyde (**5c**; Commercially Available).* White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, J = 8.6 Hz, 2H), 7.83 (d, J = 8.6 Hz, 2H), 9.99 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 129.4 (2C), 130.9 (2C), 134.7, 140.9, 190.8. IR (neat): 1689, 1587, 1573, 1385, 1209, 1091 cm^{-1}.

*4-Methylbenzaldehyde (**5a**; Commercially Available).* Colorless oil (method A, 60.0 mg, >99%; method B, 59.8 mg, >99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.44 (s, 3H), 7.33 (d, J = 8.0 Hz, 2H), 7.77 (d, J = 8.0 Hz, 2H), 9.96 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 129.7 (2C), 129.8 (2C), 134.2, 145.5, 191.9. IR (neat): 1701, 1686, 1604, 1388, 1208, 1168 cm^{-1}.

*4-Fluorobenzaldehyde (**5b**; Commercially Available).* Colorless oil (method A, 57.5 mg, 93%; method B, 61.7 mg, >99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (t, J = 8.9 Hz, 2H), 7.92 (dd, J = 8.9, 5.5 Hz, 2H), 9.98 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 116.3 (d, J = 22.0 Hz, 2C), 132.2 (d, J = 10.5 Hz, 2C), 132.9 (d, J = 2.9 Hz), 116.5 (d, J = 257.7 Hz), 190.5. ^{19}F NMR (471 MHz, $CDCl_3$): δ −102.2. IR (neat): 1693, 1595, 1505, 1227, 1202, 1148 cm^{-1}.

*3-Chlorobenzaldehyde (**5d**; Commercially Available).* Colorless oil (method A, 70.1 mg, >99%; method B, 69.8 mg, >99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (t, J = 7.9 Hz, 1H), 7.61 (ddd, J = 7.9, 2.0, 1.3 Hz, 1H), 7.77 (td, J = 7.9, 1.3 Hz, 1H), 7.86 (t, J = 2.0 Hz, 1H), 9.98 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 127.9, 129.3, 130.3, 134.4, 135.4, 137.8, 190.8. IR (neat): 1697, 1572, 1385, 1192, 1072 cm^{-1}.

*2-Chlorobenzaldehyde (**5e**; Commercially Available).* Colorless oil (method A, 54.1 mg, 77%; method B, 68.1 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ, 7.40 (td, J = 7.8, 0.7 Hz, 1H), 7.46 (dd, J = 7.8, 0.7 Hz, 1H), 7.51−7.57 (m, 1H), 7.93 (dd, J = 7.8, 1.4 Hz, 1H), 10.49 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 127.3, 129.3, 130.6, 132.4, 135.1, 137.9, 189.8. IR (neat): 1694, 1591, 1442, 1266, 1197, 1052 cm^{-1}.

*1-Octanal (**5f**; Commercially Available).* Colorless oil (method A, 25.6 mg, 40%; method B, 20.7 mg, 32%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, J = 6.8 Hz, 3H), 1.21−1.39 (m, 8H), 1.63 (quin, J = 7.4 Hz, 2H), 2.42 (td, J = 7.4, 1.8 Hz, 2H), 9.77 (t, J = 1.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.0, 22.6, 29.0, 29.1, 31.6, 43.9, 203.0. IR (neat): 2926, 1726, 1465, 1379, 1145 cm^{-1}.

General Procedure for Bromide-Catalyzed Oxidation of Alcohols (8) with Metal Bromides and TEMPO under Basic Conditions (Scheme 6). To a solution of **8a** (87.1 mg, 0.50 mmol), KBr (11.9 mg, 0.10 mmol), TEMPO (15.6 mg, 0.10 mmol), and $NaHCO_3$ (126.0 mg, 1.50 mmol) in CH_2Cl_2 (2 mL) was added Oxone (307.4 mg, 0.50 mmol) at room temperature, and the mixture was stirred for 24 h. Saturated Na_2SO_3 aqueous solution (10 mL) was added to the reaction mixture, and the product was extracted with ether (15 mL × 3). The combined extracts were washed with brine (10 mL) and dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography (eluent hexane/AcOEt 50/1), to give the desired product **9a** (83.1 mg, 97% yield).

*1-Phenylhex-1-yn-3-one (**9a**).*[17c] Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00 (t, J = 7.6 Hz, 3H), 1.78 (sext, J = 7.6 Hz, 2H), 2.65 (t, J = 7.6 Hz, 2H), 7.38 (t, J = 7.6 Hz, 2H), 7.46 (t, J = 7.6 Hz, 1H), 7.58 (d, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5, 17.7, 47.4, 87.8, 90.5, 120.0, 128.6 (2C), 130.6, 133.0 (2C), 188.2. IR (neat): 2964, 2200, 1666, 1278, 1124, 1059 cm^{-1}.

*(E)-Chalcone (**9b**; Commercially Available).* White solid (103.9 mg, >99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.45 (m, 3H), 7.50 (t, J = 7.4 Hz, 2H), 7.54 (d, J = 15.8 Hz, 1H), 7.59 (tt, J = 7.4, 1.4 Hz, 1H), 7.61−7.67 (m, 2H), 7.82 (d, J = 15.8 Hz, 1H), 8.03 (d, J = 7.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 122.0, 128.4 (2C), 128.5 (2C), 128.6 (2C), 128.9 (2C), 130.5, 132.7, 134.8, 138.2, 144.8, 190.5. IR (neat): 1662, 1603, 1335, 1213, 1015, 977 cm^{-1}.

*1-Phenylbut-3-en-1-one (**9c**).*[17d] Colorless oil (62.1 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.76 (dt, J = 8.2, 1.4 Hz, 2H), 5.18−5.27 (m, 2H), 6.09 (ddt, J = 17.3, 10.4, 6.8 Hz, 1H), 7.47 (t, J = 7.5 Hz, 2H), 7.57 (t, J = 7.5 Hz, 1H), 7.97 (d, J = 7.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.4, 118.7, 128.2 (2C), 128.6 (2C), 131.0, 133.1, 136.5, 198.0. IR (neat): 1682, 1448, 1333, 1208, 1004, 920 cm^{-1}. MS (ESI): calcd for $C_{10}H_{10}NaO$ $[M + Na]^+$ 169.0624, found 169.0621.

■ ASSOCIATED CONTENT

Supporting Information

Figures giving ^{1}H and ^{13}C NMR spectra of compounds in the alkali metal bromide catalyzed oxidation of alcohols. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail for K.M.: moriyama@faculty.chiba-u.jp.

*E-mail for H.T.: togo@faculty.chiba-u.jp.

Notes

The authors declare no competing financial interest.

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