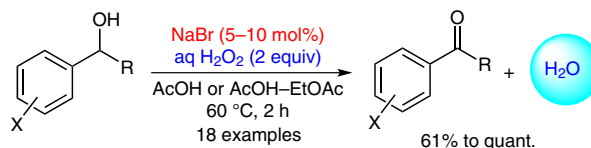H. Komagawa et al.

# Sodium Bromide-Catalyzed Oxidation of Secondary Benzylic Alcohols Using Aqueous Hydrogen Peroxide as Terminal Oxidant

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**Abstract** A halide salt, hydroperoxide and AcOH catalyst system was applied to the oxidation of secondary benzylic alcohols. This simple system can be applied to a variety of secondary benzylic alcohols and scaled up for gram-scale preparation. High secondary benzylic alcohol selectivity of the present method is demonstrated in hydroxyketone synthesis. Based on several experimental results, a catalytic cycle for our oxidation is proposed.

In the course of our continuing studies on the use of inexpensive and abundant elements and materials for organic synthesis[1] aiming at green sustainable chemistry,[2] we recently focused on the catalysis using redox property of halide ion for oxidative coupling reaction. In 2010, we have reported $n$-Bu$_4$NBr-catalyzed oxidative α-acetoxylation of ketones, where formal cross-dehydrogenative coupling (CDC) between ketone and acetic acid proceeded (Scheme 1, a).[3] More recently, we have also reported $n$-Bu$_4$NI-catalyzed intramolecular CDC reaction for the synthesis of indole derivatives, which is one of the rare examples of iodide-catalyzed oxidative carbon–carbon bond-forming reactions (Scheme 1, b).[4] Since non-metal-catalyzed oxidative transformations are quite attractive, other research groups have also focused on iodide-catalyzed reactions, and increasing reports have appeared in the last five years.[5,6] In our previous reports, we proposed that oxidation of halide ion in MX to X$_2$ in the presence of an organic substances with a sufficiently acidic hydrogen (Nu-H) co-generated the corresponding conjugate base (Nu$^-$M$^+$), as shown in Scheme 1 (c). In the case of α-acetoxylation of ketones, this Nu$^-$M$^+$ (AcO$n$-Bu$_4$N) reacts as a nucleophile with intermediate **S**–X

(α-bromo ketone) to give the product. On the other hand, in the case of indole synthesis, we demonstrated the use of Nu$^-$M$^+$ as a base instead of nucleophile made it possible for our catalyst system to create the carbon–carbon bond. This finding also suggests the possibility that various traditional oxidative transformations using stoichiometric amounts of X$_2$ and base would become catalytic.[7] Therefore, we next tried to develop oxidation of alcohols because stoichiometric oxidation reactions of hydroxyl functionality using combination of X$_2$ and base have already been known in litera-
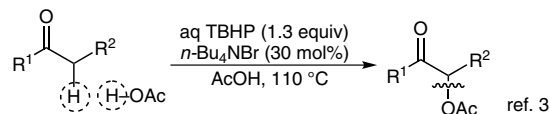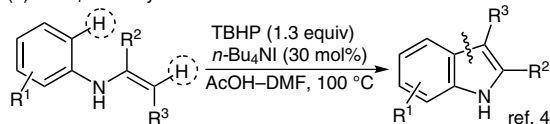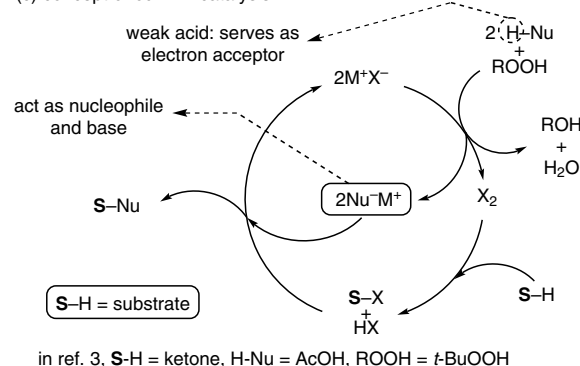


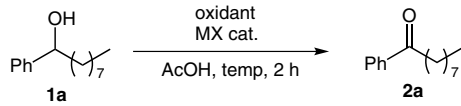**Scheme 1** Halide salt catalyzed oxidative transformation

ture[8] and would become catalytic according to our working hypothesis. Herein, we report that alkali bromide salt in acetic acid can catalyze oxidation of secondary benzylic alcohols in combination with aqueous hydrogen peroxide as terminal oxidant. Although numerous methods have been reported for catalytic oxidation of alcohols,[9] such a simple combination (NaBr, $H_2O_2$ and AcOH) has never been reported to the best of our knowledge, surprisingly.[10–14]

Initially, we optimized the reaction conditions by using 1-phenyl-1-nonanol (**1a**) as a model substrate (Table 1). Oxidation of **1a** with five equivalents of aqueous TBHP (*tert*-butyl hydroperoxide) in the presence of 10 mol% of NaBr in AcOH at 80 °C proceeded to afford the corresponding ketone **2a** in 61% yield (Table 1, entry 1). Interestingly, more environmentally benign aqueous hydrogen peroxide also worked well as an oxidant to give the ketone **2a** with slightly higher yield (Table 1, entry 2).[15] In order to increase the yield of **2a**, we performed the reaction with longer reaction time. However, the yield decreased to 62% because overoxidation of the product, which gave α-bromo and α-acetoxy ketone, took place (Table 1, entry 3). Since no improvement of conversion was observed even after longer reaction time, we assumed that the decomposition of $H_2O_2$ occurred under the conditions. In fact, stepwise addition of $H_2O_2$ was clearly effective to give **2a** in high yield (Table 1, entry 4).[16] Higher catalyst loading resulted in low yield (Table 1, entry 5). By fine-tuning of the reaction conditions, we gratifyingly found that two equivalents of $H_2O_2$ were enough to promote the reaction effectively at 60 °C. Lower reaction temperature might suppress the undesired decomposition of $H_2O_2$ (Table 1, entry 6). Although use of 5 mol% of NaBr catalyst also gave the product in synthetically acceptable high yield (Table 1, entry 7), we adopted the conditions in entry 6 (Table 1) as the optimized one for this preliminary study. Needless to say, no reaction occurred in the absence of NaBr catalyst (Table 1, entry 8). Use of KBr instead of NaBr gave similar result, although n-Bu$_4$NBr was not so effective for this alcohol oxidation (Table 1, entries 9 and 10).

With the optimized conditions in hand, we then explored the substrate scope (Scheme 2). A variety of secondary benzylic alcohols bearing substituents such as Cl, Br, NO$_2$ underwent oxidation to give the corresponding ketones in excellent yields (**2a**–**f**). Oxidation of substrate possessing electron-donating group on aromatic ring failed due to the formation of significant amounts of by-products, giving the desired alcohol **2g** in only 7% yield (vide infra). Substrate having alkyl halide moiety gave the product **2h** without any problem. Several diarylmethanol derivatives were also converted into the corresponding diaryl ketones **2i**–**k** in excellent yields.

As mentioned above, substrate having *p*-methoxypenyl group gave the product **2g** in poor yield. In this case, 4-methoxy-α-methylbenzyl acetate (**3**) and 4-methoxy-α-methylbenzyl hydroperoxide (**4**) were major products. Because

**Table 1**  Optimization of Reaction Conditions[a]



| Entry | Cat. (mol%) | Oxidant (equiv) | Temp (°C) | Yield (%)[b] |
|---|---|---|---|---|
| 1 | NaBr (10) | aq TBHP (5) | 80 | 61 (63) |
| 2 | NaBr (10) | aq $H_2O_2$ (5) | 80 | 71 (71) |
| 3[c] | NaBr (10) | aq $H_2O_2$ (5) | 80 | 62[d] (70) |
| 4 | NaBr (10) | aq $H_2O_2$ (5)[e] | 80 | 98 (100) |
| 5 | NaBr (30) | aq $H_2O_2$ (5) | 80 | 56 (56) |
| 6[f] | NaBr (10) | aq $H_2O_2$ (2)[g] | 60 | 98[h] (100) |
| 7[f] | NaBr (5) | aq $H_2O_2$ (2)[g] | 60 | 96 (99) |
| 8[f] | none | aq $H_2O_2$ (2)[g] | 60 | 0 (0) |
| 9[f] | KBr (10) | aq $H_2O_2$ (2)[g] | 60 | 97[h] (100) |
| 10[f] | n-Bu$_4$NBr (10) | aq $H_2O_2$ (2)[g] | 60 | 71 (78) |

[a] Reaction was carried out with **1a** (0.5 mmol) in AcOH (0.5 mL).
[b] Determined by $^1$H NMR analysis. Conversions of **1a** are shown in parentheses.
[c] Reaction was carried out for 6 h.
[d] Corresponding α-bromo and α-acetoxy ketones were also detected as by-products in 3% and 1% yields, respectively.
[e] 2.5 equiv of $H_2O_2$ were added at the beginning, and then an additional 2.5 equiv of $H_2O_2$ were added after 1 h.
[f] AcOH (1.0 mL) was used as solvent.
[g] 1.0 equiv of $H_2O_2$ was added at the beginning, and then an additional 1.0 equiv of $H_2O_2$ was added after 1 h.
[h] Isolated yield.



**Scheme 2**  Substrate scope under optimized conditions
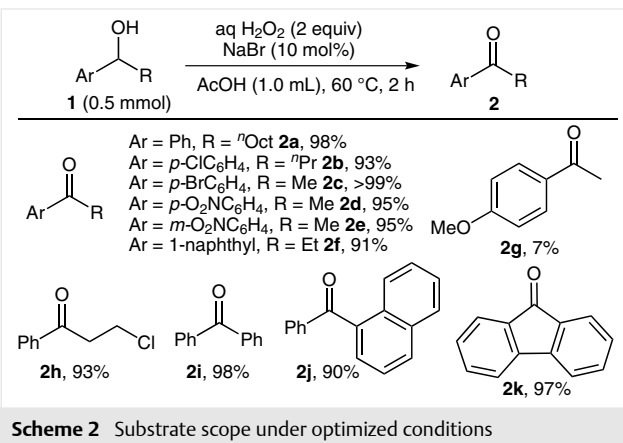
formation of compounds **3** and **4** were also observed in the reaction without NaBr catalyst,[17] formation of these products occurred independently from the oxidation reaction pathway. Since an electron-donating group on aromatic ring stabilizes the benzylic cation, these products seem to originate from the reaction of the cationic species with AcOH and $H_2O_2$. In order to overcome this issue, we again carried out the optimization of the conditions for substrate **1g** (Table 2). After testing several co-solvents, we found that a mixture of acetic acid and ethyl acetate was effective to

suppress the undesired reaction via benzylic cation. The best result was obtained when the reaction was performed in AcOH–EtOAc (3:7, 0.25 M), giving the desired ketone **2g** in 86% isolated yield (entries 1–5). This reaction condition was applied to a variety of substrates such as 1-*o*-methoxy-phenyl-1-ethanol (**1l**), cyclopropylphenylmethanol (**1m**), and various cyclic substrates **1n–p** to afford the corresponding ketones **2l–p** in good yields (Figure 1).[18]

**Table 2**  Optimization of Conditions for Substrate **1g**[a]
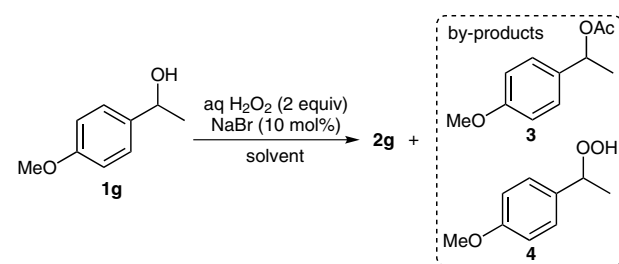


| Entry | Solvent | Yield of **2g** (%)[b] | Yield of **3** (%)[b] | Yield of **4** (%)[b] |
|---|---|---|---|---|
| 1 | AcOH | 7 | 27 | 15 |
| 2 | AcOH–EtOAc (7:3) | 31 | 31 | 10 |
| 3 | AcOH–EtOAc (5:5) | 47 | 13 | 7 |
| 4 | AcOH–EtOAc (3:7) | 60 | 5 | 4 |
| 5[c] | AcOH–EtOAc (3:7) | 86[d] | trace | trace |

[a] Reaction was carried out with **1g** (0.5 mmol) and NaBr (10 mol%) in solvent (1.0 mL) at 60 °C for 2 h.
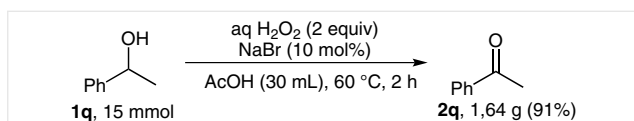[b] Determined by $^1$H NMR analysis of crude material.
[c] Volume of solvent used was 2.0 mL.
[d] Isolated yield.
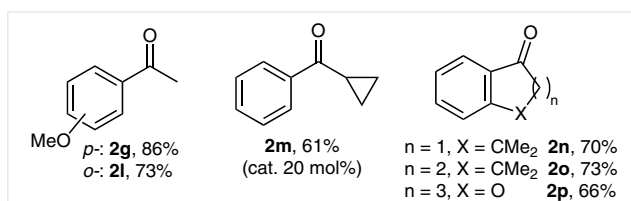


**Figure 1**  Substrate scope under the conditions in Table 2, entry 5

We next tried the gram-scale preparation. Thus the oxidation reaction using 15 mmol of 1-phenyl-1-ethanol (**1q**) gave 91% yield (1.64 g) of acetophenone (**2q**) without any technical trouble (Scheme 3).[19]



**Scheme 3**  Gram-scale preparation of acetophenone

During our studies on this halide ion catalysis, it was found that aliphatic primary alcohols are not reactive toward NaBr-catalyzed oxidation.[20] Taking advantage of this finding, a chemoselective oxidation was realized for the substrate **1r** which possesses both secondary benzylic alcohol and primary alcohol moieties. Thus the reaction of **1r** under standard optimized conditions gave 83% yield of hydroxy ketone **2r**, leaving primary hydroxy group intact. Present catalyst system and primary-alcohol-selective oxidation reported previously in literature[21] are regarded as complementary methods as demonstrated in Scheme 4.
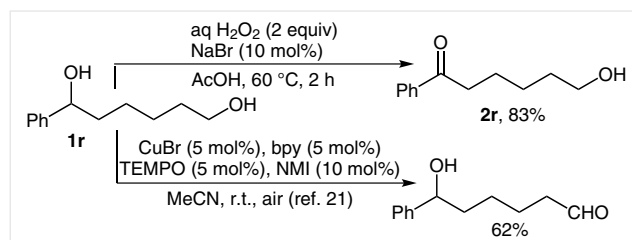


**Scheme 4**  Preliminary study on chemoselective oxidation of diol substrate

In order to gain insight on the reaction mechanism, we performed several experiments (Scheme 5). Combination of one equivalent of Br$_2$ and two equivalents of NaOAc oxidized the alcohol **1a** to afford **2a** in good yield (Scheme 5, eq. 1). On the other hand, use of Br$_2$ in the absence of NaOAc gave no desired ketone (Scheme 5, eq. 2). In this case, 2-bromo-1-phenylnonan-1-one, 1-phenyl-1-nonene and 1,2-dibromo-1-phenylnonane were observed in crude mixture, suggesting that HBr-catalyzed dehydration of benzylic alcohol **1a** and subsequent bromination of the resulting olefin occurred along with α-bromination of initially formed **2a**.[22] These experiments clearly indicated the importance of NaOAc. Addition of one equivalent of TEMPO resulted in low yield of oxidation product (Scheme 5, eq. 3). It should be noted here that formation of organic radical species might be ruled out because radical clock substrate possessing cyclopropyl ring underwent the oxidation to afford the corresponding ketone **2m** without skeletal rearrangement (vide supra, Figure 1).[23] Moreover, Br$_2$/NaOAc oxidation was not inhibited by TEMPO as shown in Scheme 5, eq. 4. We then investigated the effect of adding TEMPO in more detail (Scheme 5, eqs. 5–7). The reaction of 0.90 mmol of NaBr with 0.45 mmol of H$_2$O$_2$ in AcOH at 60 °C for one hour gave pale brown solution containing 0.12 mmol of Br$_2$.[24,25] To the resulting mixture was added 0.45 mmol of **1a**, and the mixture was stirred for two hours at that temperature. From this experiment, 0.11 mmol of **2a** was isolated, that means the yield of **2a** was 92% based on generated Br$_2$ (Scheme 5, eq. 5). As a control experiment, when TEMPO was added at an early stage, the yield of **2a** was dramatically decreased as shown in Scheme 5, eq. 6. On the other hand, addition of TEMPO after the formation of Br$_2$

not only did not inhibit but also promoted the reaction (Scheme 5, eq. 7). Formation of 267% of **2a** based on initially formed $Br_2$ means that some re-oxidation step with TEMPO exists in this reaction although the detail is not clear at this stage. Anyway, the low yield observed in Scheme 5, eq. 3 was undoubtedly attributed to inhibition of the formation of $Br_2$ from NaBr by TEMPO.[26]
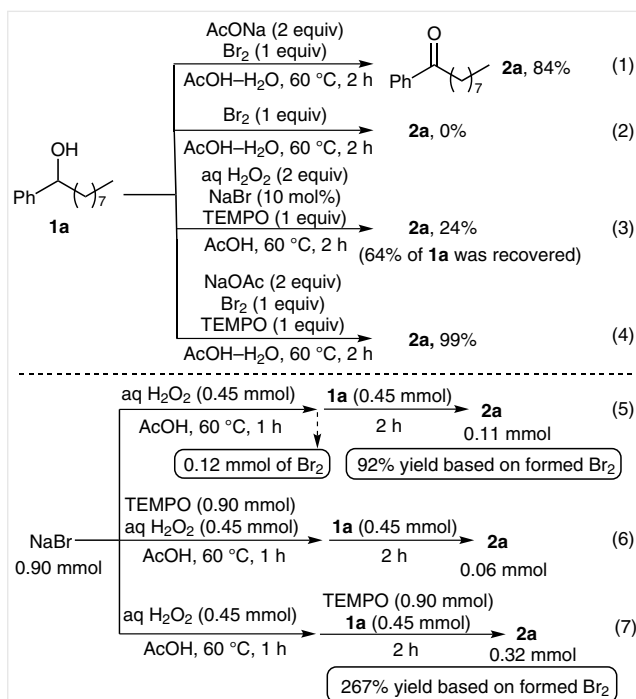


**Scheme 5** Mechanistic study

Based on the above-mentioned experimental results, a plausible catalytic cycle for the present oxidation is illustrated in Scheme 6. Thus the oxidation of NaBr with $H_2O_2$ in the presence of AcOH as proton source gives $Br_2$ along with the corresponding conjugate base NaOAc (*step A*). Then the reaction of $Br_2$ with benzylic alcohol proceeds in ionic manner to afford the corresponding hypobromite intermediate (*step B*), from which dehydrobromination (*step C*) occurs to
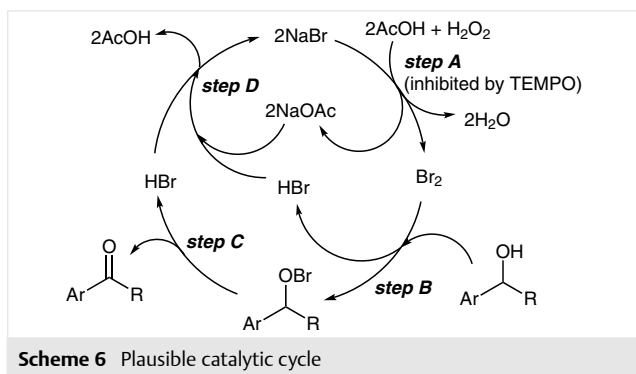


**Scheme 6** Plausible catalytic cycle

give ketone.[27] Hydrogen bromide formed at *steps B* and *C* are ambushed by initially formed NaOAc to furnish the catalytic cycle (*step D*).[28]

In summary, we have developed a simple NaBr-catalyzed oxidation of secondary benzylic alcohols.[29] A wide variety of functional groups are tolerated under the conditions and the reaction is scalable. This oxidation is highly chemoselective toward a secondary hydroxy group at the benzylic position. Further applications of this halide ion catalysis are in progress in our laboratory.

## Acknowledgment

## Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560549.

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(17) Reaction of **1g** with 0.5 equiv of $H_2O_2$ in AcOH for 1 h at 60 °C in the absence of NaBr gave **3** and **4** in 59% and 20% yields, respectively.

(18) In Togo's catalyst system (see ref. 13), cyclic substrate like 1-tetralol does not undergo oxidation.

(19) We did not perform the reaction in more than 15-mmol scale.

(20) We have tried the oxidation of 1-hexadecanol (aliphatic primary alcohol) under optimized condition. However no oxidation took place, resulting in recovery of the starting material. Oxidation of 3-undecanol (aliphatic secondary alcohol) under optimized conditions proceeded sluggishly to afford the corresponding ketone in 38% yield. Furthermore, oxidation of substrates possessing alkenyl moiety such as 1-phenyl-5-hexen-1-ol and cinnamyl alcohol did not proceed well probably due to the rapid consumption of catalytically active $[Br^+]$ species by olefin.

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(25) The amount of $[Br^+]$ was determined by titration using cyclohexene in hexane (three independent experiments). After titration, usual aqueous work up was performed, and major product from the reaction with cyclohexene was found to be *trans*-1,2-dibromocyclohexane, indicating the formation of $Br_2$ instead of other $[Br^+]$ species, see the Supporting Information.

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(28) NaOAc-assisted dehydrobromination like E2-elimination is an alternative possibility for *step C*.

(29) **General Procedure for NaBr-Catalyzed Oxidation**: Under a nitrogen atmosphere, to a solution of substrate alcohol (0.5 mmol) in AcOH (1.0 mL) or AcOH–EtOAc (3:7, 2.0 mL) was added a stock solution of aq NaBr solution (1.94 M, 25 μL) and 30% aq $H_2O_2$ (50 μL, 0.5 mmol). After stirring the mixture for 1 h at 60 °C, additional 30% aq $H_2O_2$ (50 μL, 0.5 mmol) was added, and stirring was continued for another 1 h. After cooling, the mixture was poured into a sat. aq $NaHCO_3$ solution (ca. 30 mL) with the aid of $CH_2Cl_2$, and the resulting mixture was extracted with $CH_2Cl_2$. The combined organic layers were dried over anhyd $MgSO_4$, filtered and concentrated in vacuo. The residue was chromatographed on silica gel (flash column or preparative TLC) to afford the corresponding ketone. **Caution**: When the reaction is carried out on a large scale, treatment of the combined organic layers with aq $Na_2S_2O_3$ solution is recommended to avoid unexpected explosion.

**1-Phenylnonan-1-one (2a)**: Compound **2a** was obtained according to the general procedure and purified by preparative TLC (hexane–EtOAc, 20:1) as a colorless oil. $^1$H NMR (500 MHz, CDCl$_3$): δ = 7.96 (d, *J* = 7.5 Hz, 2 H), 7.54–7.57 (m, 1 H), 7.45–7.48 (m, 2 H), 2.96 (t, *J* = 7.5 Hz, 2 H), 1.74 (m, 2 H), 1.27–1.44 (m, 10 H), 0.88 (t, *J* = 6.9 Hz, 3 H). $^{13}$C NMR (125 MHz, CDCl$_3$): δ = 200.6, 137.0, 132.8, 128.5, 128.0, 38.6, 31.8, 29.4, 29.3, 29.1, 24.3, 22.6, 14.1. The NMR data are in agreement with those previously reported in literature (see ref. 30).

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