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Redox Catalysis of Halide Ion for Formal Cross-dehydrogenative Coupling: Bromide Ion-catalyzed Direct Oxidative α-Acetoxylation of Ketones

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A novel catalytic approach for formal cross-dehydrogenative coupling using the redox property of bromide ion is reported. Simple bromide salts MBr can work as catalyst for direct oxidative α-acetoxylation of ketones.

Recent growing interest in green sustainable chemistry for the next generation requires the development of organic transformations using safe, environmentally benign, and abundant elements and materials.[1] In the course of our continuing studies of the use of inexpensive and abundant metal catalysts for organic transformations,[2] we recently pursued the use of the redox property of halide ions for organic synthesis and uncovered that alkaline metal bromide and related bromide salts MBr can be used as catalysts for dehydrogenative coupling reactions. An outline of this MBr catalysis is shown in Chart 1. The bromide ion in MBr is known to undergo oxidation by various oxidants in an appropriate acidic medium. For example H_2O_2 oxidation of KBr in aqueous H_2SO_4 gives molecular bromine along with K_2SO_4 according to the following fundamental chemical equation: $2KBr + H_2O_2 + H_2SO_4 = Br_2 + 2H_2O + K_2SO_4$.[3] In this reaction H^+ acts as an electron acceptor (oxygen acceptor) at oxidation. When proton is provided from organic substance having sufficient acidic hydrogen (NuH) instead of inorganic strong Brønsted acid, the total oxidation process should give molecular bromine and MNu. Incorporation of bromine atom at higher oxidation state into a substrate followed by nucleophilic attack by MNu, *which is generated from MBr in the oxidation step*, will regenarate MBr along with the formal dehydrogenative coupling product **S**–Nu (Scheme 1, eqs 1–4). Although a few examples using atom transfer redox catalysis using halide ions have been reported to date, external nucleophiles were used in all cases,[4] and to the best of our knowledge there is no report on using nucleophile cogenerated at the step of oxidation of bromide ion to molecular bromine. Moreover, it is very surprising that such a catalysis has never been reported although each elementary reaction shown in eqs 1–4 is classical, fundamental, and well-known to organic chemists. We chose direct oxidative α-acetoxylation of ketone[5] as an initial trial for realizing such attractive and atom economical catalytic reaction and for demonstrating our concept of MBr catalysis for formal cross-dehydrogenative coupling.[6]

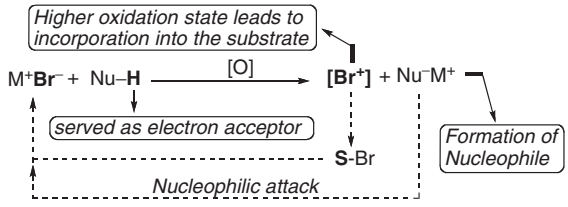
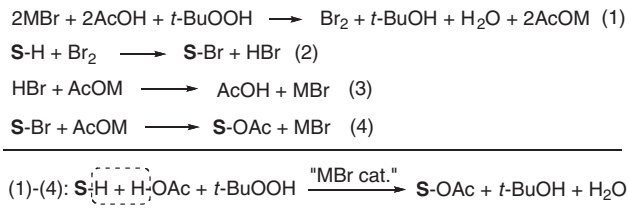


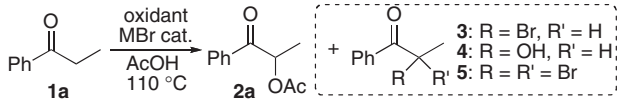
Chart 1. Concept of MBr catalysis.



Scheme 1. Elementary step in MBr catalysis for cross-dehydrogenative coupling between **S**–H and AcOH (**S**–H = ketone in this study).

Initially, we carried out the optimization of reaction conditions by using propiophenone (**1a**) as a model substrate. The reaction of **1a** with aq. TBHP in the presence of 100 mol % of NaBr in AcOH gave the corresponding α-acetoxylation product **2a** in 48% yield as expected, while no reaction occurred in the absence of NaBr (Table 1, Entries 1 and 2). In the case of using H_2O_2 as oxidant very poor conversion was observed although the color change of the reaction mixture from colorless to brown suggested that oxidation of bromide ion to Br_2 occurred (Entry 3). In this case rapid decomposition of H_2O_2 in the presence of Br_2 was probably the main reason.[7] LiBr, KBr, and NH_4Br also gave the product but efficiency was low (Entries 4–6). Low efficiency observed in Entries 1, 4, 5, and 6 were undoubtedly attributed to remaining intermediate α-bromoketone **3**, which retarded the effective catalytic turnover of Br^-. These results are consistent with the well-known fact that nucleophilicity of hard ionic nucleophiles decreases in protic solvent because of solvation of the anion via hydrogen bonding.[8] Among the bromide salts tested, *n*-Bu_4NBr was found to be a good candidate. In this case, no by-product **3** was observed, indicating the rate of the reaction of *n*-Bu_4NOAc with **3** was fast enough even in protic solvent, probably because of the minimal ion pairing between bulky *n*-Bu_4N^+ and AcO^- (Entry 7).[9] With the conditions giving complete conversion of **3** in hand, we then tried to reduce the catalyst loading. In the presence of 50 mol % of *n*-Bu_4NBr, the reaction proceeded with similar efficiency although conversion was still not satisfactory (Entries 8 and 9). Longer reaction time did not improve the conversion signifi-

Table 1. Optimization of conditions[a]



Entry	MBr/mol %	Oxidant (equiv)	AcOH /mL	Time /h	Conv. /%[b]	Yield/%[b] 2a	3	4	5
1	NaBr (100)	TBHP (5)	1.0	16	82	48	19	5	3
2	none	TBHP (5)	1.0	16	N.R.[e]	0	0	0	0
3	NaBr (100)	H_2O_2 (5)	1.0	16	8	0	8	0	0
4	LiBr (100)	TBHP (5)	1.0	16	61	38	16	4	0
5	KBr (100)	TBHP (5)	1.0	16	89	61	10	4	8
6	NH_4Br (100)	TBHP (5)	1.0	16	96	37	7	0	30
7	*n*-Bu_4NBr (100)	TBHP (5)	1.0	16	88	68	0	9	0
8	*n*-Bu_4NBr (100)	TBHP (2)	1.0	16	77	67	0	5	3
9	*n*-Bu_4NBr (50)	TBHP (2)	1.0	16	83	69	2	4	2
10	*n*-Bu_4NBr (50)	TBHP (2)	1.0	43	88	65	0	12	1
11	*n*-Bu_4NBr (50)	TBHP (1.3)	0.25	24	66	54	0	5	<1
12	*n*-Bu_4NBr (50)	TBHP (1.3)[c]	0.25	24	95	77	0	4	<1
13	*n*-Bu_4NBr (30)	TBHP (1.3)[d]	0.25	24	94	76	0	5	<1
14	*n*-Bu_4NBr (20)	TBHP (1.3)[d]	0.25	24	90	68	0	3	<1

[a]**1a** (1.5 mmol), 70% aq. TBHP or 30% aq. H_2O_2 were used. [b]Estimated by ^{1}H NMR analysis of crude material using CH_3NO_2 as internal standard. [c]0.25 equiv of TBHP was added in portions every 2.5 h. [d]0.25 equiv of TBHP was added in portions every 3 h. [e]N.R.: no reaction.

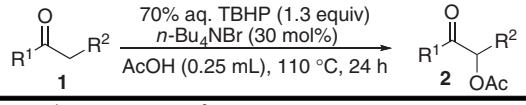
cantly, suggesting that the decomposition of TBHP occurred under the conditions (Entry 10). Indeed stepwise addition of TBHP was found to be clearly effective, resulting in high conversion and good yield of the desired α-acetoxy ketone by using only 1.3 equiv of TBHP (Entries 11 and 12). Finally we were able to reduce the catalyst loading to 30 mol % without loss of efficiency of the catalysis (Entry 13).

This catalytic system was applicable to a variety of ketones including aryl alkyl ketones with both electron-donating and electron-withdrawing groups on the aromatic ring to give the corresponding α-acetoxyketone in moderate to good yields except for acetophenone (Table 2). In the case of acetophenone, rapid overbromination retarded the catalysis under the present conditions and this issue is to be resolved in the future.[10]

As shown in Scheme 2, the reaction of **1a** with Br_2 in acetic acid gave 93% of α-bromoketone **3** with no **2a**, suggesting that the present system did not proceed via simple solvolysis of **3** with acetic acid (eq 5). On the other hand, addition of *n*-Bu_4NOAc in the above reaction gave **2a** instead of **3** as a major product (eq 6). Moreover, the reaction of **1a** with TBHP in the presence of both *n*-Bu_4NOAc and α-bromovalerophenone (**6**) gave the corresponding α-acetoxyketones **2a** and **2b** in good yields (eq 7). These results clearly showed that regeneration of *n*-Bu_4NBr and subsequent reoxidation, incorporation of resulting Br_2 into **1a**, and nucleophilic substitution reaction occurred as proposed in Scheme 1 (from eqs 4 → 1 → 2,3 → 4).

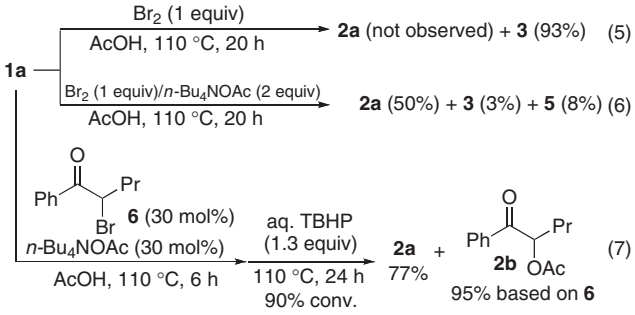
In summary, we have demonstrated a novel catalytic approach for formal dehydrogenative coupling using the redox property of bromide ions in MBr. This system also showed the oxidative recycling of MBr waste generated from the substitution reaction between MNu and RX, which was originally not an atom-economical reaction, enabling it to be a net atom-economical transformation.[11] Further applications of this concept are now in progress in our laboratory.

Table 2. Substrate scope of Br^--catalyzed direct α-acetoxylation[a]



Entry	R^1	R^2	α-Acetoxyketone (**2**)	Yield/%[b]
1	Ph	Me	**2a**	74
2[c]	Ph	*n*-Pr	**2b**	63
3	Ph	Ph	**2c**	41[d]
4	Ph	H	**2d**	15
5	*p*-BrC_6H_4	Me	**2e**	68
6	*p*-ClC_6H_4	Me	**2f**	70
7	*p*-$MeOC_6H_4$	Me	**2g**	67
8	*p*-$TfOC_6H_4$	Me	**2h**	69
9[e]	2-naphthyl	Me	**2i**	63
10[f]	*t*-Bu	Me	**2j**	40 (52)[g]

[a]Reaction scale: 1.5 mmol of **1**. 0.25 equiv of TBHP was added 5 times once every 3 h. [b]Isolated yield after column chromatography. [c]0.25 equiv of TBHP was added 7 times once every 3 h (total 1.8 equiv). [d]1,2-Diphenylethandione was also isolated in 22% yield. [e]AcOH (0.30 mL) was used. [f]3.0 mmol scale. [g]GC yield in parenthesis.



Scheme 2. Support for expected mechanism.

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