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Oxidative oxygen-nucleophilic bromo-cyclization of alkenyl carbonyl compounds without organic wastes using alkali metal reagents in green solvent†

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A bromo-lactonization of alkenyl carboxylic acids and a bromo-cyclization of *N*-allyl amides as oxygen-nucleophilic bromo-cyclization reactions were developed *via* the oxidative umpolung of bromide using alkali metal bromide and inorganic oxidant to provide the corresponding cyclization products in high yields. In particular, the use of AcOEt, the solvent of choice for green sustainable reactions, led to the high reactivities of the present reactions. This methodology is highly recommended for green sustainable chemistry because it uses stable and non-hazardous reagents instead of other bromo reagents and oxidants, and does not produce organic wastes that pollute the environment.

Introduction

The halogenation of organic molecules is a very important tool for producing the carbon halides, which are indispensable intermediates for a variety of transformations.[1] Electrophilic bromination of π-electron donors has employed molecular bromine (Br_2)[2] and organic bromo reagents, such as *N*-bromo-succinimide (NBS),[3] 1,3-dibromo-5,5-dimethylhydantoin (DBH),[4] 2,4,4,6-tetrabromohexa-2,5-dienone (TBCO),[5] and pyridinium tribromide.[6] However, when utilizing these reagents it is difficult to avoid handling of hazardous compounds or producing stoichiometric amounts of the corresponding organic wastes, which must be purified by silica gel chromatography (Fig. 1, eqn (1)). On the other hand, oxidative transformations *via* the umpolung of halides (I^-, Br^-, and Cl^-) into halonium ions (X^+) using oxidants are an essential process in many organisms[7] and have attracted much attention as a green sustainable method in organic synthesis.[8] Alkali metal halides are one of the most abundant natural resources on earth; they are stable in air, easy to handle, neutral, and non-toxic, and non-elaborating products polluted the environment. We have developed various oxidative transformations *via* the umpolung of bromide using alkali metal bromide including intramolecular bromo-amination of *N*-alkenylsulfonamides and *N*-alkenoxysulfonamides,[9a] direct benzylic oxidation of alkylarenes,[9b] Hofmann-type rearrangement of cyclic imides,[9c] KBr-catalyzed oxidation of alcohols,[9d] and debenzylation of *N*-benzylamide and *O*-benzyl ethers.[9e] However, those methods require such problematic solvents for health, safety, and environment as $MeNO_2$ and MeCN. The oxygen-nucleophilic bromo-cyclization is a very effective method for producing oxygen-containing heterocycles, which are useful building blocks of natural products and pharmaceuticals.[10] For the oxygen-nucleophilic bromo-cyclization of alkenyl carbonyl compounds with NBS, organocatalysts or activating reagents have been adopted to promote the electrophilic addition of bromonium ion (Br^+) to alkenes.[11] Recently, some oxidative bromo-lactonization reactions of alkenyl carboxylic acids using alkali metal bromides have been reported. However, those reactions also require a stoichiometric or catalytic amount of

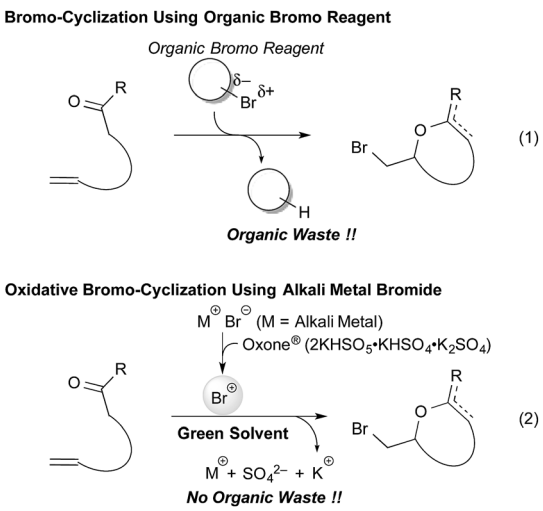

Fig. 1 Oxidative bromo-cyclization of alkenyl carbonyl compounds.

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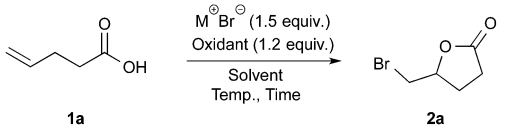
† Electronic supplementary information (ESI) available: General procedures, characterization data (^1H and ^{13}C NMR, IR, and HRMS), and ^1H and ^{13}C NMR spectra of compounds for the bromo-lactonization and the bromo-cyclization. See DOI: 10.1039/c5ra19851h

organic chalcogen compounds, such as organotelluride,[12a,b] arylselenic acid,[12c] aryl benzyl selenoxide,[12d,e] organic diselenide,[12f,g] and methyl phenyl sulfoxide,[12h] or hypervalent iodine, such as (diacetoxy)iodobenzene.[12i] We also disclosed diastereoselective bromo-lactonization of α-substituted 4-pentenoic acids and 4-pentenamides using alkali metal bromide but this method is limited to α-substituted alkenyl carbonyl compounds.[9f] Nevertheless, the high performance of bromonium ion species generated from alkali metal bromide with oxidant has possibility of various oxygen-nucleophilic bromo-cyclization of alkenyl carbonyl compounds without any additives. In this regard, both research laboratories and chemical industry are looking into the possibility of using green solvents, such as H_2O, alcohols, and acetic esters, for green sustainable chemistry.[13] We report herein an oxidative oxygen-nucleophilic bromo-cyclization in a green solvent, which involves the umpolung of bromide into bromonium ion using alkali metal bromide and inorganic oxidant without activating organic reagents. The reaction is a green sustainable method because it proceeds under mild conditions and does not produce any organic wastes (Fig. 1, eqn (2)).

Results and discussion

First, we investigated the oxidative bromo-lactonization of alkenyl carboxylic acids using alkali metal bromides and oxidants. We screened for solvents, oxidants, and alkali metal bromide or alkaline metal bromide for the oxidative bromo-lactonization of 4-pentenoic acid **1a** (Table 1). When **1a** was treated with KBr and Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) in MeCN at room temperature, 5-(bromomethyl)butyrolactone (**2a**) was obtained in 69% yield (Entry 1). Whereas the reaction in THF showed similar reactivity to that in MeCN, the reactions in CH_2Cl_2, AcOEt, and toluene gave **2a** in low yields (Entries 2–5). The reaction in $MeNO_2$ gave **2a** in 98% yield (Entry 6). Other oxidants, such as H_2O_2 aq., *m*CPBA, $PhI(OAc)_2$, and $K_2S_2O_8$, were much less effective than Oxone® (Entries 7–10). Use of NaBr and $CaBr_2$ instead of KBr decreased the yields of **2a** (Entries 11 and 12). Fortunately, the bromo-lactonization of **1a** with AcOEt was completed in 26 h, and its yield was similar to that of the bromo-lactonization in $MeNO_2$ (92% *vs.* 98% for Entries 13 *vs.* 6, respectively). It was reported that AcOEt is the solvent choice for green sustainable reactions.[13] Lowering the reaction temperature gave the best results in the presence of both solvents (Entries 14 and 15).

Table 1 Screening for alkali metal bromide or alkaline metal bromide, oxidant, and solvent for oxidative bromo-lactonization of **1a**



1a **2a**

Entry	MX	Oxidant	Solvent	Time (h)	Yield (%)
1	KBr	Oxone®	MeCN	5	69
2	KBr	Oxone®	CH_2Cl_2	20	14
3	KBr	Oxone®	AcOEt	20	57 (28)[a]
4	KBr	Oxone®	THF	5	71
5	KBr	Oxone®	Toluene	20	38
6	KBr	Oxone®	$MeNO_2$	20	98
7	KBr	H_2O_2 aq.	$MeNO_2$	20	9 (64)[a]
8	KBr	*m*CPBA	$MeNO_2$	20	54 (15)[a]
9	KBr	$PhI(OAc)_2$	$MeNO_2$	20	26 (36)[a]
10	KBr	$K_2S_2O_8$	$MeNO_2$	20	7 (35)[a]
11	NaBr	Oxone®	$MeNO_2$	20	72
12	$CaBr_2$	Oxone®	$MeNO_2$	20	17 (49)[a]
13	KBr	Oxone®	AcOEt	26	92
14[b]	KBr	Oxone®	$MeNO_2$	23	97
15[b]	KBr	Oxone®	AcOEt	30	98

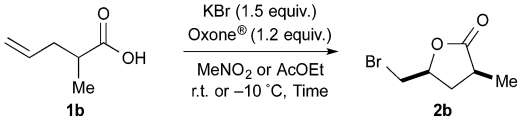
[a] Numbers in the parenthesis indicate the recovery of **1a**. [b] The reaction was carried out at −10 °C.

The bromo-lactonization of α-substituted alkenyl carboxylic acid is problematic in terms of the diastereoselectivity of the product. Indeed, the reaction of 2-methyl-4-pentenoic acid (**1b**) with alkali metal bromide at room temperature provided the bromo-lactonization product (**2b**) in a quantitative yield with moderate diastereoselectivity (dr = 67 : 33 to 72 : 28) (Table 2, Entries 1 and 2). Treatment of **1b** with KBr and Oxone® in $MeNO_2$ or AcOEt at −10 °C slightly increased the diastereoselectivity of the bromo-lactonization (Entries 1 *vs.* 3 and 2 *vs.* 4).

To explore the scope of the oxidative bromo-lactonization *via* the umpolung of bromide using alkali metal bromide, various alkenyl carboxylic acids **1** were examined under the optimum conditions (Table 3).

For the bromo-lactonization in $MeNO_2$, various substrates bearing α,α-disubstituents (**1c** and **1d**) as well as *geminal*-disubstituted (**1e** and **1f**) and *vicinal*-disubstituted (**1g–1j**) alkenes were converted into the corresponding products (**2c–2j**) in high yields, respectively (Entries 1–8). When β-substituted alkenyl carboxylic acid (**1k**) was used, β,γ-disubstituted γ-lactone (**2k**) was obtained in 90% yield with moderate diastereoselectivity (dr = 63 : 37) (Entry 9). Moreover, the six-membered ring cyclization by bromo-lactonization proceeded efficiently to give δ-substituted δ-lactone (**2l**) in 81% yield (Entry 10). The bromo-lactonization in AcOEt using KBr and Oxone® showed similar reactivity to that in $MeNO_2$ except for the six-membered-ring bromo-lactonization

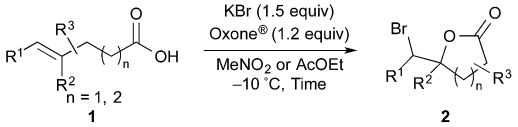
Table 2 Oxidative bromo-lactonization of α-substituted alkenyl carboxylic acid **1b**

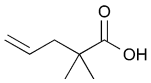
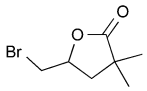
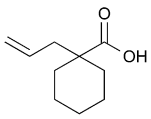
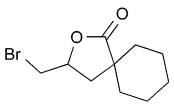
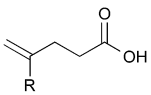
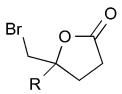
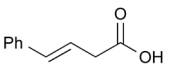
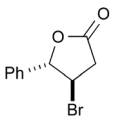
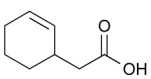
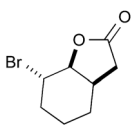
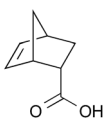
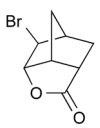
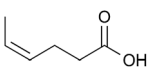
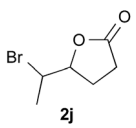
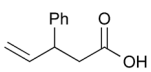
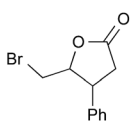
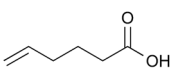
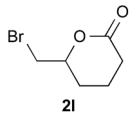


1b **2b**

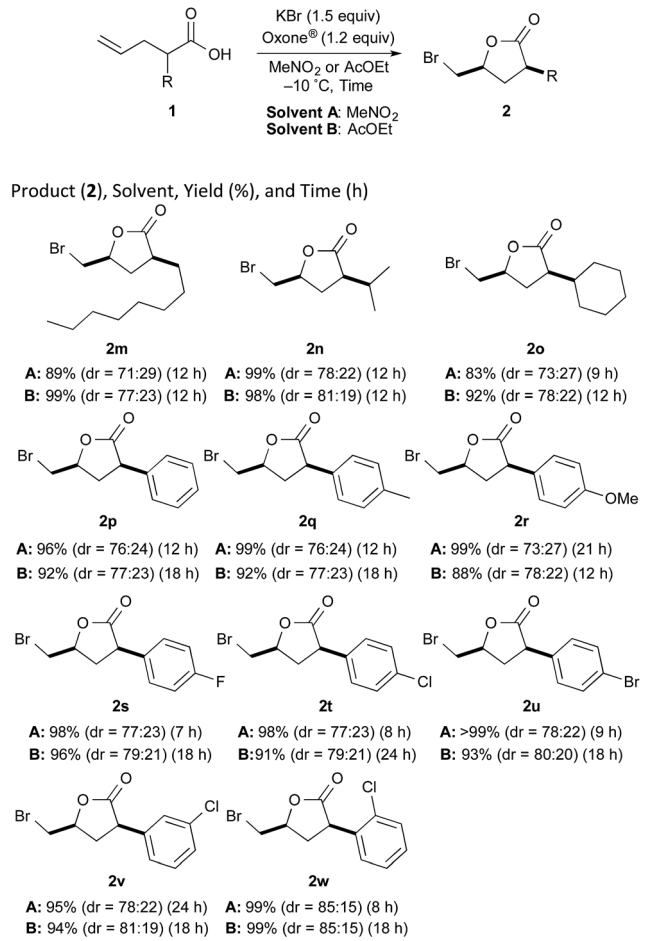
Entry	Solvent	Temp. (°C)	Time (h)	Yield (%)	dr of **2b**
1	$MeNO_2$	r.t.	18	99	67 : 33
2	AcOEt	r.t.	12	99	72 : 28
3	$MeNO_2$	−10	12	99	72 : 28
4	AcOEt	−10	12	98	77 : 23

Table 3 Oxidative bromo-lactonization of **1** using KBr and Oxone®



Entry	Substrate	Product	Yields (%) $MeNO_2$	Yields (%) AcOEt
1	 **1c**	 **2c**	99% (12 h)	95% (12 h)
2	 **1d**	 **2d**	95% (18 h)	95% (18 h)
3	 R = Me (**1e**)	 **2e**	99% (12 h)	98% (24 h)
4	R = Ph (**1f**)	**2f**	99% (10 h)	99% (12 h)
5	 **1g**	 **2g**	91% (dr = >99 : <1) (28 h)	90% (dr = >99 : <1) (28 h)
6	 **1h**	 **2h**	85% (dr = >99 : <1) (12 h)	85% (dr = >99 : <1) (12 h)
7	 **1i**	 **2i**	89% (dr = >99 : <1) (8 h)	94%[a] (dr = >99 : <1) (20 h)
8	 **1j**	 **2j**	87%[b] (dr = >99 : <1) (30 h)	86%[c] (dr = >99 : <1) (45 h)
9	 **1k**	 **2k**	90% (dr = 63 : 37) (18 h)	81% (dr = 53 : 47) (18 h)
10	 **1l**	 **2l**	81%[d,e] (7 h)	0%[d] (48 h)

[a] The reaction was carried out in AcOEt (0.125 M). [b] The reaction was carried out in AcOEt (0.0625 M). [c] The reaction was carried out at −40 °C. [d] TsOH (10 mol%) was added. [e] The reaction was carried out in a solution of $MeNO_2$ and toluene (3 : 1).



Scheme 1 Oxidative bromo-lactonization of α-substituted 4-pentenoic acid (**1**).

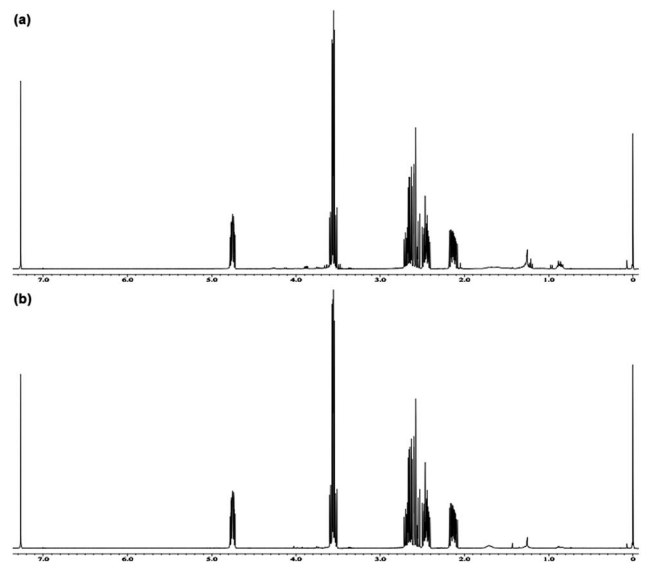
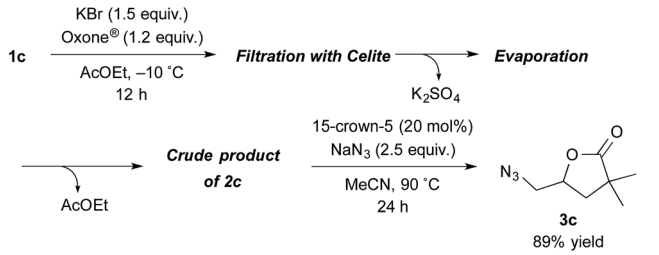


Fig. 2 NMR spectra of **2a** after the bromo-lactonization using KBr and Oxone®. (a) NMR spectrum of crude product **2a** obtained by filtration with Celite and evaporation (Table 1, Entry 15). (b) NMR spectrum of product **2a** purified by column chromatography.



Scheme 2 Transformation into γ-azidomethyl lactone (**3c**) from **1c** without purification of **2c** *via* oxidative bromo-lactonization using KBr and Oxone®.

(Entries 1–10, right column). Subsequently, the bromo-lactonization of α-substituted 4-pentenoic acids (**1m–1w**) was investigated by performing the oxidation of bromide in both $MeNO_2$ and AcOEt (Scheme 1). The reaction of α-alkylated pentenoic acids (**1m–1o**) also provided α,γ-disubstituted γ-butyrolactones (**2m–2o**) in high yields (83–99%) with moderate diastereoselectivities (dr = 71 : 29 to 81 : 19). α-Arylated alkenyl pentenoic acids bearing various substituents on the aromatic ring (**1p–1w**) were also transformed into the corresponding products (**2p–2w**) in excellent yields (95–99%) with moderate diastereoselectivities (dr = 74 : 26 to 85 : 15). The reactivity of the bromo-lactonization when AcOEt was used as the solvent (Solvent B) was similar to that when $MeNO_2$ was used as the solvent (Solvent A).

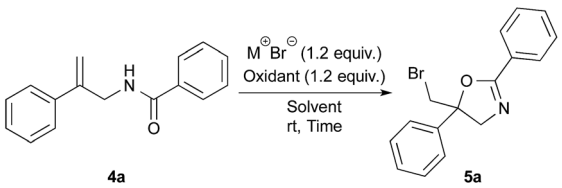
To confirm that the KBr/Oxone® system did not generate organic waste in the present reaction, the NMR spectrum of crude product **2a**, which was obtained by filtration with Celite and evaporation *in vacuo*, was compared with that of pure **2a** (Fig. 2). It was found that crude product **2a** obtained by the reaction with the KBr/Oxone® system had sufficiently high purity that was comparable to that of the pure product (Fig. 2(a) *vs.* (b)).

Then, we attempted to perform a transformation into γ-azidomethyl lactone (**3c**) from **1c** without purification of intermediate (**2c**) through the bromo-lactonization, followed by the nucleophilic substitution with sodium azide (Scheme 2). After the bromo-lactonization of **1c** using KBr and Oxone® in AcOEt at −10 °C, the reaction mixture was filtered with Celite and evaporated to remove K_2SO_4, and AcOEt, respectively. The crude product of **2c** was reacted with NaN_3 in the presence of 15-crown-5 as the catalyst in MeCN at 90 °C. The nucleophilic substitution proceeded to provide desired product **3c** in 89% yield. Therefore, it was confirmed that the KBr/Oxone® system, which does not produce organic waste that pollutes the environment, is an effective methodology for applicative transformations.

Next, we attempted to construct dihydrooxazoles bearing a quaternary carbon center *via* the bromo-cyclization of *N*-allyl amides (**4**) to expand the oxygen-nucleophilic transformation using alkali metal bromide and oxidant. To this end, we screened for solvent, oxidant, and alkali or alkaline metal bromide for the reaction with *N*-(2-phenylallyl)benzamide (**4a**) (Table 4).

Treatment of **4a** with KBr and Oxone® in MeCN at room temperature provided bromomethyl dihydrooxazole (**5a**) in 97% yield (Entry 1). The use of other solvents, such as CH_2Cl_2, AcOEt, THF, $MeNO_2$, and toluene, decreased the yield of **5a** (Entries

Table 4 Screening for alkali or alkali metal bromide, oxidant, and solvent for oxidative bromo-cyclization of *N*-allyl amide **4a**



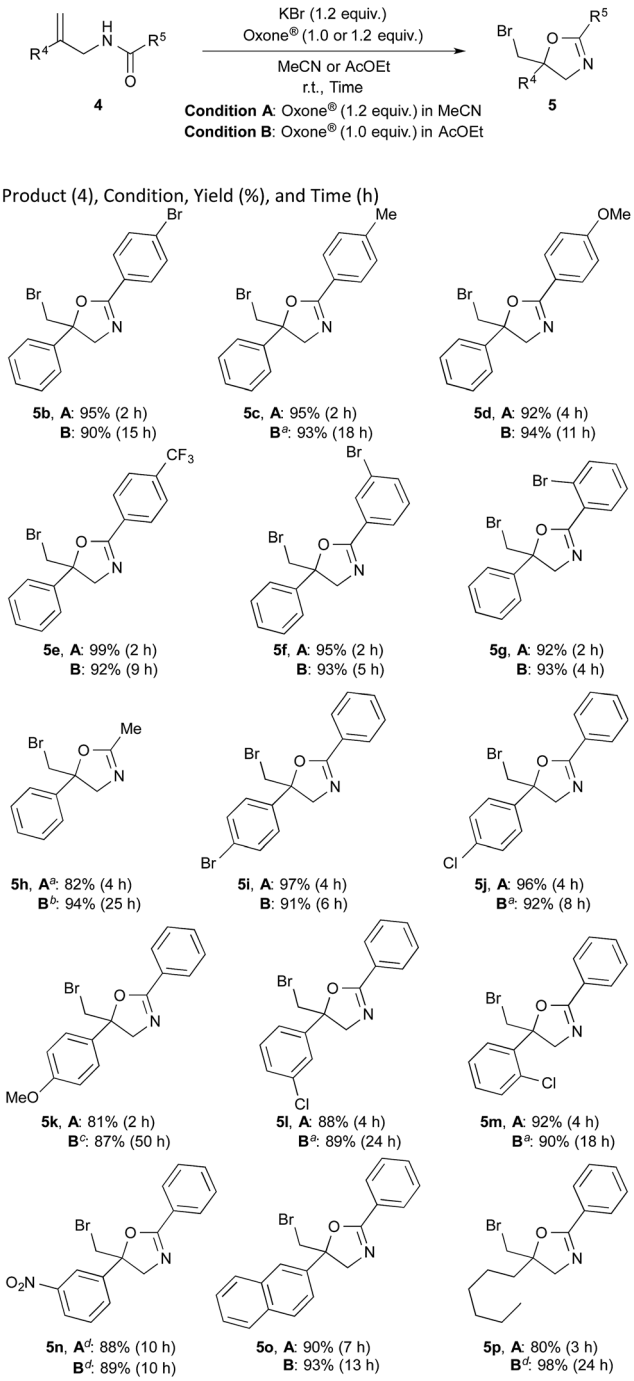
4a **5a**

Entry	MX	Oxidant	Solvent	Time (h)	Yield (%)
1	KBr	Oxone®	MeCN	2	97
2	KBr	Oxone®	CH_2Cl_2	2	89
3	KBr	Oxone®	AcOEt	6	65 (28)[a]
4	KBr	Oxone®	THF	6	37 (54)[a]
5	KBr	Oxone®	$MeNO_2$	6	40 (43)[a]
6	KBr	Oxone®	Toluene	6	84
7	KBr	*m*CPBA	MeCN	6	65 (23)[a]
8	KBr	$PhI(OAc)_2$	MeCN	6	89 (2)[a]
9	KBr	H_2O_2 aq.	MeCN	6	0 (99)[a]
10	NaBr	Oxone®	MeCN	6	88
11	$CaBr_2$	Oxone®	MeCN	6	9 (79)[a]
12	KBr	Oxone®	AcOEt	13	86
13[b]	KBr	Oxone®	MeCN	5	95
14[b]	KBr	Oxone®	AcOEt	13	92

[a] Numbers in the parenthesis indicate the recovery of **4a**. [b] Oxone® (1.0 equiv.) was used.

2–6). **5a** was obtained in lower yield when *m*CPBA, $PhI(OAc)_2$, and H_2O_2 aq. were used as the oxidant, than when Oxone® was used (Entries 7–9). NaBr was an effective bromo source for the present reaction, whereas $CaBr_2$ was much less effective than alkali metal bromides (Entries 10 and 11). It was noteworthy that extending the reaction time in the reaction using AcOEt improved the yield of **5a** to 85% (Entry 12). Decreasing the amount of Oxone® to 1.0 equiv. in the reaction using AcOEt improved the bromo-cyclization, whereas use of the same amount of Oxone® in MeCN slightly reduced the yield of **5a** (Entries 13 and 14).

To explore the substrate scope for the bromo-cyclization of *N*-allyl amides (**4**) *via* the oxidative umpolung of bromide using KBr, various *N*-allyl amides (**4**) were examined under the optimum conditions (Scheme 3). When MeCN was used in the bromo-cyclization (Condition A), substrates bearing various benzamides, such as 4-Br (**4b**), 4-Me (**4c**), 4-OMe (**4d**), 4-CF_3 (**4e**), 3-Br (**4f**), and 2-Br (**4g**) benzamide, and acetamide (**4h**) gave the corresponding products (**5b–5h**) in excellent yields (82–99%). Various 2-arylallylamino groups, bearing 4-Br (**4i**), 4-Cl (**4j**), 4-OMe (**4k**), 3-Cl (**4l**), 2-Cl (**4m**), and 2-NO_2 (**4n**) on the aromatic ring, were also converted into the dihydrooxazoles (**5i–5n**) in excellent yields (80–97%). When *N*-allyl amides bearing 2-naphthyl (**4o**) and *n*-hexyl (**4p**) at 2-position of the allyl amino moiety were used, desired products (**5o** and **5p**) were obtained in 99% and 92% yields, respectively. Fortunately, the reactivities when AcOEt was used as the solvent for the present reaction (Condition B) were similar to those when MeCN was used (87–98% yield), although a long time was required for the transformation into



Scheme 3 Oxidative bromo-cyclization of *N*-allyl amide **4**. [a] The reaction was carried out in AcOEt (0.125 M) at 0 °C. [b] The reaction was carried out at −40 °C. [c] The reaction was carried out in AcOEt (0.063 M) at 0 °C. [d] The reaction was carried out at 0 °C.

bromomethyl dihydrooxazoles (**5**) (4–25 h). Thus, AcOEt can be utilized as a solvent in the present reaction in spite of having less reactivity than that in MeCN (2–10 h).

Conclusions

In conclusion, we have developed an oxygen-nucleophilic bromo-cyclization of alkenyl carbonyl compounds *via* the

oxidative umpolung of bromide using alkali metal bromide and an inorganic oxidant. In particular, AcOEt, the recommended solvent for green sustainable reactions, is minimum amounts of stable reagents, and does not produce any organic wastes that pollute the environment. We hope that the present transformation *via* the oxidative umpolung of halides using alkali metal halides would be applicable to fine organic synthesis.

Experimental

General methods

^{1}H NMR spectra were measured on a JEOL ECS-400 (400 MHz) spectrometer at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; sep = septet; m = multiplet; br = broad), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on a JEOL ECS-400 (100 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.0 ppm). High-resolution mass spectra were recorded with Thermo Fisher Scientific Exactive Orbitrap mass spectrometers. Infrared (IR) spectra were recorded on a JASCO FT/IR 4100 spectrometer. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60GF254 0.25 mm) were used. The products were purified by neutral column chromatography on silica gel (Kanto Chemical Co., Inc. silica gel 60N, Prod. no. 37560-84; Merck silica gel 60, Prod. no. 1.09385.9929). Visualization was accomplished with UV light (254 nm), anisaldehyde, $KMnO_4$, and phosphomolybdic acid. In experiments that required dry solvents, the solvents were distilled prior to use.

General procedure for oxidative bromo-lactonization of alkenyl carboxylic acids (1) (in AcOEt solution)

To a solution of **1a** (25.1 mg, 0.25 mmol) and KBr (44.6 mg, 0.375 mmol) in AcOEt (1.0 mL) was added Oxone® (184.4 mg, 0.30 mmol) at −10 °C. After stirring at −10 °C for 30 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 = 2/1) to give desired product **2a** (43.8 mg, 98%).

One-pot transformation of 1c into γ-azidomethyl lactone (3c)

To a solution of **1c** (32.1 mg, 0.25 mmol) and KBr (44.6 mg, 0.375 mmol) in AcOEt (1.0 mL) was added Oxone® (184.4 mg, 0.30 mmol) at −10 °C. After stirring at −10 °C for 12 h, the reaction mixture was filtered through Celite with AcOEt to remove the precipitate. The filtrate was concentrated under reduced pressure and the crude product was dissolved with MeCN (1.2 mL). 15-Crown-5-ether (10 μL, 0.05 mmol) and NaN_3 (32.5 mg, 0.50 mmol) were added to the solution at room temperature under argon atmosphere. After stirring at 90 °C for 6 h, NaN_3 (8.2 mg, 0.125 mmol) was again added to the reaction mixture. After stirring at 90 °C for 18 h, the reaction mixture was cooled to room temperature, and the suspension was filtered through Celite with AcOEt. The filtrate was concentrated under reduced pressure and the crude product was purified by silica gel column chromatography (eluent: hexane/AcOEt = 3/1) to give desired product **3c** (37.6 mg, 89%).

General procedure for oxidative bromo-cyclization of *N*-allyl amides (4) (in AcOEt solution)

To a solution of **4a** (59.4 mg, 0.25 mmol) and KBr (35.7 mg, 0.30 mmol) in AcOEt (1.0 mL) was added Oxone® (153.7 mg, 0.25 mmol) at room temperature. After stirring at room temperature for 13 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 desired product **5a** (72.7 mg, 92%).

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Notes and references

1 (*a*) A. Kleemann and J. Engel, in *Pharmaceutical Substances*, New York, NY, 4th edn, 2001; (*b*) M. J. Dagani, H. J. Barda, T. J. Benya and D. C. Sanders, in *Ullmann's Encyclopedia of Industrial Chemistry: Bromine Compounds*, Wiley-VCH, Weinheim, 2002; (*c*) A. de Meijere and F. Diederich, in *Metal-catalyzed Cross-coupling Reactions*, Wiley-VCH, Weinheim, Germany, 2nd edn, 2004; (*d*) G. W. Gribble, *J. Chem. Educ.*, 2004, **81**, 1441–1449; (*e*) G. W. Gribble, *Acc. Chem. Res.*, 1998, **31**, 141–152.

2 (*a*) T. R. Hoye and M. J. Kurth, *J. Org. Chem.*, 1978, **43**, 3693–3697; (*b*) R. C. Cambie, P. S. Rutledge, R. F. Somerville and P. D. Woodgate, *Synthesis*, 1988, 1009–1011; (*c*) C. Chiappe, D. Capraro, V. Conte and D. Pieraccini, *Org. Lett.*, 2001, **3**, 1061–1063; (*d*) I. Ryu, H. Matsubara, S. Yasuda, H. Nakamura and D. P. Curran, *J. Am. Chem. Soc.*, 2002, **124**, 12946–12947; (*e*) Y.-P. Yen and J.-H. Chen, *The New Journal for Organic Synthesis*, 2006, **38**, 500–504; (*f*) N. Windmon and V. Dragojlovic, *Beilstein J. Org. Chem.*, 2008, **4**, 1–6.

3 (*a*) Y. Tamaru, S. Kawamura, K. Tanaka and Z. Yoshida, *Tetrahedron Lett.*, 1984, **25**, 1063–1066; (*b*) Y. Tamaru, S. Kawamura, T. Bando, K. Tanaka, M. Hojo and Z. Yoshida, *J. Org. Chem.*, 1988, **53**, 5491–5501; (*c*) A. Sakakura, K. Ukai and K. Ishihara, *Nature*, 2007, **445**,

900–903; (*d*) J. Tanuwidjaja, S.-S. Ng and T. F. Jamison, *J. Am. Chem. Soc.*, 2009, **131**, 12084–12085; (*e*) L. Zhou, C. K. Tan and Y.-Y. Yeung, *J. Am. Chem. Soc.*, 2010, **132**, 10245–10247; (*f*) L. Zhou, C. K. Tan, X. Jiang, F. Chen and Y.-Y. Yeung, *J. Am. Chem. Soc.*, 2010, **132**, 15474–15476.

4 (*a*) K. Murai, T. Matsushita, A. Nakamura, S. Fukushima, M. Shimura and H. Fujioka, *Angew. Chem., Int. Ed.*, 2010, **49**, 9174–9177; (*b*) K. Moriyama, K. Ishida and H. Togo, *Chem. Commun.*, 2015, **51**, 2273–2276.

5 (*a*) T. Kato and I. Ichinose, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1051–1056; (*b*) H.-M. Shieh and G. D. Prestwich, *Tetrahedron Lett.*, 1982, **23**, 4643–4646; (*c*) T. Kato, M. Mochizuki, T. Hirano, S. Fujiwara and T. Uyehara, *J. Chem. Soc., Chem. Commun.*, 1984, 1077–1078; (*d*) A. Tanaka and T. Oritani, *Biosci., Biotechnol., Biochem.*, 1995, **59**, 516–517; (*e*) D. C. Braddock, R. Bhuva, D. S. Millan, Y. Pérez-Fuertes, C. A. Roberts, R. N. Sheppard, S. Solanki, E. S. E. Stokes and A. J. P. White, *Org. Lett.*, 2007, **9**, 445–448; (*f*) H. J. Lee and D. Y. Kim, *Tetrahedron Lett.*, 2012, **53**, 6984–6986.

6 (*a*) B. Trost and M. J. Krische, *J. Am. Chem. Soc.*, 1999, **121**, 6131–6141; (*b*) K. Tanaka, R. Shiraishi and F. Toda, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3069–3070.

7 (*a*) G. W. Gribble, *Chemosphere*, 2003, **52**, 289–297; (*b*) A. Butler and J. N. Carter-Franklin, *Nat. Prod. Rep.*, 2003, **21**, 180–188; (*c*) C. S. Neumann, D. G. Fujimori and C. T. Walsh, *Chem. Biol.*, 2008, **15**, 99–109.

8 For review on transformation *via* umpolung of halide: (*a*) M. Eissen and D. Lenoir, *Chem.–Eur. J.*, 2008, **14**, 9830–9841; (*b*) A. Podgorsek, M. Zupan and J. Iskra, *Angew. Chem., Int. Ed.*, 2009, **48**, 8424–8450.

9 (*a*) K. Moriyama, Y. Izumisawa and H. Togo, *J. Org. Chem.*, 2011, **76**, 7249–7255; (*b*) K. Moriyama, M. Takemura and H. Togo, *Org. Lett.*, 2012, **14**, 2414–2417; (*c*) K. Moriyama, K. Ishida and H. Togo, *Chem. Commun.*, 2012, **48**, 8574–8576; (*d*) K. Moriyama, M. Takemura and H. Togo, *J. Org. Chem.*, 2014, **79**, 6094–6104; (*e*) K. Moriyama, Y. Nakamura and H. Togo, *Org. Lett.*, 2014, **16**, 3812–3815; (*f*) K. Moriyama, T. Sugiue, C. Nishinohara and H. Togo, *J. Org. Chem.*, 2015, **80**, 9132–9140.

10 (*a*) H. M. R. Hoffmann and J. Rabe, *Angew. Chem., Int. Ed.*, 1985, **24**, 94–110; (*b*) B. S. Davidson, *Chem. Rev.*, 1993, **93**, 1771–1791; (*c*) S. S. C. Koch and A. R. Chamberlin, *Studies in Natural Products Chemistry*, ed. A.-u. Rahman, Elsevier Science, Amsterdam, 1995, vol. 16, pp. 687–725; (*d*) R. Badichhor, B. Nosse and O. Reiser, *Top. Curr. Chem.*, 2005, **243**, 43–72; (*e*) S. Castellano, D. Kuck, M. Sala, E. Novellino, F. Lyko and G. Sbardella, *J. Med. Chem.*, 2008, **51**, 2321–2325.

11 (*a*) R. C. Cambie, P. S. Rutledge, R. F. Somerville and P. D. Woodgate, *Synthesis*, 1988, 1009–1011; (*b*) X.-L. Cui and R. S. Brown, *J. Org. Chem.*, 2000, **65**, 5653–5658; (*c*) S. R. Mellegaard and J. A. Tunge, *J. Org. Chem.*, 2004, **69**, 8979–8981; (*d*) D. C. Braddock, G. Cansell and S. A. Hermitage, *Chem. Commun.*, 2006, 2483–2485; (*e*) S. R. Mellegaard-Waetzig, C. Wang and J. A. Tunge, *Tetrahedron*, 2006, **62**, 7191–7198; (*f*) S. M. Ahmad, D. C. Braddock, G. Cansell, S. A. Hermitage, J. M. Redmond and A. J. P. White, *Tetrahedron Lett.*, 2007, **48**, 5948–5952; (*g*) S. M. Ahmad, D. C. Braddock, G. Cansell and S. A. Hermitage, *Tetrahedron Lett.*, 2007, **48**, 915–918; (*h*) F. Chen, X. Jiang, J. C. Er and Y.-Y. Yeung, *Tetrahedron Lett.*, 2010, **51**, 3433–3435; (*i*) S. J. Balkrishna, C. D. Prasad, P. Panini, M. R. Detty, D. Chopra and S. Kumar, *J. Org. Chem.*, 2012, **77**, 9541–9552; (*j*) Y. A. Cheng, T. Chen, C. K. Tan, J. J. Heng and Y.-Y. Yeung, *J. Am. Chem. Soc.*, 2012, **134**, 16492–16495.

12 (*a*) D. E. Higgs, M. I. Nelen and M. R. Detty, *Org. Lett.*, 2001, **3**, 349–352; (*b*) M. Abe, Y. You and M. R. Detty, *Organometallics*, 2002, **21**, 4546–4551; (*c*) M. D. Drake, M. A. Bateman and M. R. Detty, *Organometallics*, 2003, **22**, 4158–4162; (*d*) M. A. Goodman and M. R. Detty, *Organometallics*, 2004, **23**, 3016–3020; (*e*) S. M. Bennett, Y. Tang, D. McMaster, F. V. Bright and M. R. Detty, *J. Org. Chem.*, 2008, **73**, 6849–6852; (*f*) S. Kumar, J.-C. P. Helt, J. Autschbach and M. R. Detty, *Organometallics*, 2009, **28**, 3426–3436; (*g*) E. E. Alberto, A. L. Braga and M. R. Detty, *Tetrahedron*, 2012, **68**, 10476–10481; (*h*) S. Klimczyk, X. Huang, C. Frarès and N. Maulide, *Org. Biomol. Chem.*, 2012, **10**, 4327–4329; (*i*) D. C. Braddock, G. Cansel and S. A. Hermitage, *Synlett*, 2004, 461–464.

13 D. Prat, J. Hayler and A. Wells, *Green Chem.*, 2014, **16**, 4546–4551.

