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Indium-Mediated Synthesis of Benzylic Hydroperoxides

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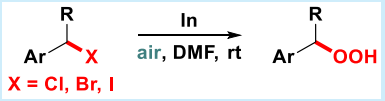
Supporting Information

ABSTRACT: An indium(0)-metal-mediated efficient synthesis of benzylic hydroperoxides is described. The reaction proceeds efficiently with a broad range of benzyl bromides under aerobic conditions at room temperature to afford benzyl hydroperoxides in good to excellent yields. In addition, the tandem hydroperoxidation-Michael addition of (*E*)-1-(bromomethyl)-2-(2-nitrovinyl)benzene was also demonstrated.



Peroxides and hydroperoxides exist widely in natural products, and many of them have therapeutic values.[1] For instance, Artemisinin (Qinghaosu) (**1**),[2] a traditional Chinese medicine, is widely used as an antimalarial drug; Yingzhaosu C (**2**)[3] and many 1,2,4-troxiane analogues[4] were shown to possess potential antimalarial activity and Peroxyferolide (**3**),[5,1c] from the leaves of *L. tulipifera* showed cytotoxic and anticancer activities. 15-Hydroperoxydehydroabietic acid (**4**)[6,1d] and a peroxy-generated derivative **5** of the indole alkaloid ibogaine exhibit contact allergenic properties and have been related to delayed hypersensitivity toward Portuguese gum rosin (colophony) and Swedish tall oil rosin. Furthermore, the mimic synthesis of peroxidic compounds as antimalaria or anticancer drugs became very interesting. For instance, lophine peroxide (**6**)[1d] and its derivatives have been synthesized, tested for anticancer activities, and obtained satisfactory results (see Figure 1). In addition, benzylic

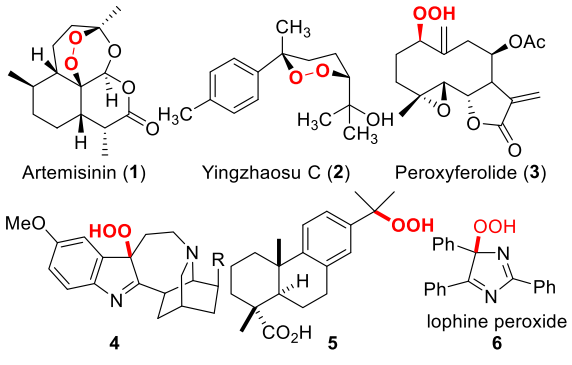
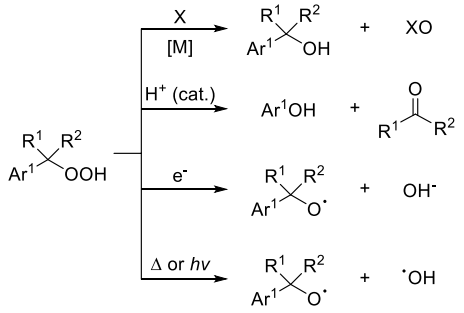


Figure 1. Important peroxides and hydroperoxides.

hydroperoxides are widely used as starting materials in the synthesis of hydroxyl-substituted arenes, and act as active oxygen-atom compounds in oxidation catalysis, or as precursors for the generation of oxygen-center radicals in polymer science, physical organic chemistry, organometallics, and bioorganic investigations (see Scheme 1).[7] In biological systems, the radical or ion generated by the cleavage of peroxide bond plays an important role in biological activities.[1b] Considering the importance and potential synthetic value of

Scheme 1. Chemistry of Benzylic Hydroperoxides



such types of compounds, it came as a surprise to us that the facile synthesis of hydroperoxides from readily available starting materials is still rare. Consequently, we reported herein a highly efficient indium(0)-mediated synthesis of benzylic hydroperoxides from benzylic halides.

Traditionally, there are several synthetic approaches to benzylic hydroperoxides: (1) oxidation of alcohols by H_2O_2,[8] (2) oxidation and hydrolysis of Grignard reagents,[9] (3) addition of singlet oxygen with alkene and autoxidation of alkane,[10] etc.[11] However, none of these methods is truly general, and many of them suffer from stringent conditions or poor yields, require a high concentration of H_2O_2, need inert conditions for the preparation of Grignard reagents, or require a high temperature for the direct oxidation of alkenes. Recently, Dussault and co-workers reported a convenient approach for synthesis of alkyl hydroperoxides via alkylation of 1,1-dihydroperoxides followed by acidic deprotection of the derived bisperoxyacetals.[12] However, the starting materials are complicated and the atom efficiency is low. In consideration of the advantages of low cost, safety, environmental protection, and fewer side reactions, molecular oxygen has become a preferred oxidant to replace H_2O_2 in hydroperoxidation reaction.[13] Woerpel reported a Cu^I-catalyzed synthesis of propargyl hydroperoxides via the oxidation of enynes, which employed molecular oxygen as the source of oxygen atoms.[14]

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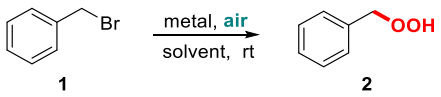
Makino disclosed a manganese-catalyzed aerobic hydroperoxidation method for conjugated alkenes.[15] Su and co-workers reported a hydroperoxidation/lactonization of α-ethereal C−H bonds by singlet O_2 under mild conditions, with modest to high yields and excellent site selectivity.[16] Dussault and Berrien independently introduced a hemiketalized version of hydrogen peroxides as hydroperoxidation reagents in a two-step hydroperoxidation of organohalides and alkenes.[17] Despite the progresses made in this field, the development of more atom economic and practical methods such as using molecular oxygen as environmentally friendly oxidant for the hydroperoxidation reaction is still highly desirable.

Indium, because of its unique properties of being tolerant to oxygen and moisture, has been demonstrated to be an efficient and promising metal to mediate organic reactions in recent years.[18,19] In principle, neutral radical species are not affected by the presence of water,[20] and indium can be used as radical initiator through the single electron transfer (SET) process. The utilization of indium species as a radical initiator in several organic transformations has been reported by Naito and co-workers[21] and Loh and co-workers.[22] We envisioned that the generation of neutral free radicals would be the key factor for the success of the reaction. Herein, we report an efficient method for the hydroperoxidation reaction of benzyl halides to form benzylic hydroperoxides by using indium(0) metal under an aerobic atmosphere.

To begin with, benzyl bromide (**1a**) was employed as a model substrate in the presence of indium(0) metal (100 mesh powder) as the radical initiator under a variety of conditions to study the feasibility of radical initiation, as well as the subsequent hydroperoxidation under aerobic conditions. A series of solvents were first screened with 1.1 equiv of indium powder at room temperature, as shown in Table 1. When the reaction performed in a less-polar solvent, such as toluene, ethyl acetate (EtOAc), and tetrahydrofuran (THF), proceeded sluggishly to give trace amount of the desired product (Table 1, entries 1−3). Attempts to improve the reaction efficiency by using more polar solvents were performed. Gratifyingly, moderate yields (65% and 55%) could be achieved in CH_3CN and dimethyl sulfoxide (DMSO) (Table 1, entries 4 and 5). It was found that protonic solvents metahnol (MeOH) and ethanol (EtOH) accelerated the reaction rate significantly and improved the yields to 72% (Table 1, entries 6 and 7). However, when water was used, only 18% yield was afforded (Table 1, entry 8). When dimethyl formamide (DMF) was employed, the yield could be increased to 79% (Table 1, entry 9). We then moved to study the stoichiometry of indium metal. A higher yield (86%) was achieved when 1.3 equiv of indium was used and the reaction time was shortened to 12 h (Table 1, entries 10 and 11). It was found that the reaction was significantly influenced by the surface and particle size of the indium powder. The finer indium particles (200 mesh), which have a larger specific surface area, gave the hydroperoxidation product in higher yield with shorter reaction time (Table 1, entries 12 and 13). In addition, other metals, such as zinc, were also investigated (Table 1, entry 14) and a lower yield was achieved. These results demonstrated that indium is highly unique and efficient for the reaction. After the establishment of the optimized reaction conditions, we subsequently set up a study toward exploring the scope by using different benzylic bromides as substrates.

Table 1. Optimization of the Reaction Conditions[a]



1 2

entry	solvent	metal (equiv)	time (h)	yield[b] (%)
1	toluene	In (1.1)[c]	24	trace
2	EtOAc	In (1.1)	24	trace
3	THF	In (1.1)	24	trace
4	CH_3CN	In (1.1)	16	65
5	DMSO	In (1.1)	37	55
6	MeOH	In (1.1)	5	72
7	EtOH	In (1.1)	14	72
8	H_2O	In (1.1)	24	18
9	DMF	In (1.1)	30	79
10	DMF	In (1.2)	23	81
11	DMF	In (1.3)	12	86
12	DMF	In (1.3)[d]	24	54
13	DMF	In (1.3)[e]	4	89
14	DMF	Zn (1.3)	20	8

[a]Conditions: indium(0) powder, benzyl bromides (0.3 mmol) in solvent (1.0 mL) under air at room temperature (rt). [b]Yield of isolated product. [c]100 mesh indium powder was used. [d]60 mesh indium powder was used. [e]200 mesh indium powder was used.

As shown in Table 2, a wide range of primary benzylic halides effectively underwent the hydroperoxidation reaction under air in DMF to produce the corresponding products in good to excellent yields. Substrates with electron-donating groups (Table 2, entries 2−4), electron-withdrawing groups (Table 2, entries 6−10), and electron-neutral groups (Table 2, entries 11 and 12) on the phenyl ring could all be well-tolerated; a series of important functional groups (e.g., cyano, fluoro, and bromo groups) survived the present reaction conditions and were kept intact during the course of the reaction. In addition to benzylic bromide (**2a**), benzylic chloride (**2b**) and iodide (**2c**) (Table 2, entries 1−3) were proven to be suitable partners for the reactions; however, the yield of benzylic chloride was lower. It is noteworthy that the secondary benzylic bromides were also demonstrated to be appropriate substrates for the reaction, leading to the anticipated products **2o** and **2p** in good yields (62% and 65%; see Table 2, entries 13 and 14). Moreover, heterobenzyl bromide containing thienyl substituents worked equally well under the optimal reaction conditions to give the desired product in moderate yield (Table 2, entry 15). In addition, allylic bromide **1r** was also a good substance for the reaction, the corresponding product could be obtained in 60% yield. Unfortunately, when alkyl halide **1s** was used, no reaction happened. The structure of 4-(hydroperoxymethyl)-benzonitrile (**2l**) was confirmed by X-ray crystallography (Figure 2) and analysis of the NMR data of the product.

Having established the hydroperoxidation of benzyl halides, we investigated the feasibility of a tandem hydroperoxidation-Michael addition reaction of (*E*)-1-(bromomethyl)-2-(2-nitrovinyl)benzene (**I**) under the optimized reaction conditions, it was found that the corresponding product **II** containing cyclic peroxide moiety was afforded in moderate yield (Scheme 2a). Furthermore, when the indium mediated hydroperoxidation reaction was performed by using AcOH as a solvent, benzyl alcohol (**III**) instead of benzyl hydroperoxide was formed (Scheme 2b). Furthermore, the reaction could be

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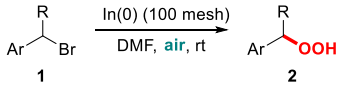
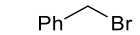
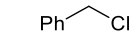
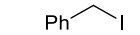
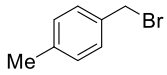
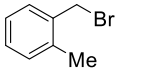
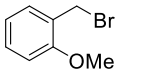
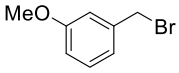
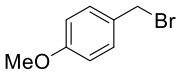
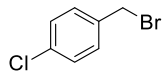
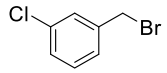
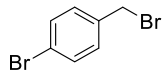
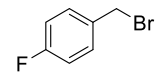
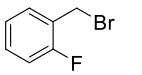
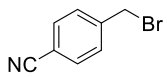
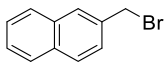
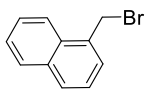
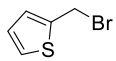
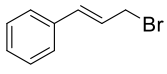
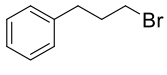
Table 2. Reaction Scope of the Hydroperoxidation Reaction[a]



entry	1	2	t (h)	yield (%)[b]
1		**2a**	20	86
2			48	41
3			14	81
4		**2b**	12	84
5		**2c**	12	85
6		**2d**	20	74
7		**2e**	20	86
8		**2f**	21	79
9		**2g**	12	88
10		**2h**	16	80
11		**2i**	12	81
12		**2j**	12	75
13		**2k**	11	80
14		**2l**	43	74
15		**2m**	22	81
16		**2n**	20	69
17		**2o**	37	62
18		**2p**	14	65
19		**2q**	12	66
20		**2r**	12	60
21		**2s**	48	nr.[c]

[a]Conditions: indium(0) (0.39 mmol, 1.3 equiv), benzyl bromides (0.3 mmol, 1.0 equiv) in DMF (1.0 mL) under aerobic conditions at rt. [b]Yield of isolated product. [c]No reaction.

scaled-up: 1.00 g of **1a** afforded the desired **2a** in 83% yield under standard conditions.

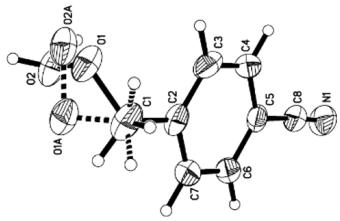
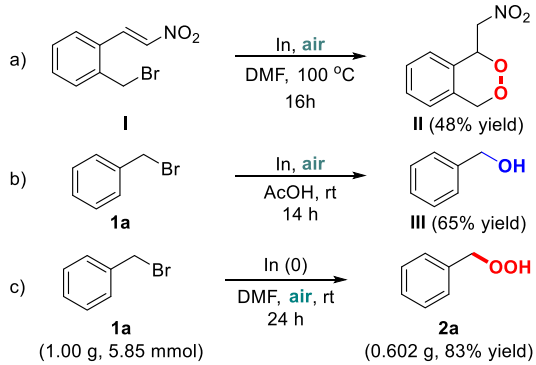


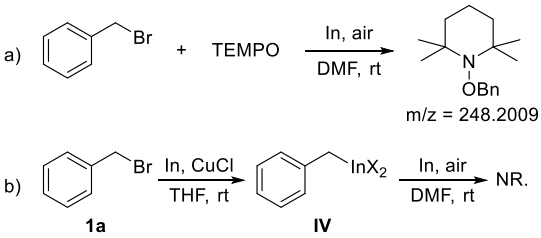
Figure 2. X-ray crystal structure of **2l**.

Scheme 2. Synthetic Utility of the Hydroperoxidation Reaction



In order to investigate the reaction mechanism, some control experiments were performed (see Scheme 3). TEMPO

Scheme 3. Control Experiments



was added into the model reaction system. The fact that the desired product was not formed in the reaction indicated that the reaction proceeded through a radical mechanism based on the SET process. Butsugan and co-workers reported an example of aerobic oxygenation of allylic indium reagents to generate hydroperoxide species, which was further reduced to alcohols.[23] We then prepared the benzylic indium compound according to the literature[22e] and applied in the aerobic hydroperoxidation reaction. It was found that the organo-indium compound **IV** is quite stable in air and the reaction could not proceed, which means that the indium compound **IV** is relatively unreactive[19a,b,24] and the reaction is unlikely to proceed through an oxidative addition of indium to the carbon−halogen bond and subsequent C−O bond formation process. Then, benzyl zinc bromide prepared from benzyl bromide and zinc powder under anhydrous conditions was applied in the aerobic hydroperoxidation reaction. It was found that the benzyl hydroperoxide could be obtained in moderate yield, which indicates that benzyl zinc bromide is more reactive than benzylic indium compound and the reaction proceeds through an oxidative addition of zinc to the carbon−halogen bond and subsequent C−O bond formation process. However,

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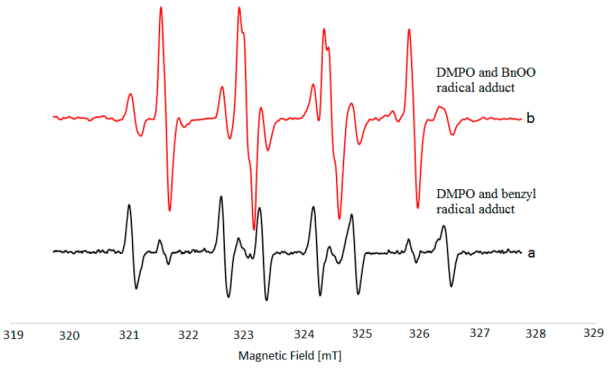
when we use tribenzylboron as the starting material, no reaction happened. (See the Supporting Information.)

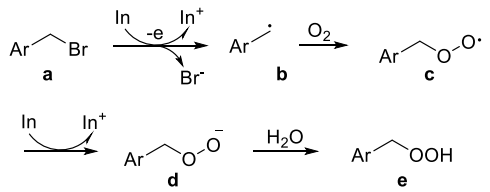
To gain a deep insight into the radical formation, electron paramagnetic spectroscopy (EPR) experiments were performed in the presence of 5,5-dimethyl-1-pyrrolidine-*N*-oxide (DMPO) (see Scheme 4). When we mixed **1a** with indium

Scheme 4. ESR Spectra Obtained from the Indium Mediated Hydroperoxidation Reaction of Benzyl Bromide in the Presence of DMPO



powder in DMF under degassed conditions, a strong benzyl radical signal (g_{factor} = 2.003) was detected (Scheme 4, black line), and a strong BnOO• radical signal (g_{factor} = 2.003) was observed when the radical trapping test was performed in air (see Scheme 3, red line). Inspired by the above results, a plausible reaction mechanism was proposed and illustrated in Scheme 5; the reaction is initiated by indium to generate

Scheme 5. Proposed Reaction Mechanism



radical **b** with the generation of In(I) species, which was supported by several literature works.[25] The radical intermediate **b** then reacts with O_2 to form peroxide radical **c**. Indium-promoted reduction of intermediate **c**, followed by the protonation of the peroxide anion **d**, affords the final product **e**.

In summary, we have developed a facile and efficient method for the preparation of benzylic hydroperoxides using benzyl halides and indium (0) under an aerobic atmosphere at room temperature (rt). This extremely simple and practical protocol is very promising, as many peroxide structures exist widely in natural products that have potential biological activities. Further investigation of this methodology will be directed toward its application in the synthesis of natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01070.

Experimental procedures, characterization data ^{1}H and ^{13}C NMR spectra for compounds, and X-ray data for **2l** (PDF)

Accession Codes

CCDC 740902 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_ request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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Notes

The authors declare no competing financial interest.

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