Conversion of Alkyl Halides into Alcohols Using a Near Stoichiometric Amount of Molecular Oxygen: An Efficient Route to ^{18}O- and ^{17}O-Labeled Alcohols

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Abstract: In the presence of near stoichiometric amount of molecular oxygen, various alkyl halides were converted to the corresponding alcohols in high yields through aerobic radical reaction promoted by a $Bu_2(t\text{-Bu})SnCl/NaBH_3CN$ catalytic system. Isotope-labeled alcohols were prepared with $^{18}O_2$ and $^{17}O_2$ without loss of the isotopic purities of the starting oxygen gases.

Molecular oxygen has found wide applications in organic synthesis. Molecular oxygen, whose solubility in most solvents is low,[1] is usually used in a large excess regardless of the actual stoichiometry of the reaction. Here we report our finding that an organotin chloride-catalyzed conversion of alkyl halides into alcohols can be achieved most efficiently with only a near stoichiometric amount of molecular oxygen rather than excess. This stoichiometric aerobic reaction finds its utility in an efficient synthesis of ^{18}O- and ^{17}O-labeled alcohols by the use of $^{18}O_2$ and $^{17}O_2$ gases. Since the current oxygen-isotope sources and chemical reactions available for the preparation of oxygen-labeled organic compounds are limited, the present reaction will provide a new practical entry to the preparation of isotope-labeled alcohols.[2]

During the course of our studies on aerobic halide-to-alcohol conversion, of which we reported a stoichiometric version previously (2 equiv of Bu_3SnH and excess O_2),[3-5] we found that the reaction (eq 1) can be carried out best with near stoichiometric molecular oxygen (1-2 equiv diluted with N_2) in the presence of small amouts of AIBN (1 mol%) and Bu_3SnCl or $Bu_2(t\text{-Bu})SnCl$ (5 mol%), and a stoichiometric amount of a reducing agent ($NaBH_3CN$, 2 equiv).[6,7] The use of a limited amount of oxygen turned out to be especially important in reducing the amount of AIBN[4] and the tin catalyst. The selection of the reaction temperature (60 °C in *t*-BuOH) was also important. Comparison data obtained for the reactions of secondary alkyl iodide **1a** are summarized in Table 1. Under continuous bubbling of air, the reaction with 5 mol % of Bu_3SnCl stopped before completion, giving, after 16 h, only 34% of the desired alcohol (**2a**) together with 11% of the reduction product (**3a**) (entry 1). Notably, the reaction under the same conditions except for the use of an only near stoichiometric amount of molecular oxygen (O_2:N_2 = 1:4) led to complete conversion of the halide and gave the alcohol in nearly quantitative yields (93 and 90% with 2.0 and 1.5 equiv of O_2, respectively; entries 2, 3).[8]

Table 1. Aerobic Conversion of $PhCH_2CH_2CHIBu$ (1a) to $PhCH_2CH_2CH(OH)Bu$ (2a) Promoted by $Bu_3SnCl/NaBH_3CN$ Catalytic System[a]

entry	O_2, equiv (condition)	conv of **1a**,[b,c] %	yield of **2a**,[c] %	yield of **3a**,[c] %
1	(bubling the air)	45	34	11
2	2.0 (O_2:N_2 = 1:4)	100	93 (92)[d]	7
3	1.5 (O_2:N_2 = 1:4)	100	90	10

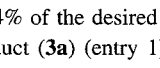
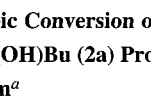
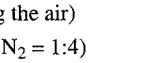
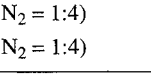
[a] Reaction in *t*-BuOH (2 mL) at 60 °C for 16 h. **1a** (0.5 mmol):$NaBH_3CN$:Bu_3SnCl:AIBN = 1:2:0.05:0.01. [b] [**2a**/(**1a**+**2a**+**3a**)]x100 (%). [c] Determined by ^1H NMR of crude product. [d] Value in parenthesis refers to isolated yield.

$$\underset{\textbf{1a-f}}{R\text{–}X} + O_2 + NaBH_3CN \xrightarrow[t\text{-BuOH, 60 °C}]{\substack{R_3SnCl\ (5\ mol\ \%)\\ AIBN\ (1\ mol\ \%)}} \underset{\textbf{2a-f}}{R\text{–}OH} + \underset{\textbf{3a-f}}{R\text{–}H} \quad (1)$$

In the present reaction, molecular oxygen would act not only as a source of the oxgyen atom in the product but also as a radical initiator.[9] On the other hand, it will kill the tin radical by forming inactive dead end species such as $R_3SnOSnR_3$.[10] We speculate that the use of the smallest possible amount of molecular oxygen does help preventing such side reactions. The favorable ratio of the oxygenated product **2a** against the reduced product **3a** as observed experimentally must crucially depend on the higher reactivity of carbon radicals toward molecular oxygen[10] than toward the tin hydride.[11]

Next, we examined the reaction of various alkyl halides with 1.5 equiv of molecular oxygen at 60 °C in *t*-BuOH (eq 1 and Table 2). The reaction is applicable to various alkyl halides including primary (**1b,c**), secondary (**1a**) and tertiary (**1f**) alkyl iodides, and an allylic bromide, giving the corresponding alcohols in good to excellent isolated yields. Primary alkyl bromide **1d** was also converted smoothly to alcohol **2c** by carrying out the reaction in the presence of NaI (*in situ* conversion of bromide to iodide). Reaction of cinnamyl bromide (**1e**) took place with complete retention of stereo- and regiochemical integrity of the starting halide to give exclusively *trans*-cinnamyl alcohol. While both Bu_3SnCl and $Bu_2(t\text{-Bu})SnCl$[12,13] can be used as a tin catalyst, the latter is more widely applicable and recommended for the reaction of primary alkyl halides, where the formation of the reduction product **3** may be problematic (entries 2 vs 4, 5 vs 6). Alternatively, the yield of the primary alcohol can be dramatically increased by adding a small amount of perfluorodecaline (3 equiv to the halide) to the reaction mixture (entry 3). While perfluoroalkanes are often employed to increase the oxygen solubility in the reaction mixture,[14] the effectiveness of the use of only a small amount of this cosolvent is of particular interest.

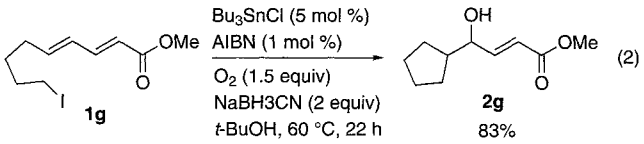
Table 2. Aerobic Conversion of Alkyl Halides (1) to Alcohols (2) (eq 1) [a]

entry	alkyl halide (**1**)	R_3SnCl	time, h	yield of **2**,[b] %	ratio of **2**:**3**[c]
1	 (**1a**)	$Bu_2(t\text{-Bu})SnCl$	10	92	93:7
2[d]	$C_{10}H_{21}$-I (**1b**)	Bu_3SnCl	16	68	70:30
3	**1b**	Bu_3SnCl	14	93	93:7
4	**1b**	$Bu_2(t\text{-Bu})SnCl$	19	82	91:9
5	 (**1c**)	Bu_3SnCl	19	77	84:16
6	**1c**	$Bu_2(t\text{-Bu})SnCl$	11	88	91:9
7[e]	$C_{12}H_{25}$-Br (**1d**)	$Bu_2(t\text{-Bu})SnCl$	12	90	93:7
8	 (**1e**)	$Bu_2(t\text{-Bu})SnCl$	18	69	70:30
9	 (**1f**)	Bu_3SnCl	18	94	96:4
10	**1f**	$Bu_2(t\text{-Bu})SnCl$	20	96	97:3

[a] Reaction in *t*-BuOH at 60 °C. **1** (0.25 M):$NaBH_3CN$:R_3SnCl:AIBN = 1:2:0.05:0.01. [b] Isolated yield. [c] Determined by ^1H NMR of crude product. [d] 3 equiv of perfluodecaline was added. [e] 2 equiv of NaI was added.

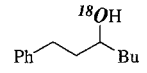
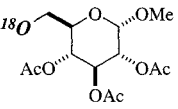
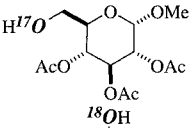
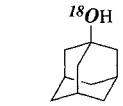
In the reaction of olefinic alkyl halides (**1g**), the intermediate carbon radical formed by dehalogenation may undergo highly efficient

carbocyclization before being quenched by molecular oxygen or the tin hydride reagent (eq 2).

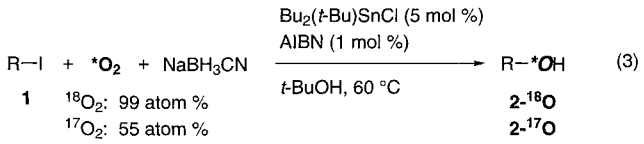


Finally, the merit of the new synthetic protocol is demonstrated by the efficient preparation of isotope labeled alcohols (eq 3). As shown in Table 3, the reactions with near stoichiometric amounts of $^{18}O_2$ (99 atom %) and $^{17}O_2$ (55 atom %) gases proceeded as smoothly as with $^{16}O_2$, and the isotopic purity of the labeled alcohols was essentially the same as those of the $^{18}O_2$ and $^{17}O_2$ gases, respectively, as determined by their mass spectra.[15] As in entries 2 and 3, the mild reducing conditions kept the ester group remain intact.

Table 3. Synthesis of Isotope-Labeled Alcohols 2-*O (eq 3)[a]

entry	1	*O_2[b]	time, h	2-*O	yield,[c] %	isotopic purity,[d] atom %
1	**1a**	$^{18}O_2$	15		98	>95
2	**1c**	$^{18}O_2$	13		88	>85
3	**1c**	$^{17}O_2$	13		80	55
4[e]	**1f**	$^{18}O_2$	16		98	>93

[a] Reaction in *t*-BuOH at 60 °C. **1** (0.25 M):$NaBH_3CN$:Bu_2(*t*-Bu)SnCl:AIBN = 1:2:0.05:0.01 unless otherwise noted. [b] $^{18}O_2$ with 99 atom % isotopic purity (2.0 equiv) and $^{17}O_2$ with 55 atom % purity (1.5 equiv) were used. [c] Isolated yield. [d] Determined by EI-Mass (GC) for **2a-^{18}O** and **2f-^{18}O** or by FAB-Mass (dir) for **2c-^{18}O** and **2c-^{17}O**. [e] Reaction with 3 equiv of $NaBH_3CN$.



In summary, various alkyl halides have been efficiently converted to the corresponding alcohols through the aerobic radical reaction promoted by the Bu_2(*t*-Bu)SnCl/$NaBH_3CN$ catalytic system with minimum loading of the tin catalyst and the oxidant. We suspect the limited stoichiometry of moleculer oxygen may exert beneficial effects on many other oxidation reactions which have been routinely carried out with excess molecular oxygen, and it will also have an obvious merit when incorporation of oxygen isotopes is intended.

References and Notes

1. Battino, R.; Rettich, T. R.; Tominaga, T. *J. Phys. Chem. Ref. Data* **1983** *12*, 163.
2. The common sources of oxygen isotopes are molecular oxygen and water, which are normally used in excess or introduced through multi-step procedures, and the synthetic transformations are not necessarily effcient; for example, see: (a) Schöttler, M.; Boland, W. *Synlett* **1997**, 91. (b) Sowa, G. A.; Hengge, A. C.; Cleland, W. W. *J. Am. Chem. Soc.* **1997**, *119*, 2319.
3. Nakamura, E.; Inubushi, T.; Aoki, S.; Machii, D. *J. Am. Chem. Soc.* **1991**, *113*, 8980.
4. Prandi et al. also did similar modification of our procedure (ref 3), where they needed to use *excess molecular oxygen and 1 equiv of AIBN* in the presence of 10 mol% Bu_3SnCl and excess $NaBH_4$. See: Mayer, S.; Prandi, J. *Tetrahedron Lett.* **1996**, *37*, 3117.
5. For a related halide-to-alcohol conversion, see: Barrett, A. G.; Rys, D. J. *J. Chem. Soc., Chem. Commun.* **1994**, 837.
6. Two equivalents of the reagent may be stoichiometric, since the use of less reagent results in lower yield (i.e., only a single hydride used for reduction).
7. For the use of a catalytically generated tin hydride for reduction, see: Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1975**, *40*, 2554.
8. Typical procedure: AIBN (5.6 mg, 0.034 mmol), $NaBH_3CN$ (427 mg, 6.8 mmol), and Bu_3SnCl (46.0 mL, 0.17 mmol) were placed under nitrogen in a 300 mL three-necked round bottomed flask, which was connected to an empty thick-wall, natural latex rubber balloon. Through a rubber septum *t*-BuOH (13.6 mL), halide **1a** (1.03 g, 3.4 mmol) and 122 mL (5.1 mmol at 24 °C) of oxygen gas was successively injected into the flask. The mixture was stirred vigorously with a magnetic stirrer (1350 rpm, with a stir bar of 2.5-cm length) at 60 °C for 19 h. The reaction mixture was poured into water and extracted four times with ether. The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford 0.60 g (92%) of **2a**. $NaBH_4$ may be employed in place of $NaBH_3CN$ in the expense of some increase of the simple reduction product (**3a**).
9. Hence, the presence of AIBN was not mandatory, though it greatly accelerated the reaction.
10. Maillard, B.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 5095.
11. Neumann, W. P. *Synthesis* **1987**, 665.
12. Bu_2(*t*-Bu)SnCl was prepared from Bu_2SnCl_2 and *t*-BuMgBr: Davies, A. G.; Muggleton, B.; Robberts, B. P.; Tse, M.-W.; Winter, J. N. *J. Organomet. Chem.* **1976**, *118*, 289.
13. For the use of Bu_2(*t*-Bu)SnCl, see: Nakamura, E.; Sato, K.; Imanishi, Y. *Synlett* **1995**, 525.
14. Riess, J. G.; Le Blanc, M. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 621. etc.
15. Preparation of **2a-$^{18}O_2$**: Under nitrogen atmosphere, AIBN (0.8 mg, 0.005 mmol), $NaBH_3CN$ (62.8 mg, 1.0 mmol) and Bu_2(*t*-Bu)SnCl (7.0 mL, 0.025 mmol) were mixed in a degassed *t*-BuOH (2.0 mL, via freeze-thaw cycles) in a 50-mL two-necked round-bottomed flask. Iodide **1a** (115 mL, 0.5 mmol) was added with a syringe through a rubber septum and the mixture was quickly degassed by one freeze-thaw cycle. After being refilled with nitrogen gas, the flask was connected to an empty thick-wall, natural latex rubber balloon. $^{18}O_2$ (99.2 atom%; 24 mL, 1.0 mmol at 24 °C) was collected in a messcylinder immersed into water, taken into a syringe, and injected into the reaction flask via a needle whose tip is immersed into the reaction mixture. The reaction was carried out and worked up as described for the preparation of unlabeled **2a** to afford 95.2 mg (98%) of **2a-^{18}O**. Unlabeled alcohol was not detected by GC-Mass (EI).