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Bismuth-Catalyzed Benzylic Oxidations with *tert*-Butyl Hydroperoxide

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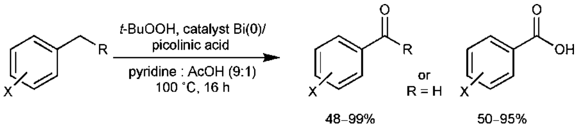
ABSTRACT



Oxidation of alkyl and cycloalkyl arenes with *tert*-butyl hydroperoxide catalyzed by bismuth and picolinic acid in pyridine and acetic acid gave the corresponding benzylic ketones (48–99%). Alternatively, oxidation of methyl arenes gave the corresponding substituted benzoic acids (50–95%). Preliminary mechanistic studies were consistent with a radical mechanism rather than a bismuth(III)–bismuth(V) cycle.

The oxidation of activated benzylic C−H bonds is of fundamental importance in the large scale synthesis of specialty chemicals.[1] Traditionally, these reactions involve the use of stoichiometric quantities of potent oxidants such as potassium permanganate or potassium dichromate.[2] In the past decade, several metal complex catalyzed processes for effecting these transformations have also been reported, using Co,[3] Cr,[4] Mn,[5] Rh,[6] Ru,[7] Zn,[8] and Fe[9] species among others.[10] Nevertheless, the main disadvantages of the use of such reagents are their toxicity, the costs of waste disposal, and the removal of residual metal from the aromatic product. In consequence, the development of a benzylic oxidation reaction with a readily available and inexpensive catalyst of low toxicity would be of considerable importance.

During the past few years the use of bismuth-based reagents in several processes has gained popularity.[11] Indeed, despite being a heavy metal, bismuth has low toxicity.[12] In 1998, Banik reported the use of sodium bismuthate for benzylic oxidation reactions.[13] However, the major drawback of this process is the poor solubility of the bismuthate (a compound with the ilmenite mineral structure), necessitating the use of a large excess of the salt and prolonged reaction times. From our understanding, bismuth has hitherto not been used as a catalyst in the oxidation of substrates with benzylic methylene or methyl groups.[14]

Herein, we now wish to report the use of bismuth-catalyzed oxidations of alkylarenes to the corresponding ketones and of methylarenes to arenecarboxylic acids using

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(1) Sheldon, R. A.; Kochi, J. K. In *Metal-Catalysed Oxidation of Organic Compounds*; Academic Press: New York, 1981.

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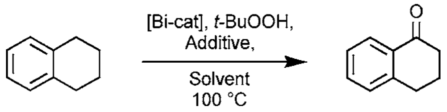
an excess of *tert*-butyl hydroperoxide as the oxidant in a GoAgg^{V}-like system, using pyridine and acetic acid.[15]

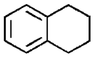
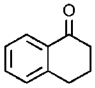
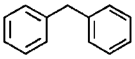
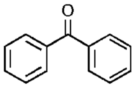
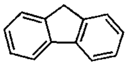
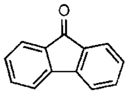
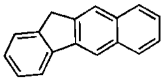
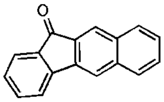
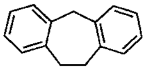
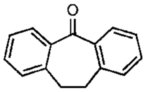
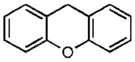
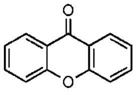
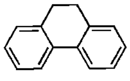
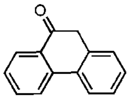
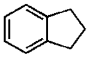
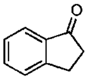
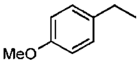
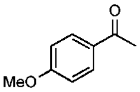
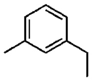
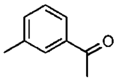
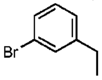
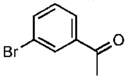
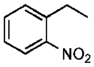
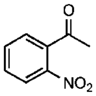
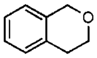
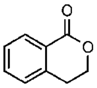
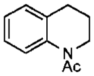
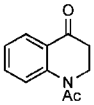
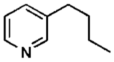
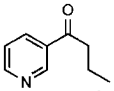
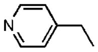
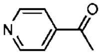
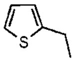
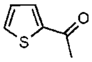
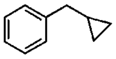
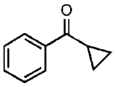
Initial experiments were focused on the oxidation of tetrahydronaphthalene to α-tetralone with $NaBiO_3$ as a catalyst (Scheme 1). Several oxidants were examined and *tert*-butyl hydroperoxide was found to be superior to hydrogen peroxide, peracids, and oxygen. The background reaction with *tert*-butyl hydroperoxide, in the absence of any bismuth catalyst, gave α-tetralone albeit in erratic yields (14−54%), possibly due to traces of metal impurities in one of the reagents. We next investigated the effect of the source of bismuth on the reaction. Both sodium and potassium bismuthate proved to be poor catalysts with low conversions to α-tetralone. The use of alternative bismuth(III) sources such as $(BiO)_2CO_3$, $BiCl_3$, Bi_2O_3, or $Bi(NO_3)_3$ and *tert*-butyl hydroperoxide resulted in low to moderate conversions to α-tetralone. Surprisingly, the most efficient oxidation conditions utilized elemental bismuth (20 mol %) as a precatalyst. This probably resulted from an enhancement of the solubility or reduction in the particle size of the bismuth catalyst generated in situ on reaction with *tert*-butyl hydroperoxide.[16] The catalyst loading could be reduced to 5 mol % but increased reaction times were needed to achieve equivalent conversions. Additives, particularly pyridine and pyrazine, enhanced the rate of benzylic oxidation. The use of equimolar quantities of picolinic acid and bismuth(0) in pyridine and acetic acid (9:1) were especially effective and gave α-tetralone in 77% yield. The optimized procedure involved the use of bismuth(0) (20 mol %), picolinic acid (20 mol %), and 70% *tert*-butyl hydroperoxide in water (6 equiv), in pyridine and acetic acid (9:1) at 100 °C.[17,18] The benzylic oxidation reaction was applied to a range of substrates (Table 1).

Scheme 1. Bismuth-Catalyzed Oxidation of Tetrahydronaphthalene to α-Tetralone



Excellent yields were obtained with substrates containing doubly activated benzylic positions (entries 2−6 and 13) or highly activated rings (entry 9). A substrate bearing a strongly electron-withdrawing substituent underwent oxidation in good yield albeit after longer reaction times (entry 12). It is noteworthy that the regioselective oxidation of a benzylic methylene group was possible in the presence of an arene methyl substituent (entry 10) and a cyclic benzylic ether was

Table 1. Bismuth-Catalyzed Oxidations of Cyclic and Acyclic Alkylarenes[a]

entry	substrate	product	yield (%)[b]
1			77
2			95
3			91
4			99
5			70
6			88
7[19]			50
8			65
9			93
10			54
11			71
12			68[c]
13[20]			91
14[21]			56
15[22]			48
16			74
17			72
18			72

[a] Reaction conditions: see general procedure, ref 17. [b] Yields after chromatography (the samples were all ≥95% pure by comparisons of ^{1}H and ^{13}C NMR spectra of samples with commercial materials or, for noncommercial compounds in entries 7, 13, 14, and 15, by comparisons with published data). [c] The mixture was allowed to react for 46 h.

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(14) The oxidation of allylic CH_2 groups to provide enones with use of *t*-BuOOH catalyzed by $BiCl_3$ has been recently reported, see: Salvador, J. A. R.; Silvestre, S. M. *Tetrahedron Lett.* **2005,** *46*, 2581.

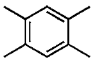
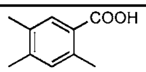
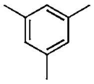
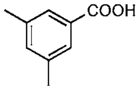
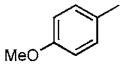
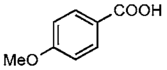
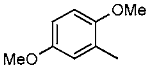
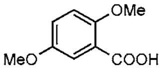
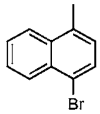
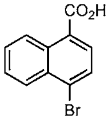
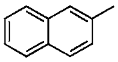
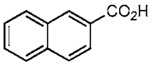
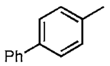
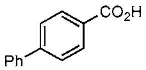
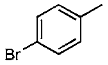
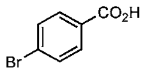
(15) (a) Barton, D. H. R.; Chavasiri, W. *Tetrahedron* **1994**, *50*, 19. (b) Barton, D. H. R.; Wang, T.-L. *Tetrahedron* **1994**, *50*, 1011.

(16) Although commercially available bismuth (Aldrich; 100 mesh) could be used, higher yields were obtained with bismuth(0) generated from Bi_2O_3 by reduction with $NaBH_4$. This is likely to be related to the generation of higher surface area bismuth particles.

oxidized to the corresponding lactone in excellent yield (entry 13). Conveniently, the oxidation reaction was also effective with heterocyclic systems (entries 15−17) without appreciable oxidation of the heteroatom. Finally, benzylcyclopropane was smoothly oxidized to the corresponding ketone without rearrangement (entry 18).

In addition to the bismuth-catalyzed *tert*-butyl hydroperoxide oxidation of substrates with alkyl-CH_2 groups to ketones, we also examined the oxidation of methylarenes to produce arenecarboxylic acids. The use of the standard oxidation[17] on a variety of substrates resulted in moderate to good conversions (entries 1−4; Table 2) albeit with 40 mol % catalyst and 48 h reaction times. The use of bismuth triflate (20 mol %) gave superior yields of the carboxylic acids[23] (Table 2).

Table 2. Bismuth-Catalyzed Oxidations of Methylarenes

entry	substrate	product	yield (%)^{a,b}	yield (%)^{b,c}
1			65	72 (59)
2			78	74 (65)
3			91	87 (72)^{d}
4			25	61 (49)
5			-	58 (56)^{e}
6			-	54 (50)
7			-	67 (60)
8			-	67 (63)

[a] Reactions carried out following ref 23 but with Bi(0) (40 mol %) at 110 °C instead of 100 °C. [b] Approximate yield, based on GC/MS. Yields after chromatography (the samples were all ≥95% pure by comparisons of ^1H and ^{13}C NMR spectra of samples with commercial materials). [c] Reactions carried out following the procedure in ref 23. [d] Reaction carried out with $Bi(OTf)_3$ (5 mol %), picolinic acid (2.5 mol %), and Me_2CO (0.5 mL) as a cosolvent. [e] Reaction carried out with $Bi(OTf)_3$ (10 mol %), picolinic acid (10 mol %), and *t*-BuOOH in PhH (1.78 M; 7 equiv).

The mechanism of these oxidation processes has not yet been established. Bismuth(V) is known to be a very potent oxidant, capable of oxidizing lower valent manganese salts to permanganate.[24] In addition sodium bismuthate is also able to bring about benzylic oxidation, as reported by Banik.[13] On the other hand, it is known that peroxides can oxidize bismuth(III) to bismuth(V) under alkaline conditions.[25] These facts underscore the seductive appeal of a catalytic cycle in which bismuth(V) is the oxidizing species giving rise to the ketones and is, in turn, regenerated by reoxidation with *tert*-butyl hydroperoxide. Nevertheless, none of our experiments support this hypothesis. First, the yields of ketones were poor when bismuthate was used for the reaction (even with stoichiometric amounts). Second, the background reaction in the absence of bismuth is consistent with a radical oxidation mechanism. Third, when other Lewis acids were used, such as hafnium triflate, trimethylsilyl triflate, or boron trifluoride etherate, enhanced rates of benzylic oxidation were observed.[26,27] These results are consistent with the bismuth(III) acting as a Lewis acid thereby modifying the reactivity of the peroxide rather than acting in a bismuth(V)−bismuth(III) cycle.[28] The role of the picolinic acid in the reaction was also examined. This could be acting as a ligand facilitating the solubilization of the bismuth(III) species or it could be oxidized to the corresponding *N*-oxide and thereby be directly involved in the oxygen transfer.[29] When the oxidation of tetrahydronaphthalene was carried out in the presence of picolinic acid *N*-oxide instead of picolinic acid, α-tetralone was formed but in reduced yield (59%). In addition, the use of 6 equiv of picolinic acid *N*-oxide instead of *tert*-butyl hydroperoxide failed to bring about the oxida-

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[17] **General procedure for the oxidation of alkylarenes to ketones**: $NaBH_4$ (18 mg, 0.48 mmol) was added with vigorous stirring to a suspension of Bi_2O_3 (37 mg, 0.08 mmol) in distilled H_2O (1.5 mL) at room temperature giving a finely divided, black precipitate of bismuth metal. This was washed with H_2O (2 × 2 mL), then pyridine (0.8 mL), AcOH (0.08 mL), picolinic acid (20 mg, 0.16 mmol), substrate (0.8 mmol), and *t*-BuOOH in H_2O (70%; 0.66 mL, 4.8 mmol) were added. The mixture was sonicated for 30 min and heated at 100 °C for 16 h (sealed vessel), cooled, diluted with CH_2Cl_2, filtered through Celite, and rotary evaporated. The resulting oil was analyzed (NMR and GCMS) and chromatographed to yield the corresponding ketone.

(18) It should be noted that the system does not require the use of special precautions and could be carried out in the presence of water and under air. The use of sealed vessels was merely for convenience on the scale of these experiments (0.8 mmol).

(19) For the product ketone see: Nashed, N. T.; Sayer, J. M.; Jerina, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 1723.

(20) For the product ketone see: Lehmann, J.; Nieger, M.; Witt, T. *Heterocycles* **1994**, *38*, 511.

(21) For the product ketone see: Crabb, T.; Soilleux, S. L. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1381.

(22) For the product ketone see: Langhals, E.; Langhals, H.; Ruechardt, C. *Liebigs Ann. Chem.* **1982**, 930.

(23) **General procedure for the oxidation of methylarenes to arenecarboxylic acids**: A suspension of $Bi(OTf)_3$ (105 mg, 0.16 mmol), pyridine (0.8 mL), AcOH (0.13 mL), picolinic acid (10 mg, 0.08 mmol), substrate (0.8 mmol), and *t*-BuOOH in H_2O (70%; 0.77 mL, 5.6 mmol) was sonicated for 30 min and then heated at 110 °C for 20 h (sealed vessel). After cooling, EtOAc was added and the resulting suspension was washed with aqueous HCl (10%; 10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$) and rotary evaporated and the resulting oil was analyzed (NMR and GCMS) and subsequently chromatographed to yield the corresponding carboxylic acid.

(24) (a) Scholder, R.; Stobbe, H. *Z. Anorg. Chem.* **1941**, *247*, 392. (b) Rigby, W. *J. Chem. Soc., Abstr.* **1950**, 1907−13.

(25) Barth, J. A. *Z. Anorg. Allg. Chem.* **1980**, *470*, 25.

(26) $Hf(OTf)_4$, $Sc(OTf)_3$, and $Yb(OTf)_3$ showed excellent catalytic activity giving α-tetralone (^1H NMR; 85%, 78%, and 87%, respectively), presumably by accelerating the rate of formation of *t*-BuO$^{\bullet}$.

(27) **Example of an oxidation in the presence of a Lewis acid**: $Sc(OTf)_3$ (78 mg, 0.16 mmol) was added with vigorous stirring to picolinic acid (20 mg, 0.16 mmol) in pyridine (0.8 mL) and AcOH (0.08 mL) at room temperature giving a white precipitate. Tetrahydronaphthalene (0.8 mmol) and *t*-BuOOH in PhH (1.78 M.; 4.8 mmol) were added and the mixture was sonicated for 30 min and heated at 100 °C for 18 h (sealed vessel), then it was cooled, diluted with CH_2Cl_2, filtered through Celite, and rotary evaporated to give α-tetralone (78%).

(28) Gmouh, S.; Yang, H.; Vaultier, M. *Org. Lett.* **2003**, *5*, 2219.

(29) Ueyama, N.; Yoshinaga, N.; Okamura, T.; Zaima, H.; Nakamura, A. *J. Mol. Catal.* **1991**, *64*, 256.

tion. These results preclude picolinic acid *N*-oxide as a significant intermediate in the reaction pathway.

Finally, mechanisms involving free radicals have been reported in *tert*-butyl hydroperoxide mediated oxidations.[6,7,9] Indeed, when 2 equiv of 2,6-di-*tert*-butyl-4-methylphenol, a well-known oxyl radical trap,[30] were added during the oxidation of tetrahydronaphthalene, unreacted starting material was recovered unchanged. On the other hand, 2-methyl-1-phenylprop-2-yl hydroperoxide (MPPH) has been used as a mechanistic probe for *tert*-butoxyl radical formation.[31] This probe relies on the fact that if the corresponding *tert*-alkoxyl radical was formed it would rapidly undergo β-scission preventing hydrogen abstraction from the substrate. Indeed, when MPPH was used as the oxidant only 4% of the α-tetralone was obtained and dibenzyl was isolated as the major byproduct (17%). Additionally, according to Minisci,[32] pyridine acts as a hydrogen bond acceptor with *tert*-butyl hydroperoxide thereby decreasing the reaction rate of the formation of the *tert*-butylperoxyl radical (t-BuOO$^\bullet$) but not the *tert*-butoxyl radical (t-BuO$^\bullet$). Indeed, when the oxidation of tetrahydronaphthalene was carried out in the presence of the stronger hydrogen bond acceptors 4-methylpyridine or 4-methoxypyridine, similar yields of α-tetralone (76% and 79%, respectively) were observed. On the other hand, the use of the less effective hydrogen bond acceptor 3-cyanopyridine led to a lower conversion (47%). These results are consistent with an enhancement of the rate of formation of the *tert*-butoxyl radical in Gif-GoAgg oxidations where the iron is replaced by bismuth.

In conclusion, bismuth has proved to be a useful catalyst for the oxidation of alkylarenes to the corresponding ketones or carboxylic acids with use of *tert*-butyl hydroperoxide as the stoichiometric oxidant. These procedures should find considerable use in synthesis.

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Supporting Information Available: Experimental procedures, characterization data for 4-bromo-1-naphthoic acid, and representative ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(31) Arends, I. W. C. E.; Ingold, K. U.; Wayner, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 4710.

(32) Minisci, F.; Fontana, F.; Araneo, S.; Recupero, F.; Banfi, S.; Quici, S. *J. Am. Chem. Soc.* **1995**, *117*, 226.