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Iron-Catalyzed Benzylic Oxidation with Aqueous *tert*-Butyl Hydroperoxide

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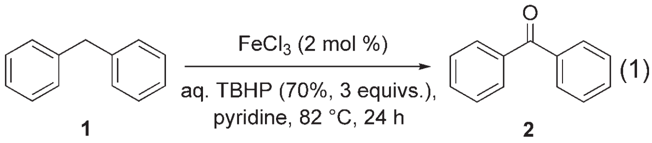
Abstract: A small amount of iron(III) chloride (2 mol %) catalyzes benzylic oxidations with *tert*-butyl hydroperoxide (TBHP) as oxidant in pyridine. The corresponding carbonyl compounds are obtained in high yields.

Keywords: carbonyl compounds; catalysis; C–H activation; ferric chloride; iron; oxidation

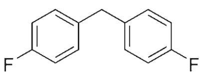
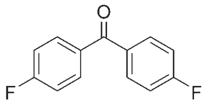
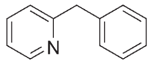
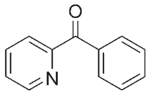
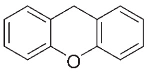
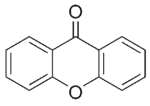
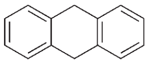
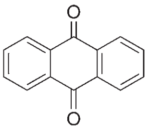
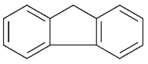
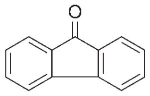
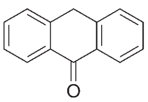
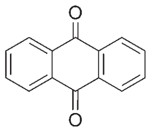
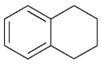
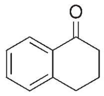
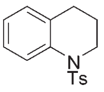
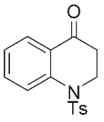
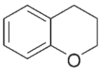
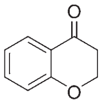
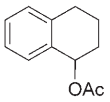
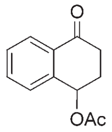
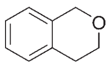
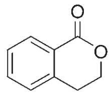
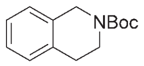
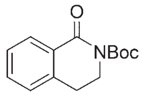
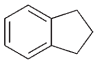
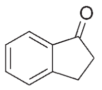
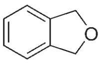
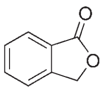
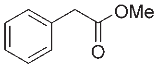
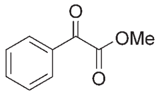
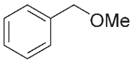
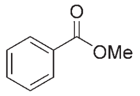
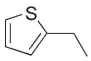
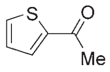
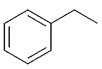
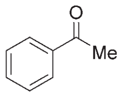
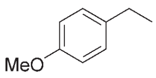
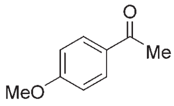
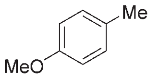
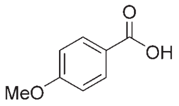
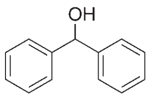
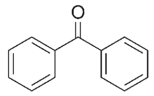
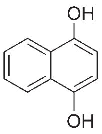
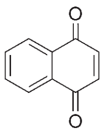
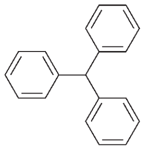
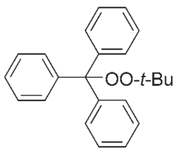
Benzylic oxidation is one of the most significant and synthetically useful methods in organic chemistry. Classically, stoichiometric quantities of oxidants such as potassium permanganate or potassium dichromate were used in these reactions.[1] During the last decades a number of oxidation catalysts have been described,[2] but most of them involve toxic metals[3–8] and their applicability is limited in terms of substrate range. Consequently, further improvements in this area are desirable. In particular on the industrial scale the application of environmentally benign oxidation catalysts in combination with "green oxidants" is essential. In that scenario, low cost and non-toxic iron appears to be a prime element of choice.[9] In 1983, Barton introduced a particular type of iron-catalyzed oxidation,[10] and since then his "Gif chemistry" has further been developed.[11] Recently, Kim and coworkers demonstrated the applicabilty of a related iron catalysis for the oxidation of activated methylene groups.[12] Herein we report an alternative oxidation protocol, which allows one to efficiently oxidize benzylic compounds under mild and convenient reaction condition. The following characteristics are important: 1) Iron(III) chloride is used as inexpensive, non-toxic catalyst in small quantities (2 mol %). 2) Neither an acid (as in the systems by Barton[10,11] and Kim[12]) nor a ligand needs to be added. Probably, the solvent (pyridine) serves as coordinating agent.[13] 3) A cheap and convenient to use solution of TBHP in water (instead of TBHP in hydrocarbons) can be applied as oxidant. 4) A slow addition of reagents (for example, by syringe pump; as in the Kim[12] system) is unnecessary. A typical oxidation [the conversion of diphenylmethane (**1**) into diphenyl ketone (**2**)] is illustrated in Eq. (1).



In the initial phase of the project, diphenylmethane (**1**) was chosen as substrate for the optimization of the catalysis protocol. In the presence of 2 mol % of iron(III) chloride, several oxidants such as hydrogen peroxide,[14] cumene hydroperoxide, NaOCl and dioxygen[15] were tested (in pyridine at 82 °C). Under these conditions the first oxidant decomposed, and also the latter two gave no product at all. Only cumene hydroperoxide afforded ketone **2** in 58 % yield. Finally, the best result was achieved with TBHP (91 % yield of **2**). In the absence of this oxidant, no reaction occurred. Surprisingly, an (open flask) aerobic atmosphere was beneficial, whereas under argon the yield of **2** was only 13 % (as determined by GC). Other iron salts proved also applicable independent of their oxidation states [$Fe(ClO_4)_2$: 70 %; $Fe(ClO_4)_3$: 94 %; $FeCl_2$: 87 %; $Fe(acac)_3$: 40 %]. Although the yield of **2** was slightly higher with $Fe(ClO_4)_3$ as catalyst, $FeCl_3$ was used in subsequent studies in order to avoid the presence of the potentially dangerous perchlorate ion. Compared to other solvents such as acetonitrile, acetic acid and *N*-methylimidazole, which afforded **2** in 73, 48, and 42 % yield, respectively, pyridine proved superior. In summary, use of a 2 mol % of $FeCl_3{\cdot}6H_2O$ and 3 equivs. of TBHP (applied as a 70 % aqueous solution) in pyridine at 82 °C under air led to the formation of ketone **2** in 91 % yield [Eq. (1)].[16]

These optimized conditions were then applied for the oxidative conversion of other substrates. Most diarylmethylene derivatives gave the corresponding

Table 1. . Benzylic oxidation of hydrocarbon derivatives.[a]

Entry	Substrate	Product	Yield [%][b]
1			93
2[c]			75
3			>99
4[d]			93
5			>99
6			62
7			41
8			60
9			54
10			66
11			74
12			30
13			61
14			45
15			30
16			48
17			15
18			17
19			84
20			53
21			86
22[e]			82
23			91

[a] Reaction conditions for a 2 mmol scale: $FeCl_3 \cdot 6\,H_2O$ (2 mol%), TBHP (70%) in H_2O (3 equivs.), pyridine, 82 °C, 24 h.

[b] All products were identified by comparison of their analytical data with those of previous reports or commercial materials.[7,8,18,19]

[c] The reaction temperature was 110 °C.

[d] TBHP (70%) in H_2O (6 equivs.) was used.

[e] The reaction was performed at ambient temperature for 10 min.

products in excellent yields (up to >99%; Table 1, entries 1–6). Less activated educts having one annelated aryl group in a cyclic system led to benzylic oxidation products in yield ranging between 30 and 74% (entries 7–14). Acyclic compounds bearing one (hetero)-aryl group were oxidized in the benzylic position with moderate yields (entries 15–19). By-products were not detected. The surprising reactivity difference between ethylbenzene (entry 18) and *p*-methoxyethylbenzene (entry 19) is attributed to the presence of the electron-donating substituent. By oxidation of *p*-methoxytoluene the corresponding carboxylic acid was obtained in 53% yield (entry 20). Diphenylmethanol gave benzophenone (86% yield, entry 21), and, interestingly, 1,4-dihydroxynaphthalene underwent oxidation to give binaphthoquinone in high yield (82%) under mild conditions (entry 22). The latter transformation is particularly important and might prove useful for the synthesis of vitamin K analogues.[17] Unexpectedly, the oxidation of triphenylmethane afforded *tert*-butyl triphenylmethyl peroxide (in 91% yield) instead of the corresponding alcohol (entry 23).

In summary, we developed a clean iron-catalyzed benzylic oxidation with TBHP as oxidant leading to the corresponding carbonyl compounds in moderate to excellent yields. The simplicity and use of environmentally benign reagents renders this system attractive for large-scale applications.

Experimental Section

Materials

Most starting materials were purchased from commercial suppliers and used without further purification. TBHP (70% in water) was obtained from Fluka. Tosyl-, acetyl- and butoxycarbonyl-protected substrates were prepared by general procedures. Chroman (Table 1, entry 9) was prepared by the previously reported protocol.[19] Pyridine has been used after drying over KOH.

Representative Procedure for the Benzylic Oxidation: Conversion of Diphenylmethane

Diphenylmethane (84.1 mg, 83.3 μL, 0.5 mmol) was added to the solution of $FeCl_3 \cdot 6H_2O$ (2.7 mg, 0.01 mmol) in pyridine (0.5 mL). After the addition of TBHP (70% in H_2O; 206 μL, 1.5 mmol), the reaction mixture was heated at 82 °C for 24 h. The mixture was then allowed to cool to room temperature and poured into a 1 N solution of aqueous HCl (10 mL) in order to remove the pyridine. The organic phase was extracted with Et_2O (40 mL), washed with brine and dried ($MgSO_4$). After filtration, the solvents of the filtrate were evaporated (rotary evaporator). The remaining mixture was separated by column chromatography (silica gel; diethyl ether:pentane = 1:20 as eluent) affording benzophenone; yield: 83 mg (91%).

Acknowledgements

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