

Cu(II)-Catalyzed Ligand-Free Oxidation of Diarylmethanes and Second Alcohols in Water

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We developed a simple and efficient Cu(II)-catalyzed ligand-free oxidation of diarylmethanes and secondary alcohols using 70% tert-butyl hydroperoxide (TBHP) in water. A series of diarylmethanes were directly oxidized into diaryl ketones in 67%–98% yields. Additionally, various secondary alcohols were also transformed into the desired products in 48%–98% yields. Importantly, the catalytic system in the absence of any organic solvent, surfactant, or phase transfer agent, had a wide substrate scope and a high tolerance for various functional groups.

Keywords Cu-catalyzed, oxidation, diarylmethane, ligand-free, water

Introduction

Aromatic ketones are key intermediates for the synthesis of insecticides, photo initiators, perfumes, and pharmaceuticals.^[1] In particular, diaryl ketones derivatives can be used in materials chemistry, such as optical materials,^[2] organic dyes,^[3] plastic additives, biomedical materials,^[4] organic light emitting materials,^[5] and organic solar cell materials.^[6] Traditionally, aromatic ketones have been synthesized by the Friedel-Crafts acylation using homogeneous Lewis acids or strong protonic acids. These processes lead to the formation of large volumes of toxic and corrosive wastes.^[7] Recently, the transition-metal catalyzed oxidation of alkylarenes and aromatic alcohols has become an extremely important method for the formation of aromatic ketones.^[8] Such catalysts include Mn,^[9] Fe,^[10] Co,^[11] Ru,^[12] Rh,^[13] Bi,^[14] and Au.^[15] However, toxic or expensive metal catalysts, hazardous oxidants, and organic solvents are still involved in most of these systems. In contrast, it is desirable to develop more effective copper catalytic systems for the oxidation of alkylarenes and aromatic alcohols, because it is cheap, readily available, and has low toxicity. In 2001, Lee *et al.* developed a simple system for the oxidation of alkyl aromatics in the presence of $\text{KMnO}_4/\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$.^[16] Einhorn *et al.* studied the oxidation of benzylic compounds using *N*-hydroxy-3,4,5,6-tetraphenylphthalimide/CuCl under mild conditions with a low catalyst loading.^[17] To date, several protocols for C–H oxidation catalyzed by metal copper complexes in organic solvent have been reported by Hooley and coworkers.^[18] Lam *et al.* reported copper-catalyzed allylic and benzylic oxidation by aqueous

TBHP in water using a recyclable fluorosulfonate ligand.^[19] Oisaki *et al.* demonstrated the synthesis of 9-fluorenone via selective aerobic photo-oxidation of 9H-fluorenes through the unique combination of catalytic amounts of $\text{Cu}(\text{MeCN})_4\text{OTf}$, $\text{Ru}(\text{bpy})_3\text{Cl}_2 \cdot 6\text{H}_2\text{O}$, and Cu(I) salts.^[20] In general, the Cu-catalyzed oxidation reactions employed some ligands and were carried out in organic solvent. Although some ligands work in water, the tedious multi-step synthesis and high cost of these ligands restrict their applications. Thus, the development of efficient, copper-catalyzed, ligand-free oxidation reactions using water as the solvent has received increasing attention. Based on our previous research works,^[21] herein we developed a simple and efficient Cu(II)-catalyzed ligand-free oxidation of diarylmethanes and secondary alcohols using 70% TBHP in water.

Experimental

Materials and instruments

Chemicals were obtained commercially and used as received. NMR spectra were recorded on a Bruker DPX-400 spectrometer using TMS as the internal standard. EI-Mass spectrum was measured on an LC/Q-TOF MS (Micromass, England). All products were isolated by short chromatography on a silica gel (200–300 mesh) column using petroleum ether (60–90 °C), unless otherwise noted. 9H-Fluorenes, diarylmethanes, and secondary alcohols substrates were of analytical grade quality, purchased from Adamas-beta Pharmaceuticals, Inc.

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General procedure for the oxidative reaction

Caution! *tert*-Butyl hydroperoxide is an exceptionally dangerous chemical that is highly reactive, flammable and toxic. It is corrosive to skin and mucous membranes and causes respiratory distress when inhaled. It may cause explosion in the presence of Cu salt.

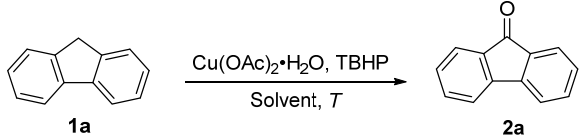
A solution of diarylmethanes or secondary alcohols (1 mmol), and 70% TBHP (6 equiv.) in the presence of Cu(OAc)₂•H₂O as a catalyst was stirred at 80 °C for 8 h. The reaction mixture was quenched with the saturated solution of sodium thiosulfate (5 mL) and extracted with dichloromethane (3 × 10 mL). The combined dichloromethane extracts were dried over anhydrous MgSO₄, filtrated, and then the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel with PE or PE/EtOAc as the eluent to obtain the desired products.

Results and Discussion

Initially, the oxidation of 9*H*-fluorene was selected as a model reaction in the presence of 70% aqueous TBHP to optimize the reaction conditions (Table 1). Only TBHP (6 equiv.) showed lower catalytic activity in water at 80 °C, and only a 27% yield was obtained (Table 1, Entry 1). The comparison of different copper sources indicates that 10 mol% Cu(OAc)₂•H₂O was superior to other sources, including CuCl, CuI, and CuSO₄•5H₂O (Table 1, Entries 2–5). When the amount of Cu(OAc)₂•H₂O was decreased from 10 mol% to 5 mol%, the reaction still afforded a 94% yield of the product (**2a**) (Table 1, entry 6). However, a significantly lower yield was obtained with 1 mol% Cu(OAc)₂•H₂O (Table 1, Entry 7). Meanwhile, the amount of TBHP was found to be a crucial parameter as the product yield decreased from 94% to 27% when the TBHP loading was decreased from 6.0 equivalents to 1.5 equivalents (Table 1, Entries 8 and 9). Similarly, the yield of the product was reduced when the reaction was carried out at 60 °C or at room temperature (Table 1, Entries 10 and 11). In addition, when H₂O₂ as oxidant was used, only trace product was obtained. Finally, the combination of Cu(OAc)₂•H₂O (5 mol%), 70% TBHP (6 equiv.) at 80 °C for 8 h in water (2 mL) was found to be the most suitable reaction conditions.

Using the optimized reaction conditions, we surveyed the scope of diarylmethane substrates for this oxidation reaction in water. As shown in Scheme 1, the substrates 2-NO₂, 2-COMe, and 2-Br substituted 9*H*-fluorenes were oxidized to the desired products **2b**–**2d** with yields of 78%–98%. Similarly, using di-substituted 9*H*-fluorenes as substrates resulted in the formation of the products **2e**–**2h** in 67%–92% yields. Additionally, the oxidative reactions involving substituted diphenylmethanes produced the corresponding products **2i**–**2k** in excellent yields ranging from 88% to 98%. The oxidations of 9*H*-xanthene were also at-

Table 1 The optimization of reaction conditions^a

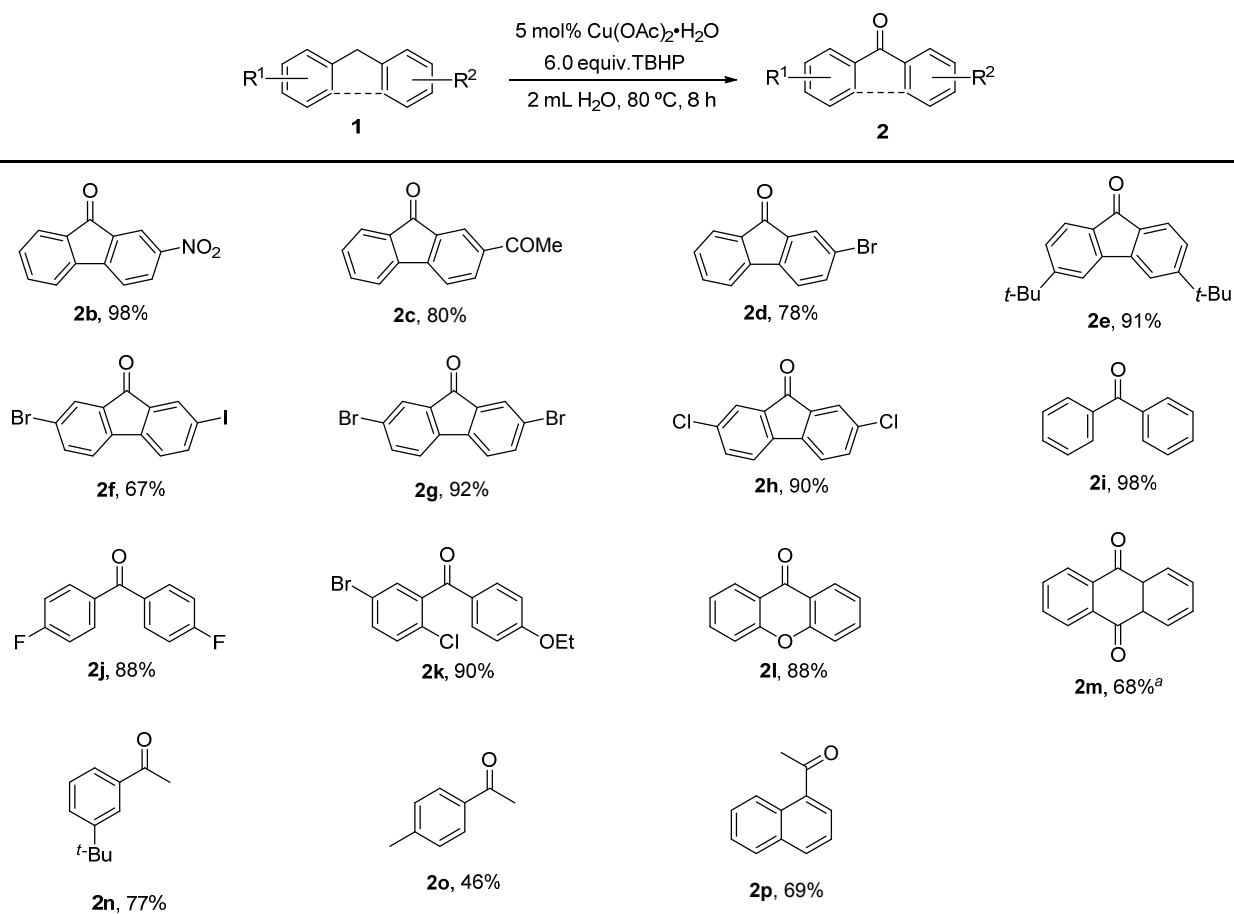


| Entry | Cu source/% | TBHP (equiv.) | T/°C | Yield ^b /% |
|-----------------|---|---------------|------|-----------------------|
| 1 | no | 6 | 80 | 27 |
| 2 | CuCl/10 | 6 | 80 | 84 |
| 3 | CuI/10 | 6 | 80 | 88 |
| 4 | CuSO ₄ •5H ₂ O/10 | 6 | 80 | 91 |
| 5 | Cu(OAc) ₂ •H ₂ O/10 | 6 | 80 | 95 |
| 6 | Cu(OAc) ₂ •H ₂ O/5 | 6 | 80 | 94 |
| 7 | Cu(OAc) ₂ •H ₂ O/1 | 6 | 80 | 75 |
| 8 | Cu(OAc) ₂ •H ₂ O/5 | 3 | 80 | 76 |
| 9 | Cu(OAc) ₂ •H ₂ O/5 | 1.5 | 80 | 27 |
| 10 | Cu(OAc) ₂ •H ₂ O/5 | 3 | 60 | 67 |
| 11 | Cu(OAc) ₂ •H ₂ O/5 | 3 | 25 | trace |
| 12 ^c | Cu(OAc) ₂ •H ₂ O/5 | 6 | 80 | trace |

^a Reaction conditions: 0.5 mmol 9*H*-fluorene, 2 mL H₂O, 8 h, 70% TBHP aqueous. ^b Isolated yield. ^c H₂O₂ as oxidation.

tempted under standard reaction conditions, affording the desired product **2l**, 9*H*-xanthen-9-one, with the yield of 88%. The substrates anthracene and 1-(*tert*-butyl)-3-ethylbenzene were also oxidized to the desired carbonyl compounds **2m** and **2n** with yields of 68% and 77%, respectively. Furthermore, the oxidations of the 1-ethyl-4-methylbenzene and 1-ethylnaphthalene were also performed under these conditions and gave the desired products **2o** and **2p** in 46% and 69% yields, respectively.

To explore the generality of this protocol, a variety of secondary alcohols were subjected to these reaction conditions. The results are summarized in Scheme 2. The substituted 9*H*-fluoren-9-ols were successfully oxidized in the presence of 70% TBHP (6 equiv.) under 5% Cu(OAc)₂•H₂O to afford the desired products **2a**, **2b**, **2d**, and **2g** with 81%–95% yields. Similarly, the oxidation of the 9*H*-xanthen-9-ol and 9,10-dihydroanthracen-9-ol was also performed under these conditions and gave the desired products **2i** and **4a** in 98% and 81% yields, respectively. Subsequently, a series of diphenylmethanol derivatives were investigated. The substituted diphenylmethanols bearing an electron-withdrawing group or an electron-donating group were all well-tolerated and were transformed to the corresponding products **2i**, **2j** and **4b**–**4i** in good yields. To further investigate the range of substrates that could be used in this process, 1-phenylethanol derivatives were investigated. The results showed that 1-phenylethanol and 1-(4-methoxyphenyl) ethanol produced the corresponding ketones **4j** and **4k** with 72% and 85% yields, respectively. The

Scheme 1 The oxidation of diarylmethanes catalyzed by $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ /TBHP

Reaction conditions: diarylmethane 1 mmol, 6 equiv. 70% TBHP, 2 mL H_2O , 80 °C, 8 h. The yields of isolated products are given. ^a Anthracene as substrate is used.

substrate 1-(4-bromonaphthalen-1-yl) ethanol was also oxidized to the desired product **4i** with a yield of 87%. Notably, the selective oxidations of 2,3-dihydro-1*H*-inden-1-ol derivatives to 2,3-dihydro-1*H*-inden-1-one derivatives were attempted using standard reaction conditions, and the desired products **4m** and **4n** were obtained in 67% and 48% yields, respectively. It is worth noting that cyclohexanol was oxidized into cyclohexanone in the presence of 70% TBHP at 80 °C, and the corresponding product **4o** was obtained in 59% GC-MS yield.

Considering the broad application and large demand of 9*H*-fluoren-9-one derivatives in many fields, we tried to conduct a scale-up preparation study based on the above optimized conditions. It is noteworthy that the reaction was performed with 10 mmol of 9*H*-fluorene, and proceeded with the yield of 91%, leading to 2.457 g of the product **2a** (Scheme 3).

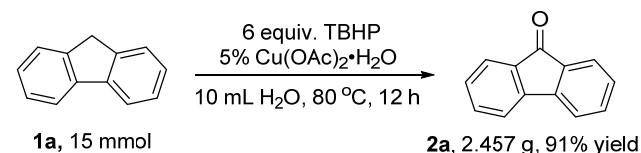
To evaluate the reusability of the $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ as the catalyst, recycling studies were carried out for the oxidative reaction of 9*H*-fluorene in water at 80 °C. After the reaction was completed, the product extracted with ethyl ether and the water phase containing the catalyst was loaded with the reactants and TBHP for the next run. As shown in Table 2, the catalyst can be recycled

two times. However, a significant loss of catalytic activity was observed in the third run.

Table 2 Recycling experiments^a

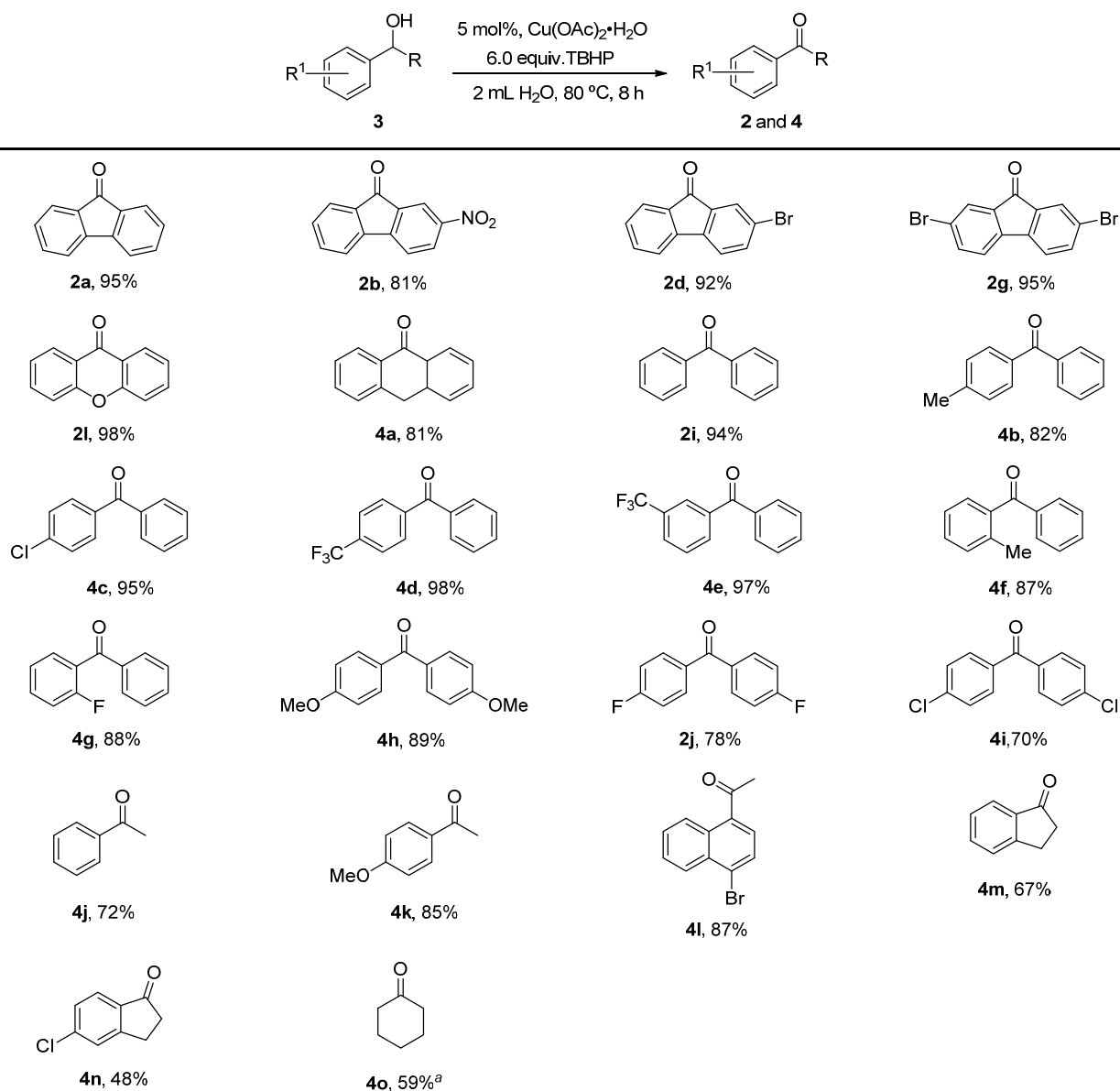
| Entry | 1 | 2 | 3 |
|-----------------------|----|----|----|
| Yield ^b /% | 95 | 75 | 45 |

^a Reaction conditions: 0.5 mmol 9*H*-fluorenes, 2 mL H_2O , 8 h, 80 °C, 5 mol% $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$, 6 equiv. TBHP. ^b Isolated yield, the reaction is performed twice.

Scheme 3 A gram-scale synthesis of product **2a**

Conclusions

In conclusion, we developed an efficient and clean protocol for the $\text{Cu}(\text{II})$ -catalyzed ligand-free oxidation of diarylmethanes and secondary alcohols using 70% TBHP in water. A series of the desired aryl ketones were obtained in moderate to excellent yields. Importantly,

Scheme 2 The oxidation of various secondary alcohols catalyzed by $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ /TBHP

Reaction conditions: second alcohol 1 mmol, 6 equiv. TBHP (70% aqueous solution), 2 mL H₂O, 80 °C, 8 h. The yields of isolated products are given. ^a GC-MS yield.

the catalytic system in the absence of any organic solvent or phase transfer agent had a wide substrate scope and a high tolerance for various functional groups.

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