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Solvent-free oxidation of alcohols by *t*-butyl hydroperoxide catalyzed by water-soluble copper complex

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Abstract—The catalytic system composed of $CuCl_2$ and 2,2′-biquinoline-4,4′-dicarboxylic acid dipotassium salt (BQC), was found to be highly efficient for the selective oxidation of secondary benzylic, allylic and propargylic alcohols to the corresponding ketones, with aqueous *t*-butyl hydroperoxide under phase-transfer catalysis conditions. The catalytic system is stable and can be recycled and reused several times without loss of activity.

The oxidation of alcohols to the corresponding aldehydes and ketones, which can be performed by a variety of methods, remains one of the most important reactions in organic synthesis.[1] Traditionally, the oxidation of alcohols are accomplished by at least stoichiometric amounts of metallic oxidants, mainly chromium (VI) reagents.[2] Safety hazards associated with these oxidants and their toxic by-products, and the difficulty to work-up the reaction mixtures are the major problems of such processes. As a consequence, numerous catalytic methods using small amounts of metallic derivatives and clean oxidants have been developed.[3] Unfortunately, the vast majority of these processes are performed in costly and toxic organic solvents. Furthermore, in the homogeneous processes, the separation of the catalysts from the reaction products and their quantitative recovery in active form are cumbersome. To overcome these inconvenients, an elegant approach for the heterogenization of homogeneous catalyst, is the concept of aqueous organometallic catalysis.[4] The water-soluble catalyst which operates and resides in water, is easily separated from the reaction products by simple decantation. In addition, the products are not contaminated with traces of metal catalyst, and the use of organic solvents, such as benzene and chlorinated hydrocarbons is circumvented. Although the advantages of aqueous phase catalysis very few water-soluble catalysts have been reported for the oxidation of alcohols in water.[5]

Table 1. Oxidation of 1-phenylethanol catalyzed by different catalytic systems[a]

Entry	Catalyst	Additive	Conversion (%)
1	$CuCl_2$	–	20
2	$CuCl_2$	MeOH (0.5 mL)	50
3	$CuCl_2$	MeCN (0.5 mL)	50
4	$CuCl_2$	*n*-Bu_4NI	53
5	$CuCl_2$	*n*-Bu_4NHSO_4	35
6	$CuCl_2$	α-Cyclodextrin	55
7	$CuCl_2$	β-Cyclodextrin	58
8	$CuCl_2$	TBAC	60
9[b]	$CuCl_2$	TBAC	65
10[c]	$CuCl_2$	TBAC	18
11[c,d]	$CuCl_2$	TBAC	11
12[d]	$CuCl_2$	TBAC	5
13	$Pd(OAc)_2$	TBAC	51
14	CrO_3	TBAC	0
15[e]	$CuCl_2$	TBAC	85
16[f]	$CuCl_2$	TBAC	100
17[c,d,g]	$CuCl_2$	TBAC	39

[a] *Reaction conditions*: 1-Phenylethanol (2 mmol), BQC (0.02 mmol), catalyst (0.02 mmol), additive (0.06 mmol), TBHP (2 mmol), Na_2CO_3 (1 mmol), water (5 mL), rt, 17 h.
[b] Na_2CO_3 (0.14 mmol).
[c] No Na_2CO_3 was added.
[d] No BQC was added.
[e] TBHP (4 mmol).
[f] TBHP (6 mmol).
[g] CH_2Cl_2 (5 mL) was used as solvent, and no water was added.

Keywords: oxidation; water-soluble catalyst; copper chloride; *t*-butyl hydroperoxide; ketones.

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Recently, we developed catalytic transformations in water including the hydration of nitriles to the corresponding amides,[6] and Oppenauer-type oxidation of secondary alcohols.[5a] In this paper we wish to report a selective, clean and cheap solvent-free oxidation of secondary benzylic, allylic and propargylic alcohols to the corresponding ketones, with aqueous *t*-butyl hydroperoxide under phase-transfer catalysis conditions. The catalytic system composed of $CuCl_2$ and BQC (2,2′-biquinoline-4,4′-dicarboxylic acid dipotassium salt), catalyzes also the oxidation of aliphatic alcohols. The system is stable and can be easily recovered and recycled several times without loss of activity.

In our preliminary experiments we investigated the oxidation of 1-phenylethanol, chosen as model substrate, under various conditions. When neat 1-phenylethanol (2 mmol) was treated with aqueous *t*-butyl hydroperoxide (TBHP) (1 equiv., 2 mmol) in the presence of $CuCl_2$ (0.02 mmol), BQC (0.02 mmol) and Na_2CO_3 (1 mmol) in distilled water, acetophenone was obtained with 20% conversion (Table 1, entry 1). No reaction was observed in the absence of $CuCl_2$ or TBHP. In aqueous organometallic catalysis, surfactants[7] and modified cyclodextrins[8] as well as polar solvents such as alcohols[9] were added to enhance the reaction rates. Thus, when the oxidation of 1-phenylethanol was repeated with added phase transfer catalysts or co-solvents, conversions ranging from 35% to 60% were obtained (Table 1, entries 2–8). The best results were achieved using β-cyclodextrin (58%) and tetrabutylammonium chloride (TBAC) (60%). In this process sodium carbonate can be used only in catalytic amounts (Table 1, entry 9), and its absence is prejudicial to the process leading to low conversion (Table 1, entry 10). The role of Na_2CO_3 is to keep the ligand BQC in its basic form. Indeed, $CuCl_2$ in distilled water generates an acidic solution where BQC is transformed by protonation to water insoluble 2,2′-biquinoline-4,4′-dicarboxylic acid (BQCH). When the reaction was performed without Na_2CO_3, green water insoluble copper complex (Cu/BQCH) was formed. Under these conditions, there is not enough contact between the catalyst and the substrate, which accounts for the poor yield obtained (entry 10). The advantage of using BQC is clearly demonstrated, since the use of copper chloride alone, or in combination with sodium carbonate, as the catalyst resulted in very low activities (Table 1, entries 11 and 12). When $Pd(OAc)_2$ was used as the catalyst in stead of $CuCl_2$, a conversion of 51% was obtained, while CrO_3 failed to catalyze the oxidation (Table 1, entries 13 and 14). Also, the substitution of TBHP with H_2O_2 (30%), sodium percarbonate or sodium perborate gave no reaction. Increasing the quantity of TBHP to 2 and 3 equiv. afforded acetophenone with 85 and 100% conversion respectively (Table 1, entries 15 and 16).

Table 2. Reuse of the aqueous phase containing the catalyst for the oxidation of 1-phenylethanol[10]

Cycle	Conversion (%)	Cycle	Conversion (%)
1	98	5	100
2	97	6	100
3	100	7	64
4	100	8	40

As we aimed the quantitative recovery and recycling of the catalyst, it is important to select judiciously a proper solvent for the extraction of the products without leaching of the catalyst to the organic phase. The aqueous phase containing $CuCl_2/BQC/Na_2CO_3$ is green–blue-coloured, and became purple when TBHP was added to the mixture. Examination of different solvents, under the oxidation conditions showed that TBHP and TBAC allowed the leaching of the catalyst from the aqueous phase to the organic one in the case of CH_2Cl_2, $ClCH_2CH_2Cl$ and PhCN which became purple, and in the case of $PhNO_2$ which strangely turned yellow. Based on the UV–visible absorptions CH_2Cl_2 extracts almost quantitatively the catalyst from the aqueous phase which became clearer. This solvent has been shown to be an excellent media for the oxidations with TBHP.[3a,j] When we performed the oxidation of 1-phenylethanol using $CuCl_2$ as the catalyst and CH_2Cl_2 as the solvent, acetophenone was obtained with a conversion of 39% (Table 1, entry 17). In the light of these results, and considering the toxicity and the cost of methylene chloride, it is largely more advantageous to use our process based on $CuCl_2$/BQC which is cheap and environmentally friendly. Other solvents, namely ethyl acetate, toluene and diethylether, allow the extraction of acetophenone without leaching of the catalyst as they remained clear solutions and as demonstrated by UV–visible absorption measurements. AcOEt was then chosen as the solvent for the extraction procedure due to its inertness to the oxidation media. After the separation of the organic layer, the aqueous phase of the reaction mixture was reused.[10] The results obtained (Table 2) demonstrate the stability and recyclability of the catalytic system which gave excellent conversions up to six cycles.

The synthetic utility and limits of our catalytic system were illustrated by various alcohols (Table 3).[11] Secondary benzylic alcohols afforded selectively the corresponding ketones with full conversions (Table 3, entries 1–8). When the oxidation of 1-phenylethanol was performed with an alcohol:TBHP:$CuCl_2$:BQC:TBAC:Na_2CO_3 ratio of 1250:3750:1:1:3:7, a turn over number (defined as mols of the product per mol of Cu) of 750 was obtained. Allylic and propargylic alcohols underwent chemoselective oxidations leading to the corresponding unsaturated ketones (Table 3, entries 9–11). In the case of 1-octen-3-ol no other products from epoxidation (1,2-epoxyoctan-3-ol and 1,2-epoxyoctan-3-one), or rearrangement[12] (2-octenal) reactions were detected. The catalytic system proved also to be able to catalyze the oxidation of aliphatic alcohols, albeit low yields (Table 3, entries 12–14). 2-Indanol and 1-phenyl-2-propanol were converted respectively with 27 and 20% conversions, while the oxidation of a mixture of 4-*t*-butylcyclohexanols (*trans*/*cis* = 4.9) led to 4-*t*-butylcyclohexanone with 39% conversion. The *cis* isomer was found to be more reactive than *trans* one as the ratio

Table 3. Oxidation of various alcohols catalyzed by $CuCl_2$/BQC[a]

Entry	Substate	Product	Conversion (%)
1	9-Fluorenol	9-Fluorenone	100
2	1-Indanol	1-Indanone	100
3	1-Tetralol	1-Tetralone	100
4	1-(4-Bromophenyl)ethanol	4′-Bromoacetophenone	100
5	1-(4-Methoxyphenyl)ethanol	4′-Methoxyacetophenone	100
6	Benzhydrol	Benzophenone	100
7	1-Phenyl-1-propanol	Propiophenone	100
8	Chromanol	Chromanone	100
9	Isophorol	Isophorone	100 (92)[b]
10	1-Octyn-3-ol	1-Octyn-3-one	100 (83)[b]
11	1-Octen-3-ol	1-Octen-3-one	100 (87)[b]
12	2-Indanol	2-Indanone	27
13	1-Phenyl-2-propanol	1-Phenyl-2-propanone	20
14[c]	4-*t*-Butylcyclohexanol	4-*t*-Butylcyclohexanone	39

[a] *Reaction conditions*: Substrate (2 mmol), BQC (0.02 mmol), $CuCl_2$ (0.02 mmol), Na_2CO_3 (0.14 mmol), TBAC (0.06 mmol), TBHP (6 mmol), water (5 mL), rt, 24 h.

[b] Isolated yields between brackets.

[c] The ratio of starting alcohols is *trans*/*cis* = 83/17, and the ratio of the remaining alcohols after the reaction is *trans*/*cis* = 89/11.

of the remaining alcohols is *trans*/*cis* = 8.1. It has been previously shown that *cis*-*t*-butylcyclohexanol is oxidized faster than the *trans* isomer with chromic acid in acetic acid.[13] It is important to mention that the oxidation of solid alcohols was proceeded without the addition of any organic solvent to dissolve the substrates.

The oxidation of $PhCD(OH)CH_3$ using our catalytic system and TBHP (1 equiv.) led to acetophenone with only 8% conversion, after 17 h (same conditions as in Table 1, entry 9). This result indicates that the rate-limiting step involves C–H bond cleavage since the isotope effect is large. This observation and the high selectivities obtained in different cases are in agreement with the reported results regarding the oxidation of alcohols in CH_2Cl_2 with $CuCl_2$/TBHP system.[3j] Thus, one electron processes are not, probably, involved in the oxidation reaction.

In conclusion, the catalytic system composed of $CuCl_2$ and 2,2′-biquinoline-4,4′-dicarboxylic acid dipotassium salt (BQC), was found to be highly efficient for the selective oxidation of secondary benzylic, allylic and propargylic alcohols to the corresponding ketones, with aqueous *t*-butyl hydroperoxide under phase-transfer catalysis conditions. The catalytic system is stable and can be recycled and reused several times without loss of activity. Preliminary experiments showed that the system is also very effective for the oxidation of benzylic and propargylic methylenes to the corresponding ketones, as demonstrated by the oxidation of ethylbenzene and 1-phenyl-1-butyne which are fully converted respectively to acetophenone and 4-phenyl-3-butyn-2-one. We are currently studying the catalytic system to establish its full range of application, and its catalytic mechanism.

Acknowledgements

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10. The aqueous phase obtained after removal of solvents was re-used with a fresh charge of the substrate (2 mmol), TBHP (6 mmol), and TBAC (0.06 mmol).
11. *Typical procedure for the oxidation of alcohols*: The reactions were performed under an air atmosphere. Into an open 25 mL round-bottom flask charged with distilled water (5 mL), $CuCl_2 \cdot 2H_2O$ (0.02 mmol), Na_2CO_3 (0.14 mmol), and BQC (0.02 mmol), was added TBAC (0.06 mmol). The green–blue solution was stirred for 5 minutes then the substrate (2 mmol) was introduced followed by aqueous 70% TBHP (6 mmol). The purple mixture was allowed to react for 24 h at room temperature. At the end of the reaction the mixture is still purple. The products and substrate, which are not soluble in water, were extracted three times with ethyl acetate (20 mL). The combined organic layers were treated with an aqueous solution of Na_2SO_3 to reduce the remaing TBHP in the organic phase.[14] After separation of the two layers, the organic phase was dried ($MgSO_4$), evaporated to dryness, then analyzed by thin layer chromatography, and ^1H and ^{13}C NMR. In the case of isolated yields, the ketones were purified using column chromatography with ethyl acetate/petroleum ether (5/95) as the eluant.
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