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A new and highly efficient water-soluble copper complex for the oxidation of secondary 1-heteroaryl alcohols by *tert*-butyl hydroperoxide

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Abstract—The water-soluble copper complex generated in situ from $CuCl_2$ and 2,2′-biquinoline-4,4′-dicarboxylic acid dipotassium salt (BQC), has been revealed as a highly efficient and selective catalyst for the oxidation of secondary 1-heteroaryl alcohols to the corresponding heteroaromatic ketones with aqueous *tert*-butyl hydroperoxide, under mild conditions. The catalytic system is compatible with different heterocycles such as pyridines, pyrroles, indoles, thiophens, furans, thiazoles, and imidazoles.

Aqueous organometallic catalysis is an elegant approach for heterogenization of homogeneous catalysts that is emerged as an active field of research in green chemistry.[1] The selective oxidation of alcohols to the corresponding aldehydes and ketones is one of the most fundamental reactions in organic synthesis.[2] Much attention has, thus, shifted toward the development of environmentally benign processes.[3] Despite the evident ecological and economical advantages of aqueous phase catalysis very few water-soluble catalysts have been reported for the oxidation of alcohols in water.[4]

A wide variety of organic compounds containing heterocyclic moieties are of great interest due to their optic, electronic, and mainly biological properties.[5] Consequently, the synthesis of heterocyclic compounds is a very active field in medicinal chemistry and different methods have been developed for the functionalization of heterocycles. 1-Heteroaromatic ketones are among the most important functionalized heterocycles that are essential precursors to a variety of biologically active compounds such as alkaloids. 1-Heteroaromatic ketones are frequently prepared by Friedel–Crafts acylation of heteroaromatic rings,[6] condensation of metalated heterocycles with nitriles,[7] and stoichiometric oxidations of 1-heteroaromatic-1-alkanols.[8] Although a plethora of catalytic methods have been developed for the oxidation of alcohols, the catalytic oxidations of 1-heteroaromatic alcohols to the corresponding ketones are limited.[9] Recently, we discovered that the water-soluble catalytic system composed of $[Ir(COD)Cl]_2$ and BQC (2,2′-biquinoline-4,4′-dicarboxylic acid dipotassium salt), catalyzes efficiently the Oppenauer-type oxidation of secondary alcohols including 1-(2-furyl) and 1-(2-thienyl)-1-alkanols.[4a] In contrast, the water-soluble palladium complexes reported by Sheldon and co-workers for the aerobic oxidation of alcohols in water failed to catalyze the oxidation of alcohols containing other functional groups such as 1-(3-pyridyl)ethanol.[4d,e] To the best of our knowledge, there are no other reports concerning the catalytic oxidation of secondary 1-heteroaromatic-1-alkanols based on water-soluble catalysts.

We have previously reported different catalytic transformations in water.[4a–c,10] We disclosed the water-soluble $CuCl_2$/BQC as a highly effective catalyst for the oxidation of secondary benzylic, allylic and propargylic alcohols with TBHP. The catalytic system is very cheap, stable and can be recycled several times without loss of activity.[4b] The above-mentioned advantages of $CuCl_2$/BQC coupled with those of TBHP,[11] the efficiency of TBHP for the CrO_3-catalyzed oxidation of oxazolopyridylcarbinols,[9a] and the fact that a general oxidation of heterocyclic alcohols is not developed in

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Keywords: Oxidation; Water-soluble catalyst; Copper chloride; *tert*-Butyl hydroperoxide; 1-Heteroaryl alcohols; Heteroaromatic ketones.

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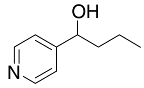
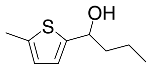
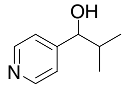
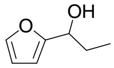
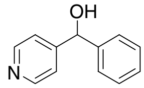
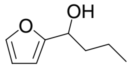
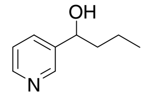
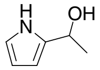
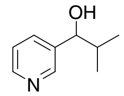
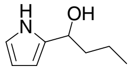
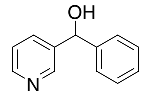
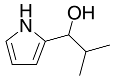
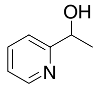
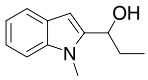
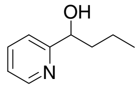
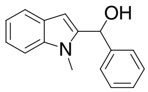
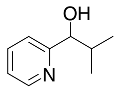
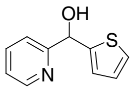
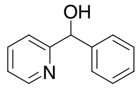
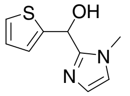
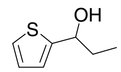
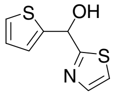
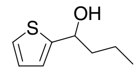
water, prompted us to investigate the catalytic activity of $CuCl_2$/BQC/TBHP system for the oxidation of 1-heteroaryl-1-alkanols. In this letter, we are pleased to disclose an unprecedented general and highly efficient method for the catalytic oxidation of secondary 1-heteroaromatic-1-alkanols in water.[12]

The oxidation of 1-(4-pyridyl)-1-alkanols (2 mmol) with aqueous *tert*-butyl hydroperoxide (TBHP) (3 equiv, 6 mmol) in the presence of $CuCl_2$ (0.02 mmol), BQC (0.02 mmol), tetrabutylammonium chloride (TBAC) (0.06 mmol), and Na_2CO_3 (1 mmol) in distilled water, proceeds smoothly at room temperature affording the corresponding 4-pyridyl ketones with full conversions (Table 1, entries 1–3). These excellent results indicate that the catalytic oxidation is not influenced by the presence of nitrogen atom, which is located far from the carbinol moieties. To study the effect of nitrogen position in the ring, various 3- and 2-pyridylcarbinols were prepared and oxidized under same conditions. While 1-phenyl-1-(3-pyridyl)methanol was fully oxidized at room temperature, 1-(3-pyridyl)-1-butanol and 2-methyl-1-(3-pyridyl)-1-propanol were converted, respectively, with 67% and 78% yields (Table 1, entries 4–6), and excellent yields were obtained at 40 °C. In the case of 2-pyridylcarbinols, where the nitrogen atom is very close

Table 1. Oxidation of various 1-heteroaryl-1-alkanols with TBHP catalyzed by $CuCl_2 \cdot 2H_2O$/BQC[a]

Entry	Substrate	*T* (°C)[b]	Yield (%)	Entry	Substrate	*T* (°C)	Yield (%)
1		rt	100	13		rt	100
2		rt	100	14		rt (40)	40 (80)
3		rt	100	15		rt (40)	57 (89)
4		rt (40)	67 (80)	16		rt (40)	40 (64)
5		rt (40)	78 (100)	17		rt (40)	54 (83)
6		rt	100	18		rt (40)	53 (77)
7		rt (40)	11 (35)	19		40	78
8		rt (40)	11 (39)	20		40	100
9		rt (40) 40[c]	0 (33) 100	21		40	93
10		rt (40) 40[c]	0 (20) 100	22		40	100
11		rt	100	23		40	100
12		rt (40)	100 (100)				

[a] Reaction conditions: substrate (2 mmol), BQC (0.02 mmol), $CuCl_2$ (0.02 mmol), Na_2CO_3 (1 mmol), TBAC (0.06 mmol), TBHP (6 mmol), water (5 mL), 24 h.

[b] Reaction performed at room temperature (rt) or at 40 °C.

[c] BQC (0.04 mmol), $CuCl_2$ (0.04 mmol), and the reaction time is 48 h.