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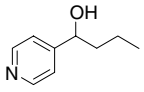
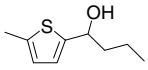
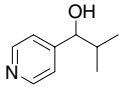
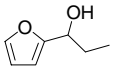
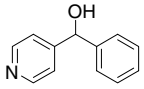
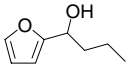
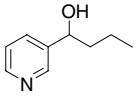
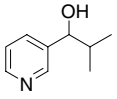
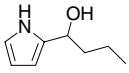
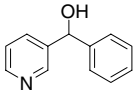
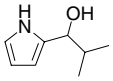
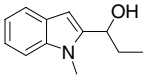
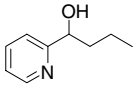
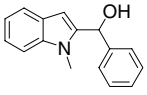
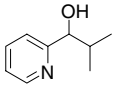
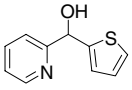
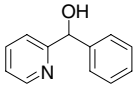
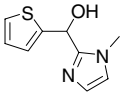
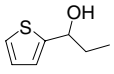
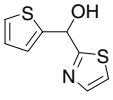
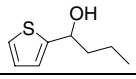
water, prompted us to investigate the catalytic activity of $CuCl_2$/BQC/TBHP system for the oxidation of 1-heteroaryl-1-alkanols. In this letter, we are pleased to disclose an unprecedented general and highly efficient method for the catalytic oxidation of secondary 1-heteroaromatic-1-alkanols in water.[12]

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.

to the hydroxyl groups, the reactions are sluggish and very poor results were obtained at room temperature (Table 1, entries 7–10). Better results were obtained by increasing the reaction temperature to 40 °C. However, the yields are still low ranging from 20% to 39%. Remarkably, the oxidation performed using higher catalyst/substrate ratio, and longer reaction time led to full conversion of the alcohols (Table 1, entries 9 and 10).

To further explore the efficiency of our catalytic system, the oxidation of hereroaromatic alcohols was extended to 2-thienyl and 2-furyl-1-alkanols (Table 1, entries 11–15). While 2-thienyl alcohols are fully converted at room temperature, 2-furyl analogs are moderately transformed to the corresponding ketones. Fortunately, excellent yields were achieved at 40 °C (Table 1, entries 14 and 15).

To evaluate the synthetic potential of $CuCl_2$/BQC/TBHP system, a range of 2-pyrrolyl and indolyl-1-alkanols were investigated. Excellent yields were reached in all the cases at 40 °C (Table 1, entries 16–20). These results indicate the significant synthetic utility of our system since the oxidations of 2-pyrrolyl alcohols were performed with free (NH)-pyrroles, and there was no need to introduce protecting groups. Furthermore, 2-ketopyrroles,[6e,f] and 2-ketoindoles[6f–h,13] are known for their biological properties. These latter compounds are generally prepared by the oxidation of the corresponding alcohols using stoichiometric amounts of PDC.[13]

In a similar manner, this system allows the synthesis of bis heteroaromatic ketones in very high yields demonstrating its broad synthetic scope. Thus, ketones containing 2-thienyl moieties coupled with 2-pyridyl, 2-imidazolyl, or 2-thiazolyl group were successfully prepared (Table 1, entries 21–23).

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 1-heteroaromatic-1-alkanols to the corresponding heteroaromatic ketones, with aqueous *tert*-butyl hydroperoxide. The catalytic system is compatible with various heterocycles such as 2-, 3-, and 4-pyridines, thiophens, furans, pyrroles, indoles, imidazoles, and thiazoles.

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References and notes

1. (a) Cornils, B. *Org. Proc. Res. Dev.* **1998**, *2*, 121; (b) Nait Ajjou, A.; Howard, A. *J. Am. Chem. Soc.* **1998**, *120*, 1466; (c) Ungváry, F. *Coord. Chem. Rev.* **1997**, *160*, 123; (d) Joó, F.; Kathó, Á. *J. Mol. Catal.* **1997**, *116*, 3; (e) Cornils, B.; Herrmann, A. W. In *Applied Homogeneous Catalysis with Organometallic Compounds*; VCH: Weinheim, Germany, 1996; Vol. 2; (f) Papadogianakis, G.; Sheldon, R. A. *New J. Chem.* **1996**, *20*, 175.
2. (a) Sheldon, R. A.; Kochi, J. K. In *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press: New York, 1981; (b) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, P. *Synthesis* **1994**, 639; (c) Hudlicky, M. *Oxidations in Organic Chemistry*; ACS: Washington, DC, 1990; (d) Cainelli, G.; Cardillo, G. *Chromium Oxidations in Organic Chemistry*; Springer: Berlin, 1984.
3. (a) Muzart, J. *Chem. Rev.* **1992**, *92*, 113; (b) Sheldon, R. A.; Arends, I. W. C. E.; Dijksman, A. *Catal. Today* **2000**, *57*, 157; (c) Almeida, M. L. S.; Beller, M.; Wang, G.-Z.; Bäckvall, J. E. *Chem. Eur. J.* **1996**, *2*, 1533; (d) Muzart, J.; Nait Ajjou, A.; Aït-Mohand, S. *Tetrahedron Lett.* **1994**, *35*, 1989; (e) Cecchetto, A.; Fontana, F.; Minisci, F.; Recupero, F. *Tetrahedron Lett.* **2001**, *42*, 6651; (f) Betzemeier, B.; Cavazzini, M.; Quici, S.; Knochel, P. *Tetrahedron Lett.* **2000**, *41*, 4343; (g) Sato, K.; Aoki, M.; Takagi, J.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 12386.
4. (a) Nait Ajjou, A.; Pinet, J.-L. *Can. J. Chem.* **2005**, *83*, 702; (b) Nait Ajjou, A.; Ferguson, G. *Tetrahedron Lett.* **2003**, *44*, 9139; (c) Nait Ajjou, A. *Tetrahedron Lett.* **2001**, *42*, 13; (d) ten Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Science* **2000**, *287*, 1636; (e) ten Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Adv. Synth. Catal.* **2002**, *344*, 355; (f) Sloboda-Rozner, D.; Alsters, P.; Neumann, R. *J. Am. Chem. Soc.* **2003**, *125*, 5280; (g) Liu, R.; Dong, C.; Liang, X.; Wang, X.; Hu, X. *J. Org. Chem.* **2005**, *70*, 729; (h) Uozumi, Y.; Nakao, R. *Angew. Chem., Int. Ed.* **2003**, *42*, 194.
5. (a) Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V. *Comprehensive Heterocyclic Chemistry II*; Pergamon: Oxford, 1996; (b) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*; Blackwell Science: Oxford, 2000.
6. (a) Richard, F.; Carreyre, H.; Pérot, G. *J. Catal.* **1996**, *159*, 427; (b) Choudary, B. M.; Sateesh, M.; Lakshmi Kantam, M.; Ranganath, K. V. S.; Raghavan, K. V. *Catal. Lett.* **2001**, *76*, 231; (c) Isaev, Y.; Fripiat, J. J. *J. Catal.* **1999**, *182*, 257; (d) Viaud, M. C.; Jamoneau, P.; Baudin, M.-L.; Savelon, L.; Guillaumet, G. *Tetrahedron* **1997**, *53*, 5159; (e) Yadav, J. S.; Reddy, B. V. S.; Kondaji, G.; Srinivasa Rao, R.; Praveen Kumar, S. *Tetrahedron Lett.* **2002**, *43*, 8133; (f) Katritzky, A. R.; Suzuki, K.; Singh, S. K.; He, H.-Y. *J. Org. Chem.* **2003**, *68*, 5720; (g) Yeung, K.-S.; Farkas, M. E.; Qiu, Z.; Yang, Z. *Tetrahedron. Lett.* **2002**, *43*, 5793; (h) Cruz, R. P. A.; Ottoni, O.; Abella, C. A. M.; Aquino, L. B. *Tetrahedron. Lett.* **2001**, *42*, 1467; (i) Chatani, N.; Fukuyama, T.; Tatamidani, H.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2000**, *65*, 4039.
7. (a) Chinchilla, R.; Najera, C.; Yus, M. *Chem. Rev.* **2004**, *104*, 2667; (b) Marcantonio, K. M.; Frey, L. F.; Murry, J. A.; Chen, C.-Y. *Tetrahedron Lett.* **2002**, *43*, 8845; (c) Frey, L. F.; Marcantonio, K. M.; Chen, C.-Y.; Wallace, D. J.; Murry, J. A.; Tan, L.; Chen, W.; Dolling, U. H.; Grabowski, E. J. J. *Tetrahedron* **2003**, *59*, 6363; (d) Chen, C.-Y.; Reamer, R. A.; Chilenski, J. R.; McWilliams, C. J. *Org. Lett.* **2003**, *5*, 5039.
8. Kernag, C. A.; Bobbitt, J. M.; McGrath, D. V. *Tetrahedron. Lett.* **1999**, *40*, 1635, and references cited therein.
9. (a) Nait Ajjou, A.; Muzart, J.; Savelon, L.; Guillaumet, G. *Synthesis* **1994**, 359; (b) Liu, R.; Liang, X.; Dong, C.; Hu, X. *J. Am. Chem. Soc.* **2004**, *126*, 4112; (c) Ansari, I. A.; Gree, R. J. *Org. Lett.* **2002**, *4*, 1507; (d) Markó, I. E.; Giles, P. R.; Tsukazaki, M.; Chellé-Regnaut, I.; Gautier, A.; Brown, S. M.; Urch, C. J. *J. Org. Chem.* **1999**, *64*, 2433; (e) Miller, R. A.; Hoerrner, R. S. *Org. Lett.* **2003**, *5*, 285.

10. (a) Nait Ajjou, A.; Pinet, J.-L. *J. Mol. Catal. A: Chem.* **2004**, *214*, 203; (b) Djoman, M. C. K.-B.; Nait Ajjou, A. *Tetrahedron Lett.* **2000**, *41*, 4845.
11. Sharpless, K. B.; Verhoeven, T. R. *Aldrichim. Acta* **1979**, 63.
12. Typical procedure for the oxidation of 1-heteroaromatic-1-alkanols: The reactions were performed under an air atmosphere. Into an open 25 mL round-bottomed flask charged with distilled water (5 mL), $CuCl_2$, $2H_2O$ (0.02 mmol), Na_2CO_3 (1 mmol), and BQC (0.02 mmol), was added TBAC (0.06 mmol). The green-blue solution was stirred for 5 min 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 was still purple. The products and substrate, which are not soluble in water, were extracted three times with ethyl acetate (20 mL). After separation of the two layers, the organic phase was dried ($MgSO_4$), evaporated to dryness, then analyzed by thin layer chromatography, and ^1H NMR and ^{13}C NMR.
13. Mahboobi, S.; Teller, S.; Pongratz, H.; Hufsky, H.; Sellmer, A.; Botzki, A.; Uecker, A.; Beckers, T.; Baasner, S.; Schächtele, C.; Überall, F.; Kassack, M. U.; Dove, S.; Böhmer, F.-D. *J. Med. Chem.* **2002**, *45*, 1002.