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An unprecedented highly efficient solvent-free oxidation of alkynes to α,β-acetylenic ketones with *tert*-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 α-oxidation of internal alkynes to the corresponding α,β-acetylenic ketones, with aqueous *tert*-butyl hydroperoxide under mild conditions. For the first time, full conversions of alkynes were reached with excellent selectivities, and propargylic *tert*-butylperoxy ethers were observed and suggested as the reaction intermediates. In the case of terminal alkynes, the oxidations are sluggish and low yields ranging from 32% to 40% were obtained.

α,β-Acetylenic ketones are essential precursors to a variety of biologically active compounds, such as C-nucleosides,[1] anti-cancer agents,[2] inhibitors of delta 5-3-oxo steroid isomerase (EC 5.3.3.1) from pseudomonas testeroni,[3] and pheromones.[4] These conjugated ynones are highly versatile building blocks for various organic compounds such as heterocycles.[5] Furthermore, the occurrence of α,β-acetylenic ketone moiety is widespread among natural products. α,β-Acetylenic ketones are frequently prepared by different methods including, acylation of alkynyl organometallic reagents,[6] cross-coupling between terminal alkynes and acyl chlorides,[7] carbonylation of terminal alkynes in the presence of aryl halides,[8] indium-mediated alkynylation of aldehydes followed by indium-mediated Oppenauer oxidation,[9] and multistep synthesis.[10]

The oxidation of hydroxyl and methylene groups to the corresponding carbonyl moieties remains one of the most fundamental reactions in organic synthesis.[11] Traditionally, most oxidations are accomplished by at least stoichiometric amounts of often toxic oxidants, especially chromium(VI) reagents. 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, different catalytic methods using small amounts of metallic derivatives and clean oxidants have been developed.[11] 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 reactions products and their quantitative recovery in active form are cumbersome. Aqueous organometallic catalysis is an excellent approach to overcome these drawbacks. The use of water as solvent is important for economical, safety, and environmental reasons. 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. α,β-Acetylenic ketones are also prepared by oxidation reactions of either propargylic alcohols or the corresponding alkynes. Although a plethora of methods have been developed for benzylic and allylic oxidations, the oxidations of propargylic hydroxyl and methylene groups are still limited in number. While the oxidation of propargylic alcohols using stoichiometric[12] or catalytic[13] processes is not frequent, direct oxidation technologies of alkynes to α,β-acetylenic ketones are scarce.[14–20] Stoichiometric and large excess amounts of chromium(VI) reagents have been used for α-oxidation of alkynes. However,

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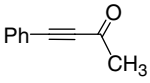
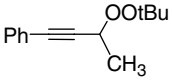
low yields were obtained.[14] Muzart and Piva reported the first Cr(VI)-catalyzed α-oxidation of alkynes with *tert*-butyl hydroperoxide (TBHP), and only moderate yields were reached although large excess of TBHP was used and long reaction time. In addition, the oxidation reactions were mostly performed in benzene.[15] SeO_2/TBHP system was also used for the oxidation of propargylic methylenes.[16] The internal alkynes studied underwent α,α′-oxidation which led to a mixture of mono- and di-oxygenated acetylenic alcohols and ketones, with ynones as minor products.[16a] Recently, Ishii and co-workers reported that alkynes were converted by aerobic oxidation into α,β-acetylenic ketones with good yields using *N*-hydroxyphthalimide combined with a transition metal.[17]

Aerobic oxidations of alkynes were also performed using hydroperoxides and metallic catalysts.[18,19] Non-heme iron complexes combined to hydrogen peroxide or TBHP led to poor yields and selectivities for α,β-acetylenic ketones,[18] while better results were obtained with Cu^{2+}/TBHP system.[19] Finally, iron phthalocyanines grafted onto silica were successfully used as catalysts for the oxidation of alkynes to ynones with excess TBHP.[20] We recently reported different transformations in water.[21] Despite the evident ecological and economical advantages of aqueous phase catalysis, to the best of our knowledge there are no reports concerning selective α-oxidation of alkynes to α,β-acetylenic ketones in water. In this letter, we are pleased to disclose an unprecedented highly efficient oxidation of alkynes to the corresponding ynones in water with aqueous *tert*-butyl hydroperoxide catalyzed by the system composed of $CuCl_2$ and BQC (2,2′-biquinoline-4,4′-dicarboxylic acid dipotassium salt).

In our preliminary experiments, we investigated the oxidation of 1-phenyl-1-butyne (**1**), chosen as a model substrate. Thus, the oxidation of **1** (2 mmol) with aqueous *tert*-butyl hydroperoxide (1 equiv, 2 mmol) in the presence of $CuCl_2$ (0.02 mmol), BQC (0.02 mmol), tetrabutylammonium chloride (0.06 mmol), and Na_2CO_3 (0.14 mmol) in distilled water gave 4-phenyl-3-butyn-2-one (**2**) and 3-*tert*-butylperoxy-1-phenyl-1-butyne (**3**)[22] with 15% and 7% yields, respectively (Table 1, entry 1). Our first experiments showed that the presence of $CuCl_2$, BQC, and Na_2CO_3 together is required to achieve the oxidation of **1** with TBHP. Also, no reaction was observed when the reaction of **1** was performed with 1 equiv of hydrogen peroxide, lithium perchlorate, sodium percarbonate, or sodium hypochlorite, alone or combined with TBHP (0.25 equiv). When the oxidation of 1-phenyl-1-butyne was repeated without TBAC, conversion of 10% was observed and product **2** was obtained with 9% yield (Table 1, entry 2). As the quantity of TBHP was increased from 2 to 4 equiv, the amounts of α,β-acetylenic ketone increased in detriment of propargylic *tert*-butylperoxy ether which decreased markedly, and full conversion of **1** to **2** with excellent selectivity was achieved with 4 equiv of TBHP (Table 1, entries 3–5). The reaction performed under argon showed that the catalytic system is as efficient as under air. Since one of the most important aspect of aqueous phase catalysis is the possibility to separate and recycle the catalyst, we investigated the durability of $CuCl_2$/BQC system by carrying out five consecutive cycles with the same catalyst aqueous phase separated from the organic phases. A fresh charge of **1** (2 mmol), TBHP (8 mmol), and TBAC (0.06 mmol) was used in each cycle. The results summarized in Table 1 show that after the second cycle the conversions decreased and mixtures of **2** and **3** were obtained (Table 1, entries 5–9).

Table 1. Oxidation of 1-phenyl-1-butyne (**1**) catalyzed by $CuCl_2{\cdot}2H_2O$/BQC[a]

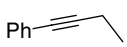
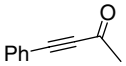
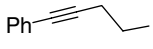
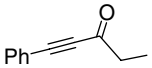
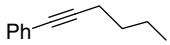
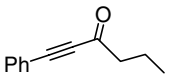
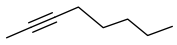
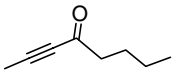
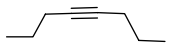
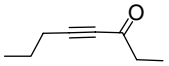
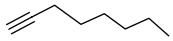
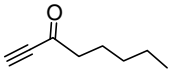
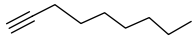
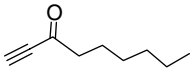
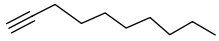
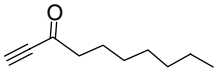
Entry	TBHP (equiv)	Conversion (%)	Yield (%)	
				
1	1	22	15	7
2[b]	1	10	9	0
3	2	72	55	17
4	3	92	89	Traces
5	4	100	98	0
6[c]	4	100	96	0
7[d]	4	64	62	Traces
8[e]	4	70	47	21
9[f]	4	58	36	20

[a] Reaction conditions: 1-phenyl-1-butyne (2 mmol), BQC (0.02 mmol), $CuCl_2$ (0.02 mmol), Na_2CO_3 (0.14 mmol), TBAC (0.06 mmol), TBHP (2–8 mmol), water (5 mL), rt, 24 h.
[b] The reaction is performed without TBAC.
[c] Second cycle of entry 5.
[d] Third cycle of entry 5.
[e] Fourth cycle of entry 5.
[f] Fifth cycle of entry 5.

To evaluate the synthetic potential of $CuCl_2$/BQC system, various aromatic and aliphatic alkynes were subjected to the oxidation with 4 equiv of TBHP (Table 2).[23] The oxidation of aromatic alkynes proceeded smoothly with excellent yields and full conversions in most cases (Table 2, entries 1–3). 1-Phenyl-1-hexyne was oxidized with 88% conversion yielding 1-phenyl-1-hexyn-3-one and the corresponding propargylic *tert*-butylperoxy ether with 78% and 9% yields, respectively. Increasing the reaction time to 48 h allowed the formation of the ynone with excellent yield (89%) and only 2% of the mixed peroxide was detected (Table 2, entry 3). Our catalytic system is also highly efficient for the oxidation of internal alkynes. Transformation of 2-octyne occurred regioselectively yielding 2-octyn-4-one with excellent conversion and selectivity, while remarkably 4-octyne was fully converted to 4-octyn-3-one as a sole product with very high selectivity (Table 2, entries 4 and 5). In the case of terminal alkynes, the oxidations are sluggish and only yields of 32–40% were reached (Table 2, entries 6–8). Moreover, no increase in the yields was observed with longer reaction time.

The previous reports that described α-oxidation of alkynes to α,β-acetylenic ketones suggested propargylic alcohols as the intermediates, and no study ever mentioned the formation of propargylic alkylperoxy ethers.[15,16a,17,19,20] To the best of our knowledge, this is the first time that the formation of propargylic alkyl-

Table 2. Oxidation of various alkynes catalyzed by $CuCl_2{\cdot}2H_2O$/BQC[a]

Entry	Substrate	Product	Conversion (%)	Yield (%)
1			100	98
2			100	96
3			88[b] (93)[c]	78[b] (89)[c]
4			90	88
5			100	99
6			38	36
7			35	32
8			43	40

[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 (8 mmol), water (5 mL), rt, 24 h.

[b] 3-*tert*-Butylperoxy-1-phenyl-1-hexyne (9%) was also obtained.

[c] The reaction time is extended to 48 h. 3-*tert*-Butylperoxy-1-phenyl-1-hexyne (2%) was also obtained.

peroxy ethers, such as 3-*tert*-butylperoxy-1-phenyl-1-butyne (**3**), was observed during the oxidation of alkynes to ynones. Unlike propargylic alkylperoxy ethers, allylic[24] and benzylic[11,25] mixed peroxides, however, are common. In this study, propargylic alcohols were not detected. Since $CuCl_2$/BQC is very efficient for the oxidation of 1-octyn-3-ol with TBHP,[21d] we, thus, propose that α,β-acetylenic ketones are formed preferentially by way of propargylic *tert*-butylperoxy ethers without excluding firmly propargylic alcohols as intermediates. Compound **3** was, indeed, fully converted under our catalytic oxidation conditions to 4-phenyl-3-butyn-2-one (**2**). Our results are in agreement with a mechanism where *tert*-butylperoxy radicals are likely involved, a key step being α-hydrogen abstraction.[19,20,25b]

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 α-oxidation of alkynes to the corresponding α,β-acetylenic ketones, with aqueous *tert*-butyl hydroperoxide under mild conditions. For the first time, full conversions of alkynes were reached with excellent selectivities and propargylic *tert*-butylperoxy ethers were observed and suggested as the reaction intermediates.

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References and notes

1. Adlington, R. M.; Baldwin, J. E.; Pritchard, G. J.; Spencer, K. C. *Tetrahedron Lett.* **2000**, *41*, 575.
2. Kundu, N. G.; Mahanty, J. S.; Spears, C. P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1497.
3. Penning, T. M.; Covey, D. F.; Talalay, P. *Biochem. J.* **1981**, *193*, 217.
4. Clennan, E. L.; Heah, P. C. *J. Org. Chem.* **1981**, *46*, 4107.
5. Cabarrocas, G.; Ventura, M.; Maestro, M.; Mahía, J.; Villalgordo, J. M. *Tetrahedron: Asymmetry* **2000**, *11*, 2483.
6. Yamaguchi, M.; Shibato, K.; Fujiwara, S.; Hirao, I. *Synthesis* **1986**, 421.
7. (a) Alonso, D. A.; Nájera, C.; Pacheco, M. C. *J. Org. Chem.* **2004**, *69*, 1615; (b) Chowdhury, C.; Kundu, N. G. *Tetrahedron* **1999**, *55*, 7011.
8. Mohamed Ahmed, M. S.; Mori, A. *Org. Lett.* **2003**, *5*, 3057.
9. Augé, J.; Lubin-Germain, N.; Seghrouchni, L. *Tetrahedron Lett.* **2003**, *44*, 819.
10. Katritzky, A. R.; Lang, H. *J. Org. Chem.* **1995**, *60*, 7612.
11. Muzart, J. *Chem. Rev.* **1992**, *92*, 113.
12. (a) Serrat, X.; Cabarrocas, G.; Rafel, S.; Ventura, M.; Linden, A.; Villalgordo, J. M. *Tetrahedron: Asymmetry* **1999**, *10*, 3417; (b) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738.
13. Maeda, Y.; Kakiuchi, N.; Matsumura, S.; Nishimura, T.; Kawamura, T.; Uemura, S. *J. Org. Chem.* **2002**, *67*, 6718.
14. (a) Shaw, J. E.; Sherry, J. J. *Tetrahedron Lett.* **1971**, *12*, 4379; (b) Sheats, W. B.; Olli, L. K.; Stout, R.; Lundeen, J. T.; Justus, R.; Nigh, W. G. *J. Org. Chem.* **1979**, *44*, 4075.
15. Muzart, J.; Piva, O. *Tetrahedron Lett.* **1988**, *29*, 2321.
16. (a) Chabaud, B.; Sharpless, K. B. *J. Org. Chem.* **1979**, *44*, 4202; (b) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526.

17. Sakaguchi, S.; Takase, T.; Iwahama, T.; Ishii, Y. *Chem. Commun.* **1998**, 2037.
18. Ryu, J. Y.; Heo, S.; Park, P.; Nam, W.; Kim, J. *Inorg. Chem. Commun.* **2004**, *7*, 534.
19. Li, P.; Fong, W. M.; Chao, L. C. F.; Fung, S. H. C.; Williams, I. D. *J. Org. Chem.* **2001**, *66*, 4087.
20. Pérollier, C.; Sorokin, A. B. *Chem. Commun.* **2002**, 1548.
21. (a) Boudreau, J.; Doucette, M.; Nait Ajjou, A. *Tetrahedron Lett.* **2006**, *47*, 1695; (b) Nait Ajjou, A.; Pinet, J.-L. *Can. J. Chem.* **2005**, *83*, 702; (c) Nait Ajjou, A.; Pinet, J.-L. *J. Mol. Catal. A: Chem.* **2004**, *214*, 203; (d) Ferguson, G.; Nait Ajjou, A. *Tetrahedron Lett.* **2003**, *44*, 9139; (e) Nait Ajjou, A. *Tetrahedron Lett.* **2001**, *42*, 13; (f) Djoman, M. C. K.-B.; Nait Ajjou, A. *Tetrahedron Lett.* **2000**, *41*, 4845.
22. 3-*tert*-Butylperoxy-1-phenyl-1-butyne (**3**): ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.45 (m, 2H), 7.25 (m, 3H), 4.85 (q, $J = 7$ Hz, 1H), 1.5 (d, $J = 7$ Hz, 3H), 1.25 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 131.8, 128.3, 128.2, 122.9, 88.8, 84.5, 80.6, 70.0, 26.5, 19.8. Authentic sample of **3** was prepared in anhydrous benzene solution of TBHP containing **1** and CuCl.[25a] Both compounds (**3** and authentic sample) gave the same NMR spectroscopic data. In addition, they were characterized with GC–MS where they showed the same retention time and same mass spectroscopy data. Furthermore, positive iodine test[25a] was observed in both cases.
23. Typical procedure for the oxidation of alkynes: into an open 25 mL round-bottomed flask charged with distilled water (5 mL), $CuCl_2$, $2H_2O$ (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 min, then the substrate (2 mmol) was introduced followed by aqueous 70% TBHP (8 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 substrates, which are not soluble in water, were extracted three times with ethyl acetate (20 mL). The combined organic layers were dried ($MgSO_4$), evaporated to dryness, then analyzed by thin layer chromatography, GC–MS (Table 1, entries 1 and 3–5; and Table 2, entry 3), ^{1}H NMR and ^{13}C NMR. Conversions and yields were determined after the reaction mixtures were purified using column chromatography (silica gel) with a gradient of petroleum ether/ethyl acetate (100 to 95/5) as the eluant.
24. Yu, J.-Q.; Corey, E. J. *Org. Lett.* **2002**, *4*, 2727.
25. (a) Muzart, J.; Nait Ajjou, A. *J. Mol. Catal.* **1994**, *92*, 141, and 277; (b) Rothenberg, G.; Feldberg, L.; Wiener, H.; Sasson, Y. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2429.