

Copper-Catalyzed Oxidative Cleavage of Electron-Rich Olefins in Water at Room Temperature

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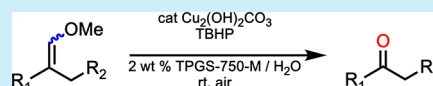
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S Supporting Information

ABSTRACT: A copper-catalyzed oxidative cleavage of electron-rich olefins into their corresponding carbonyl derivatives is described as an alternative to ozonolysis. The scope includes various precursors to aryl ketone derivatives, as well as oxidations of enol ethers bearing atypical alkyl and dialkyl substitution, the first of their kind among such metal catalyzed alkene cleavage reactions. The use of an inexpensive copper salt, room temperature conditions, an aerobic atmosphere, and water as the global reaction medium highlight the green features of this new method. Associated mechanistic investigations are also presented.



The use of ozone as a stoichiometric reagent for the generation of a carbonyl group is a fundamental reaction with valuable applications to organic synthesis. Olefin oxidation reactions in numerous total synthesis campaigns, past and present, attest to the impact of this simple, yet powerful transformation. Notwithstanding its time-honored status in the community, safety and handling issues that necessitate specific operational needs (e.g., including specialized laboratory equipment for its formation at low temperatures) present a less than ideal situation. An equivalent based on catalysis, however, might obviate these shortcomings, allowing for a more practical, safe, and user-friendly approach to this important reaction. Up until recently,¹ there were no reports on methodologies directed specifically to achieve this conversion. Only within the past few years have such reports been successfully conducted under catalytic conditions.

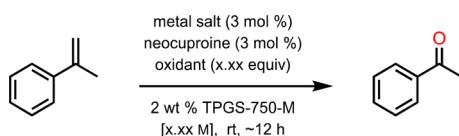
In 2006, Shi and co-workers described a gold-catalyzed oxidative cleavage of simple benzophenone precursors in water, albeit at 90 °C.² Later, an organocatalytic approach was reported utilizing *N*-hydroxyphthalimide (NHPI or PINO) in dimethylacetamide at 80 °C, with molecular oxygen as the oxidant, again providing mainly benzophenone derivatives.³ More recently, in 2015, Xiao et al. disclosed an elegant methodology based on iron(III) triflate, in hot DCE.⁴ This report described a broad scope of substrates leading to benzaldehyde, acetophenone, and benzophenone derivatives, although it relied upon the activity of a noncommercially available pyridine bis-sulfonamide ligand. Moreover, the conditions appeared not to be compatible with nitrogen within the chosen substrates. Lastly, in 2016, a photocatalytic approach employing an aromatic disulfide as catalyst was described, nearly exclusively leading to benzaldehyde products.⁵ Thus, a more general methodology that offers room temperature conditions, avoids use of waste-generating organic

solvents,⁶ relies upon a readily available and earth abundant metal,⁷ and involves a simple and safe protocol is still desirable.

Past documentation of many radical processes both promoted by, and catalytic in, copper suggested its potential as a mediator of this transformation. It was anticipated to be an attractive alternative when compared to those metals used previously (*vide supra*) due to copper's low toxicity, controllable oxidation states, relative abundance, and cost.⁸ Since copper has been previously utilized with substantial success in oxidations of alcohols to aldehydes and/or ketones,⁹ it was reasonable to anticipate its participation in an oxidative cleavage of alkenes using a peroxide as the stoichiometric oxidant. Initial experiments, inspired by Shi's prior report,² suggested that our micellar catalysis technology (i.e., using water at rt) might be amenable.

As shown in Table 1, use of either ligated gold or copper salts, together with a peroxide under micellar catalysis conditions, led to varying amounts of the desired ketone in which copper was found to significantly out-perform gold as the metal (entries 1 vs 2). These reactions were run "open-flask", thereby allowing atmospheric oxygen to participate as needed in the process. Conversely, when the analogous reaction was run under argon, no conversion of the starting α -methylstyrene was observed. However, upon addition of more peroxide (2.00 equiv) and further stirring while open to air, the same reaction began to produce the expected oxidation product (entry 3). Switching from a copper(I) to (II) salt was of little consequence (entries 1 vs 4). Running the reaction with TBHP under 1 atm of molecular oxygen, likewise, showed no benefit, and in fact, led to inferior results (entry 5). A control reaction run exposed to air, but in the absence of TBHP afforded no reaction (entry 8), while no reaction was

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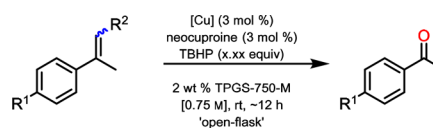
Table 1. Initial Optimization Screening of Reaction Parameters with α -Methylstyrene

entry	metal/L	oxidant (equiv)	yield ^a (%)
1	Cu(I)OAc	TBHP (2.00)	57
2	AuCl ₃	TBHP (2.00)	26
3 ^b	Cu(I)OAc	TBHP (2.00)	NR (47) ^c
4	Cu(OAc) ₂	TBHP (2.00)	59
5 ^d	Cu(OAc) ₂	TBHP (2.00)	48
6 ^e	Cu(OAc) ₂	TBHP (2.00)	16
7 ^f	Cu(OAc) ₂	TBHP (2.00)	13
8	Cu(OAc) ₂	none	NR
9	none	TBHP (2.00)	NR
10	Cu(MeCN) ₄ PF ₆	TBHP (2.00)	55
11	Cu(<i>i</i> -butyrate) ₂	TBHP (2.00)	39
12	Cu(OAc) ₂	H ₂ O ₂ (3.00)	NR
13	Cu(OAc) ₂	cumene-OOH (2.00)	NR
14	Cu(OAc) ₂	TMS-O-O-TMS (2.00)	NR
15	Cu(OAc) ₂	MCPBA (2.00)	NR
16	Cu(OH) ₂	TBHP (2.50)	65
17	CuO	TBHP (2.50)	48

^aYield of isolated products, after column chromatography. ^bReaction initially run under Ar. ^cReaction yield after additional TBHP with exposure to air. ^dReaction run under an 1 atm of O₂. ^eConcentration of [0.50 M]. ^fConcentration of [1.00 M]. NR = no reaction.

observed in the absence of copper (entry 9). Taken together, these data suggest a curious necessity for both an internal stoichiometric oxidant, as well as atmospheric (oxygen) conditions in the presence of a copper salt. From the data in entries 4, 6 and 7, a concentration of 0.75 M was determined to be optimal. Evaluation of several other sources of peroxide surprisingly led to no product formation (entries 12–15). Other copper salts were also screened, with copper hydroxide providing the best results (entry 16). Noteworthy is the role of the surfactant to safely enable this process (**Caution! Explosion risk: deploy a blast shield if uncertain of safety**) as in the absence of TPGS-750-M (i.e., the corresponding “on-water” reaction), discontinuation of stirring concentrated the peroxide together with the organic substrate, which quickly led to detonation of the reaction.

To further study the reactivity of alkenes toward a presumed electrophilic oxygen source, various substitutions at the $-R^2$ position were made (Table 2). Thus, utilizing *p*-methoxy- and *p*-bromo- α -methylstyrene as baseline cases (entries 1, 2; R² = H), the addition of alkyl chains (either methyl or *n*-pentyl groups) resulting in more bulky trisubstituted alkenes (entries 3 and 4; respectively) had a negative impact on reaction efficiency. Surprisingly, placement of a 4-methoxyphenyl group, again, at the activating $-R^2$ position completely shut down the reaction (entry 5). This is in line with the observation that simple, monoalkenyl-substituted styrenes also do not undergo oxidation under these conditions, suggesting the potential for an orthogonal strategy toward selective ketone formation. Gratifyingly, use of the corresponding methyl enol ether provided a marked improvement (entries 6 and 7).¹⁰ Decreasing the amount of TBHP by half (to 1.25 equiv) did not effect the overall extent of reaction (entries 7 vs 8). The control experiment without ligand was particularly

Table 2. Screening of Basic Copper Salts and Effect of Olefin-Activating Group

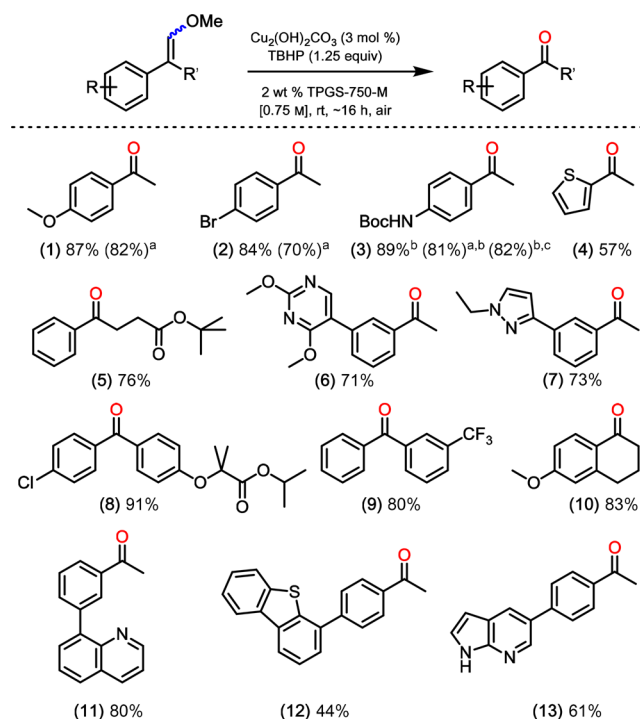
entry	3 mol % [Cu]/L	R ¹	R ²	TBHP (equiv)	yield ^a (%)
1	Cu(OH) ₂ /L	OMe	H	2.50	55
2	Cu(OH) ₂ /L	Br	H	2.50	48
3	Cu(OH) ₂ /L	OMe	Me	2.50	31
4	Cu(OH) ₂ /L	OMe	-C ₅ H ₁₁	2.50	36
5	Cu(OH) ₂ /L	Br	<i>p</i> -MeO-C ₆ H ₄	2.50	NR
6	Cu(OH) ₂ /L	OMe	OMe	2.50	69
7	Cu(OH) ₂ /L	Br	OMe	2.50	66
8	Cu(OH) ₂ /L	Br	OMe	1.25	67
9 ^b	Cu(OH) ₂ /L	Br	OMe	1.25	70
10	Cu(OH) ₂	Br	OMe	1.25	73
11	Cu ₂ (OH) ₂ CO ₃	Br	OMe	1.25	84
12 ^c	Cu ₂ (OH) ₂ CO ₃	Br	OMe	1.25	62
13 ^d	Cu ₂ (OH) ₂ CO ₃	Br	OMe	1.25	67
14 ^b	Cu ₂ (OH) ₂ CO ₃	Br	OMe	1.25	84
15 ^e	Cu ₂ (OH) ₂ CO ₃	Br	OMe	1.25	70
16 ^f	Cu ₂ (OH) ₂ CO ₃	Br	OMe	1.25	79
17 ^g	Cu ₂ (OH) ₂ CO ₃	Br	OMe	1.25	78
18 ^g	Cu ₂ (OH) ₂ CO ₃	Br	OMe	none	NR

^aYield of isolated products, after column chromatography. ^b5 mol % catalyst. ^c1 mol % catalyst. ^d2 mol % catalyst. ^eReaction run in 1,2-dichloroethane. ^fReaction run in acetonitrile. ^gReaction run under 1 atm of O₂.

informative, as use of the cupric salt alone was shown to be equally or even more effective than its use in ligated form. On the basis of the results using the more basic copper hydroxide relative to copper acetate (65% vs 59%; Table 1, entries 16 vs 4), the carbonate salt of intermediate basicity¹¹ was then assessed (Table 2, entry 11). These results indicated that the study should be continued using this source of copper(II). Lowering the catalyst loading to either 1 or 2 mol % gave slightly diminished yields, whereas increasing the loading from 3 to 5 mol % showed no observed benefit (entries 11–14). When the solvent was changed to either 1,2-dichloroethane or acetonitrile, common organic solvents for this type of transformation,^{4,5} the reactions proceeded reasonably well; however; they led to somewhat lower levels of conversion than those observed in TPGS-750-M/water (entries 11 vs 15, 16). Lastly, experiments utilizing 1 atm of oxygen, with or without TBHP, afforded inferior results (entries 17 and 18, respectively).

On the basis of these optimized conditions, the generality of the catalyst system was assessed on an array of aryl/alkyl methyl enol ethers (Scheme 1). *E/Z*-Mixtures of α -methyl-substituted educts with aryl groups containing either electron-donating or -withdrawing substituents were found to readily participate (e.g., 1–3) with substitution at the ortho-, meta-, or para- positions (e.g., 10, 6, 13, respectively). Several heterocyclic derivatives reacted without incident under these conditions, including those containing a thiophene, pyrazole, pyrimidine, azaindole, or quinoline moiety, without compromising the (nonligated) copper catalyst. Furthermore, substrates containing extended alkyl chains (e.g., leading to

Scheme 1. Scope of Aryl/Alkyl Enol Ether Oxidations

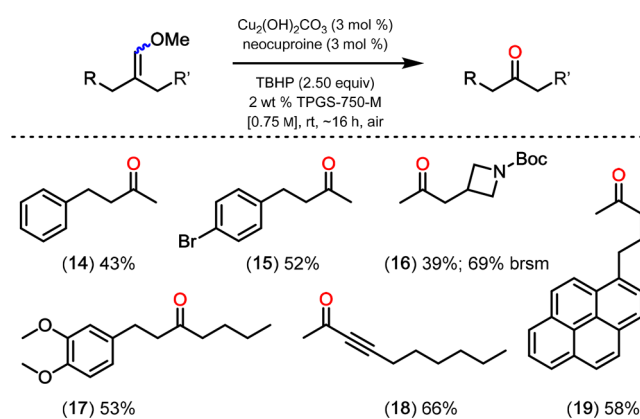


^aIsolated yield of reaction run with 3 mol % $\text{Cu}(\text{OH})_2$. ^b10% v/v THF added to increase homogeneity. ^cIsolated yield of reaction run at 1.00 mmol scale.

product 5), as well as cyclic arrays (e.g., 10) gave the desired ketones in good yields, each representing a substitution pattern that has not been found in prior reports.^{1f,2-5} 1,1-Diarylalkenyl enol ethers also smoothly formed several benzophenone derivatives in good yields, as in products 8 and 9. The former, fenofibrate (8), is used for treatment of hypercholesterolemia and hypertriglyceridemia.¹² It is noteworthy that under the aqueous conditions employed, the methyl enol ether group did not undergo hydrolysis to the corresponding aldehyde.

Extension to more challenging and previously unreported catalytic oxidative cleavage reactions of dialkyl olefins was next pursued (Scheme 2). By applying conditions similar to those shown in Table 2, only low yields of product ketone were initially observed. For this class of substrate increasing the amount of oxidant from 1.25 to 2.50 equiv provided a more

Scheme 2. Preliminary Scope of Alkyl/Alkyl Oxidations



effective combination. In most cases, although full consumption of starting materials was observed, isolated yields were consistently in the moderate category. Benzylacetone derivatives 14 and 15 were readily formed under these mild conditions. Extending the distance of the alkyl chain in pyrene-derivative 19 proceeded smoothly, likewise increasing the alkyl chain length, e.g., from methyl to *n*-butyl (leading to product 17), gave comparable yields. The presence of nitrogen, protected as its Boc derivative, in azetidine-containing product 16 was also tolerated, although the level of conversion was lower leading to a diminished isolated yield. Interestingly, the use of an unsaturated precursor ultimately affording a conjugated ketone (as in 18) led to a somewhat improved outcome.

Nonproductive pathways leading to undesired intermediates include a Kharasch-type mechanism, where allylic oxidation with a *t*-butoxy or *t*-butylperoxy radical could trap the intermediate olefinic radical prior to addition of molecular oxygen.¹³ Indeed, this type of byproduct formation was observed in initial studies with 4-methoxy- α -methylstyrene (Figure 1). Such an alternative, and competitive pathway, is

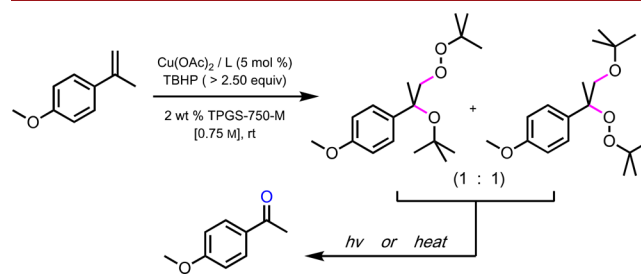


Figure 1. Competitive potential Kharasch-type allylic oxidation.

similar to that seen long ago by Kochi,¹⁴ and to some extent, more recently by Wang and co-workers.⁵ When the pure “byproduct” was isolated and then, as a mixture with authentic material, analyzed by GC–MS, the chromatograms showed a single peak with an *m/z* corresponding to the desired ketone. Moreover, heating this byproduct neat for 30 s led to a rapid reaction, with subsequent proton NMR analysis now showing a roughly 1:1 mixture of both product ketone and peroxy byproduct.¹⁵ Thus, this presumed double Kharasch intermediate undergoes either electrochemical (GC filament ionization) or thermal (heat-gun) collapse to the desired ketone. Collectively, the experimental data suggest a plausible mechanism for radical-based cooperativity, akin to that described decades ago for enamine’s engaging molecular oxygen (Figure 2).¹⁶

In summary, a mild, safe, and green protocol for converting methyl enol ethers into their corresponding ketone adducts that avoids low temperature ozonolysis has been developed. The technology avoids precious metal catalysis, utilizing an inexpensive Cu(II) salt enabled by micellar catalysis in water at room temperature. This methodology compares very favorably with existing catalytic oxidative cleavage reactions in terms of generality, and aids in further extending the substrate scope beyond prior art that was limited to formation of products in the acetophenone and benzophenone series. In the composite, these preliminary results offer considerable promise for further developments, aimed at addressing this textbook reaction in organic synthesis.

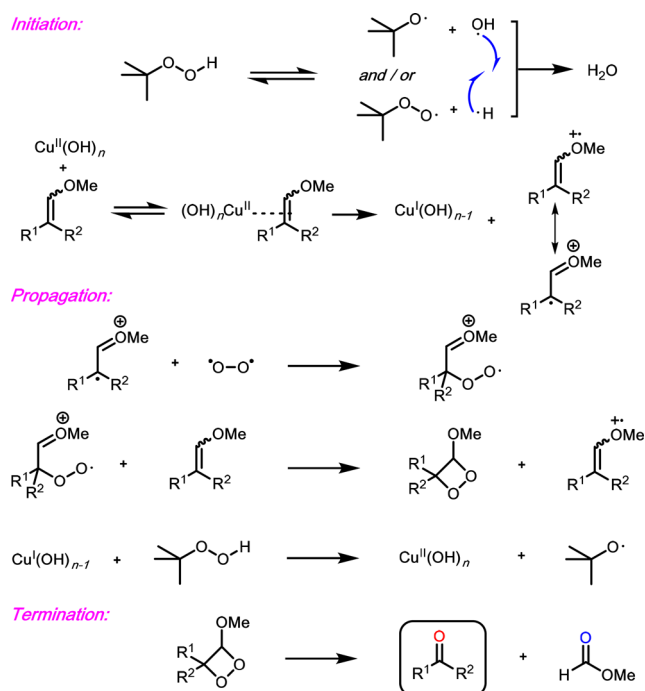


Figure 2. Proposed mechanistic radical pathways: initiation, propagation, and termination.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.8b01883](https://doi.org/10.1021/acs.orglett.8b01883).

Reaction optimization, details of control-experiments, analytical data of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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