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Reactions catalyzed by a binuclear copper complex: selective oxidation of alkenes to carbonyls with O₂

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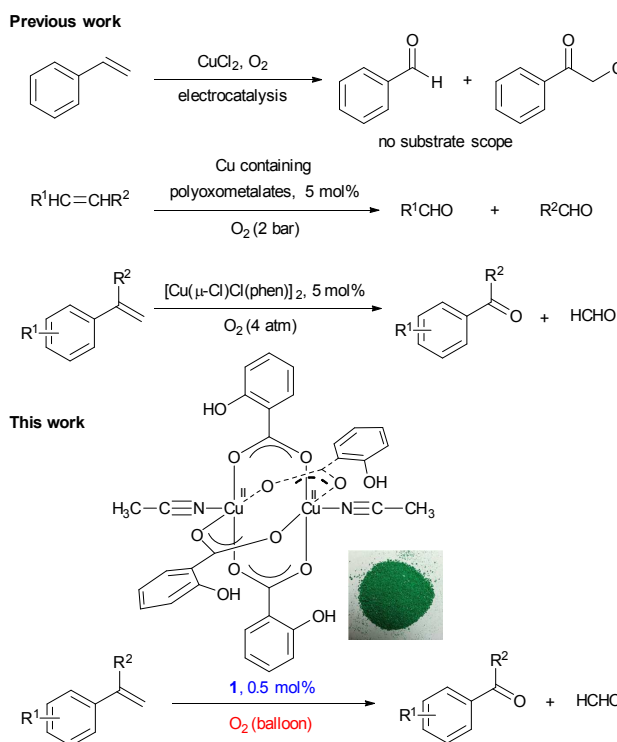
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Terminal alkenes were selectively cleaved into ketones and aldehydes catalyzed by a binuclear copper catalyst bearing simple salicylate ligand with O₂ as oxidant. The reaction was carried out under an atmosphere of O₂ balloon with 0.5 mol% of catalyst and could be performed at a gram scale, providing a convenient and practical method for the cleavage of terminal alkenes into carbonyl compounds.

The selective cleavage of alkenes to carbonyl compounds is of great importance for both industry and academia, as alkenes are abundant raw chemicals from fossil fuel as well as biomass and are common intermediates in organic synthesis.¹ The ozonolysis with oxone as oxidant, which has been developed for decades, is still the most used method for this transformation.² Stoichiometric other oxidants, e.g. KMnO₄,³ OsO₄,⁴ PhIO/HBF₄,⁵ *m*-CPBA,⁶ H₂O₂,⁷ and TBHP⁸ with or without catalysts, have also been employed for selective cleavage of alkenes. The generation of stoichiometric amount of waste and the toxicity and safety issues associated with these protocols call for the development of greener and safer methods for alkene cleavage.

Oxygen is an abundant, cheap and environmentally benign oxidant.⁹ Efforts have been made to develop catalytic systems for cleavage of alkenes with O₂ as oxidant.^{1e} Metal-free catalysts, including photosensitizers¹⁰ and free radical initiators,¹¹ were reported to be able to cleave alkene with O₂ as oxidant. Various metal catalysts, e.g. Pd,¹² Ru,¹³ Au,¹⁴ Mn,¹⁵ Fe,¹⁶ Co¹⁷ and Ni,¹⁸ have shown activity for the scission of alkene with O₂. Despite the progress, inexpensive and readily available catalysts with broad substrate scope, low catalyst loading and low oxygen pressure are still highly desirable.

Cu catalyzed aerobic oxidation has found numerous



Scheme 1. Copper-catalyzed aerobic alkene cleavage.

applications in organic synthesis¹⁹ and many oxidative enzymes contain Cu as active site.²⁰ Cu-containing enzymes have shown to catalyze alkene cleavage with O₂ under mild conditions.^{1c, 21} However, Cu-catalyzed oxidation of alkenes with O₂ has rarely been achieved (Scheme 1). In 1993, Sasaki and co-workers reported the electrocatalytic oxidative cleavage of styrene in the presence of CuCl₂, albeit with low product selectivity and yields.²² Recently, Neumann and co-workers reported that Cu-containing polyoxometalates are effective catalysts for cleavage of various alkenes under 2 bar of O₂ at 85 °C with a S/C (substrate/catalyst ratio) of 20.²³

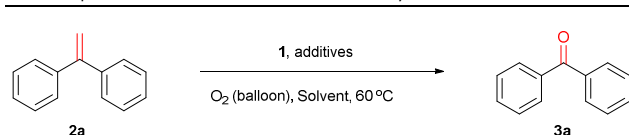
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Table 1. Optimization of reaction conditions for **1** catalyzed aerobic oxidation of **2a**^a

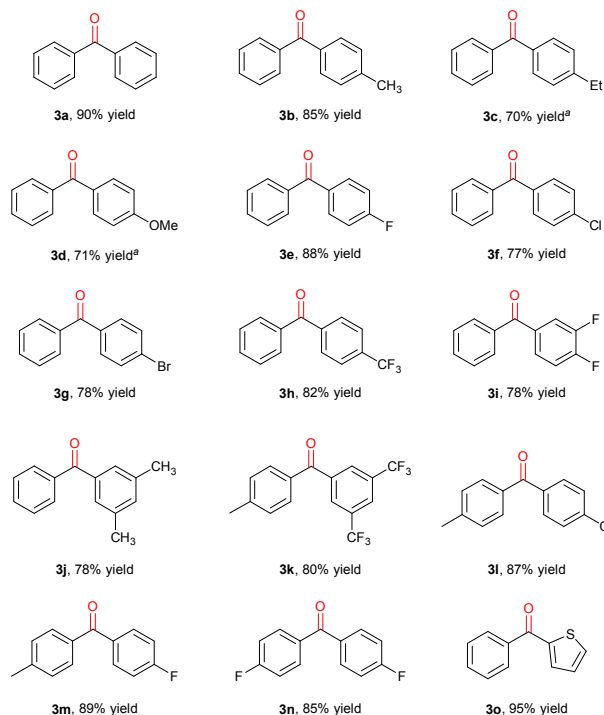
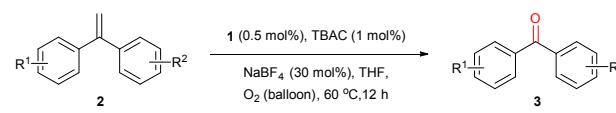
Entry	Catalyst	Additive	Solvent	Yield (%) ^b
1	-	-	THF	0
2	1	-	THF	45
3	1	TBAC	THF	70
4	-	TBAC	THF	0
5	1	TBAC+NaBF ₄	THF	90
6 ^c	1	TBAC+TBA-BF ₄	THF	89
7 ^d	1	TBAC+KPF ₆	THF	88
8 ^e	1	TBAC+NaBF ₄	THF	36
9 ^f	1	TBAC+NaBF ₄	THF	0
10	CuCl ₂	TBAC+NaBF ₄	THF	0
11	CuCl ₂	TBAC+NaBF ₄	THF/H ₂ O (9:1)	0

^a Reaction conditions: **2a** (0.5 mmol), **1** (0.5 mol%), solvent (0.5 mL), TBAC (1 mol% when added), NaBF₄ (30 mol% when added), O₂ balloon, 60 °C, 12 h. ^b Isolated yield. ^c TBA-BF₄ = Tetrabutylammonium tetrafluoroborate, 30 mol%. ^d with 30 mol% of KPF₆. ^e The reaction was carried out under air. ^f The reaction was carried out under argon.

Shyu and co-workers demonstrated that the [Cu(μ-Cl)Cl(phen)]₂ complex as well as CuCl₂ could catalyze the scission of aromatic *gem*-disubstituted alkenes under 4 atm of O₂ at 60 °C with a S/C of 20.²⁴ Herein, we disclose a structurally well-defined binuclear Cu catalyst with simple salicylate ligand for cleavage of terminal alkenes. This new catalytic system features easy catalyst preparation, relatively high productivity (S/C = 200) and low oxygen pressure (O₂ balloon), providing a convenient method for the conversion of alkenes into ketones and aldehydes.

Recently, we have discovered that a binuclear copper salicylate complex, [Cu(Sal)₂(NCMe)]₂ (Sal = salicylate) **1**, is able to catalyze the aerobic cross dehydrogenative coupling of *N*-aryltetrahydroisoquinolines²⁵ as well as aerobic oxidation of amines to amides with the aid of a VB1 analogue.²⁶ The copper complex **1** could be readily prepared from simple CuCl and salicylic acid as fine green crystals.²⁵ In continuing our interest in aerobic oxidation reactions,^{16c, 25-26} we found that **1** could also serve as catalyst for alkene cleavage.

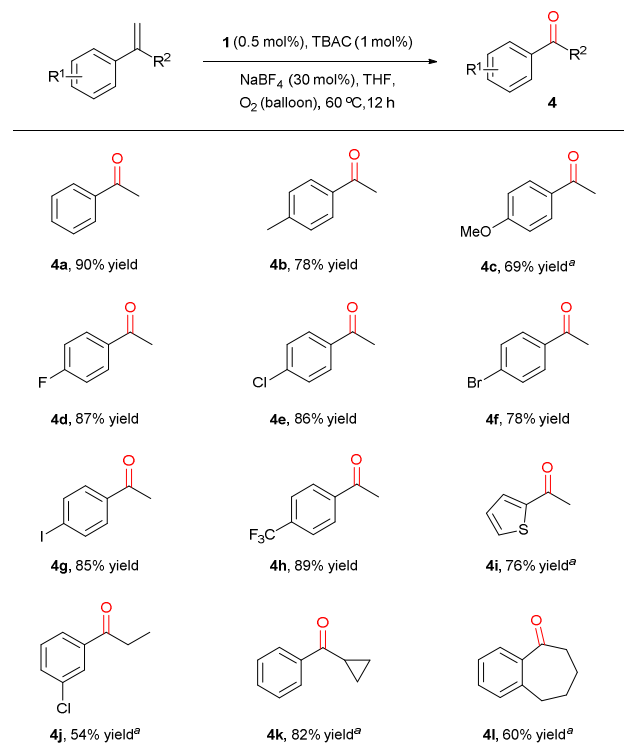
As shown in Table 1, 1,1-diphenylethylene **2a** was cleaved into benzophenone **3a** in 45% yield with 0.5 mol% of **1** in the presence of O₂ (balloon) in THF at 60 °C in 12 h (Table 1, entry 2). Interestingly, addition of TBAC (tetrabutylammonium chloride, 1 mol%) was found to improve the activity of **1** (Table 1, entry 3). The role of TBAC might be stabilisation of active catalytic intermediate via chloride anion coordination.²⁵ Background experiments showed that no reaction took place in the absence of **1** (Table 1, entries 1 and 4). Much to our surprise, when a catalytic amount (30 mol%) of NaBF₄ was introduced, the yield of **3a** was boosted remarkably to 90%



Scheme 2. Copper-catalyzed cleavage of *gem*-diarylalkenes into ketones with O₂. Reaction conditions: alkenes (0.5 mmol), **1** (0.0025 mmol, 0.5 mol%), TBAC (0.005 mmol, 1 mol%), NaBF₄ (0.15 mmol, 30 mol%), THF (0.5 mL), O₂ balloon, 60 °C, 12 h. Isolated yields. ^a The reaction time was 24 h.

(Table 1, entry 5). TBA-BF₄ (Tetrabutyl ammonium tetrafluoroborate) and KPF₆ also accelerated the reaction (Table 1, entries 6 and 7). The reason for the acceleration effect of these salts is unclear at the moment. The reaction also took place under air, albeit with a lower yield of 36% (Table 1, entry 8). As expected, no reaction took place under an argon atmosphere (Table 1, entry 9). CuCl₂ was an effective catalyst for alkene cleavage under pressurised O₂ as reported by Shyu and co-workers;²⁴ however, it is essentially inactive under our conditions (Table 1, entries 10 and 11). Examination of solvent effect revealed that freshly distilled THF is the best solvent for the reaction (See ESI, Table S1 for details).

With the optimized conditions in hand, the scope of the binuclear copper catalyzed aerobic cleavage of alkenes into ketones was examined. Various *gem*-diarylalkenes could be converted to diarylketones in good to excellent yields (Scheme 2). Both electron-donating (OMe, Me, Et) and electron-withdrawing (Br, Cl, F, CF₃) groups on the aromatic rings of 1,1-diarylethylenes were tolerated to afford the expected products (Scheme 2, **3a-3n**). Di- and tri-substituted substrates with substituents on *para*- or *meta*-positions of phenyl rings all reacted well (Scheme 2, **3i-3n**). Excellent yield was obtained for the substrate with a thiophene group (Scheme 2, **3o**). It is worth noting that the diaryl ketone products are important



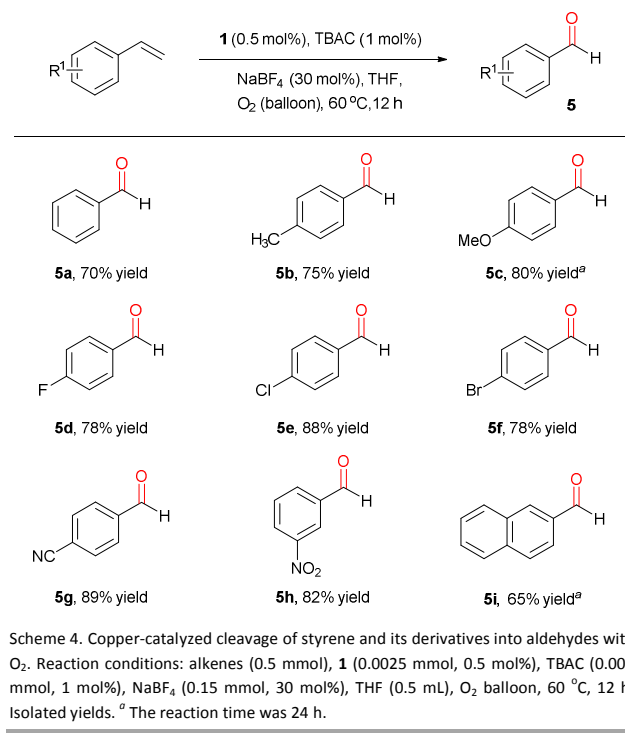
Scheme 3. Copper-catalyzed cleavage of *gem*-arylkyl disubstituted alkenes into ketones with O₂. Reaction conditions: alkenes (0.5 mmol), **1** (0.0025 mmol, 0.5 mol%), TBAC (0.005 mmol, 1 mol%), NaBF₄ (0.15 mmol, 30 mol%), THF (0.5 mL), O₂ balloon, 60 °C, 12 h. Isolated yields. ^a The reaction time was 24 h.

structure motif for pharmaceuticals, natural products and functional materials and could serve as building blocks for the synthesis of important molecules.²⁷

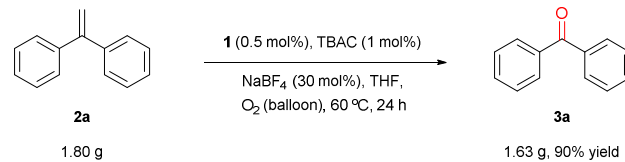
The substrate scope could be extended to *gem*-arylkyl substituted alkenes (Scheme 3). An array of 1-aryl-1-methylenes could be converted to acetophenone and its derivatives (Scheme 3, **4a-4i**). Again, aryl rings with both electron-donating and electron-withdrawing substituents are viable (**4a-4h**) and the thiophene ring was tolerated (**4i**). Replacing the methyl group with more bulky substituents resulted in lower activity (Scheme 3, **4j-4l**). Interestingly, the cyclopropyl ring was well preserved after the oxidation, which is not only synthetic useful but also shed light on the reaction mechanism (*vide infra*).

Styrene and its derivatives were further examined as substrates and the results are shown in Scheme 4. These substrates gave poor yields in the Cu catalytic system reported by Shyu and co-workers²⁴ and might have selectivity issues.^{1e} Delightfully, aldehyde products were formed selectively in high yields with our catalytic system. Electronic effect of substituents appears to have little impact on the activity of substrates (Scheme 4, **5a-5h**). Good yields were obtained even for the very electron-deficient ones, e.g. with -CN (**5g**) and -NO₂ (**5h**) groups. 2-Naphthaldehyde was obtained in moderate yield from 2-vinylnaphthalene (**5i**).

The practical usefulness of this method is demonstrated by a gram scale reaction of aerobic cleavage of **2a**. As shown in



Scheme 4. Copper-catalyzed cleavage of styrene and its derivatives into aldehydes with O₂. Reaction conditions: alkenes (0.5 mmol), **1** (0.0025 mmol, 0.5 mol%), TBAC (0.005 mmol, 1 mol%), NaBF₄ (0.15 mmol, 30 mol%), THF (0.5 mL), O₂ balloon, 60 °C, 12 h. Isolated yields. ^a The reaction time was 24 h.



Scheme 5. Gram scale preparation of benzophenone.

Scheme 5, benzophenone **3a** was isolated in 90% yield at a 10 mmol scale.

The mechanism of the reaction was then considered. There are several facts, which might have mechanistic implications. 1) The reaction only works well in ether solvents, such as THF, dioxane and diglyme, indicating that the solvent molecule might be involved in the oxidation process. 2) The cyclopropyl ring structure is preserved in product **4k** (Scheme 3), suggesting that carbon-based radicals from the olefin substrate may not be generated during the aerobic cleavage.^{16c} 3) The reaction was fully inhibited in the presence of catalytic amount of radical scavengers, such as BHT, TEMPO, *p*-benzoquinone, and diphenylamine, indicating that radicals are involved in the product formation (See ESI, section 4.1). 4) Formaldehyde could be trapped after cleavage of **2a** (See ESI, section 4.2). 5) THF could be oxidized to *gamma*-butyrolactone under standard conditions in the absence of alkene substrates.

In aerobic oxidation reaction catalyzed by Cu complexes³⁸ as well as in biological systems²⁸, it is generally believed that Cu^I complexes, rather than Cu^{II} species, could react with dioxygen to form reactive intermediates for oxidation. Complex **1** is a Cu^I-Cu^{II} complex, the binuclear structure of which is likely to be preserved during catalysis as shown by our previous studies.²⁵⁻²⁶ Complex **1** could be reduced by *N*-

aryltetrahydroisoquinolines.²⁵⁻²⁶ The reduction of Cu^{II} to Cu^I by amines was also reported by Klusmann and co-workers.²⁹ Point 1) and 5) in the above paragraph suggest that THF is essential for the reaction and could interact with the catalyst. In a related study, Lippard and co-workers suggest that THF could reduce an Fe^{III}-Fe^{III} complex to an Fe^{III}-Fe^{II} complex, generating an THF radical, which could then react with dioxygen to give a peroxy radical intermediate.³⁰ Based on the above analysis, we thus tentatively propose that the Cu^{II}-Cu^I complex might somehow promote the formation of a THF radical, which could then react with dioxygen to form a 2-peroxytetrahydrofuran radical, and it is this peroxy species that is responsible for the oxidative cleavage of alkenes to carbonyl groups, as suggested by Shyu and co-workers²⁴.

In conclusion, the structurally well-defined binuclear Cu complex 1 reported by us before²⁵⁻²⁶ has now been found to be an efficient, selective catalyst for the cleavage of aromatic alkenes into ketones and aldehydes. The catalyst is prepared from simple, cheap metal salt and ligand and the reaction can be performed with an oxygen balloon in gram scale, providing a convenient and practically useful alternative to the existing alkene cleavage chemistry.

Conflicts of interest

There are no conflicts to declare.

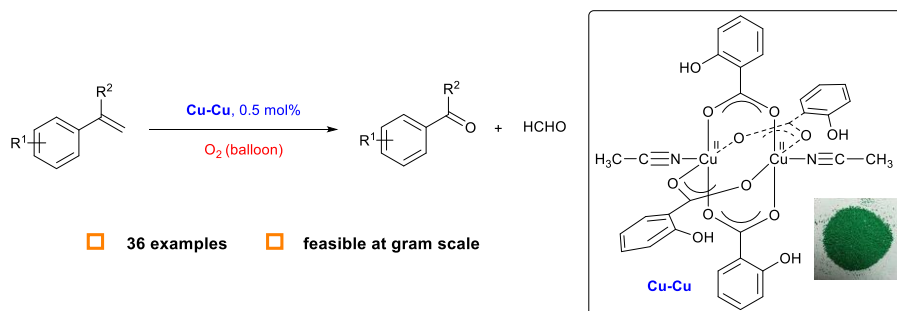
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Table of Contents

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A binuclear copper complex bearing simple salicylate ligand catalyses the efficient cleavage of styrenes into ketones and aldehydes with O₂ as oxidant. The reaction works under a balloon atmosphere of O₂ with 0.5 mol% of catalyst and could be performed at gram scale, providing an alternative to ozonolysis.