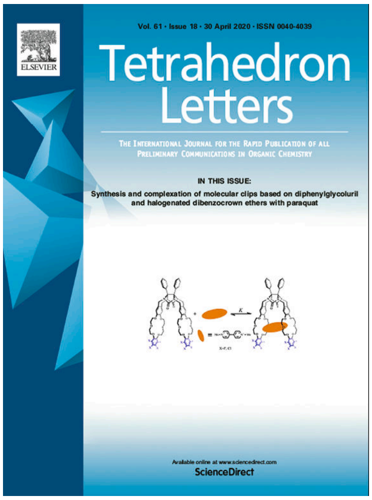

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Cu-Catalyzed aerobic oxidative cleavage of C(sp3)–C(sp3) bond: synthesis of α-ketoamides

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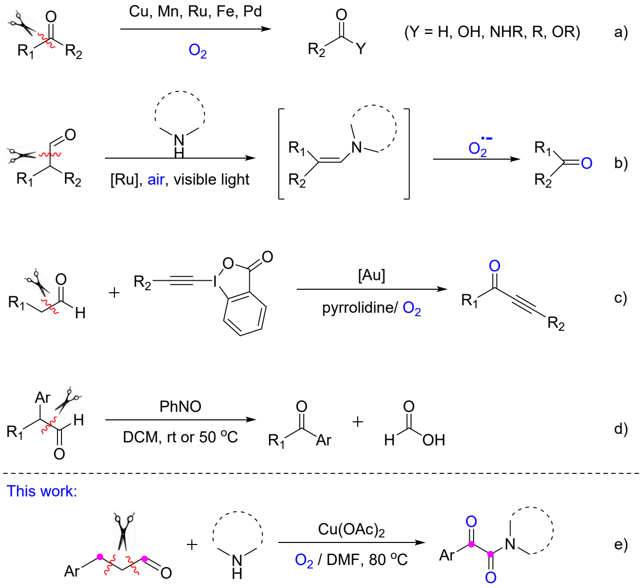
ABSTRACT

A novel synthesis of α-ketoamides from Cu-catalyzed aerobic oxidative C(sp3)–C(sp3) bond cleavage of hydrocinnamaldehydes has been developed. Readily available and environmentally benign oxygen is used as the oxidant. This reaction avoids the use of noble metal catalysts or specialized oxidants, and chemoselectively yields α-ketoamide. Moreover, based on various control experiments, a reasonable mechanism is proposed.

Keywords:Copper catalyst, Oxidative cleavage, Hydrocinnamaldehyde, α-Ketoamide, Oxygen

Hydrocinnamaldehydes are important synthetic building blocks for pharmaceuticals and fine chemicals, such as the synthesis of an intermediate for the treatment of HIV as HIV protease inhibitors.[1] Selective carbon–carbon bond cleavage attracted considerable attention in recent years[2] for its potential significance in academic research[3] and industrial applications.[4] However, the extreme thermodynamic stability of the C–C bond makes it difficult, especially the unstrained carbon–carbon bond.[5]

Nowadays molecular oxygen has been widespreadly used in chemical synthesis for its abundant, green, sustainable virtues. Nevertheless, the selective cleavage of C–C bond with O_2 as the oxidant has been a problem until the development of some creative catalyst system.[6] Historically, several pioneering discoveries on the functionalization of carbonyl compounds which used O_2 as the oxidant and were transformed into aldehydes,[7a] acids,[7b] amides,[7c] ketones[7d] and esters[7e] were reported via selective C–C(CO) bond cleavage in conjunction with transition metal catalyst such as Cu,[8] Mn,[9] Ru,[10] Fe,[11] Pd[12] and so on (Scheme 1a). Recently, Xia and his co-workers reported a Ru(II)-catalyzed cleavage of aldehydes under air atmosphere for the synthesis of ketones (Scheme 1b).[13] Moreover, the fragments from the cleavage of aldehydes were used in Huang's work for the coupling of alkynes to produce ynones under aerobic conditions (Scheme 1c).[14] Later, the contribution from Hu's work on the transformation of aldehydes to ketones without singlet oxygen showed the efficiency of C–C bond cleavage under metal-free condition (Scheme 1d).[15] However, noble metal or costly oxidant limited their application. Despite great achievements having been made in the cleavage of aldehydes, the development of efficient and environmentally friendly method under mild condition is still desirable. Herein,

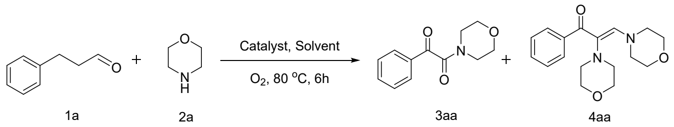


Scheme 1 C–C(CO) bond oxidative cleavage reactions.

we [illegible] mild and practical conditions (Scheme 1e). Based on the isolated intermediates, this method was experimentally found to involve two C(sp3)–C(sp3) bonds cleavage and C–N bond formation process.

We first evaluated our reaction conditions with hydrocinnamaldehyde and morpholine under an oxygen atmosphere (Table **1**). Initially, the catalytic activity of several metal compounds was investigated (Table **1**, entries 1-8). Obviously, a series of experiments revealed that copper catalysts exhibited higher efficiency compared with other metal catalysts such as $CoCl_2$, $NiBr_2$ and $FeCl_3$. Among the copper catalysts examined, CuSCN and $Cu(OAc)_2$ showed the highest reactivity with up to 85% isolated yield of **3aa** which revealed a preference for the C–C bond cleavage. Conversely, this reaction produced more coupling product when CuBr or $CuBr_2$ was involved, with 18% isolated yields of **4aa** product for the best yield.

Table 1 The cleavage of C–C(alkyl) bond of hydrocinnamaldehyde[a].



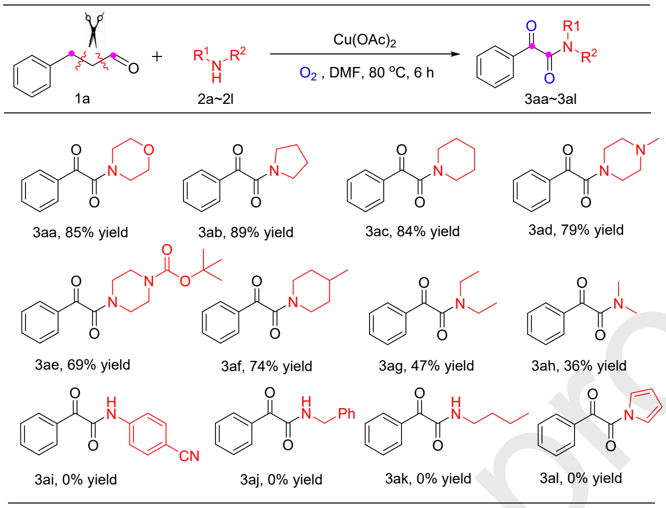
Entry	Catalyst	Base	Solvent	Yield (%) 3aa	Yield (%) 4aa
1	CuSCN	DMAP	toluene	85	6
2	CuBr	DMAP	toluene	71	16
3	$CuBr_2$	DMAP	toluene	69	18
4	$Cu(OAc)_2$	DMAP	toluene	91	0
5	$CoCl_2$	DMAP	toluene	54	9
6	$FeCl_3$	DMAP	toluene	23	5
7	$NiBr_2$	DMAP	toluene	15	0
8	$Pd(OAc)_2$	DMAP	toluene	trace	trace
9	$Cu(OAc)_2$	K_2CO_3	toluene	72	0
10	$Cu(OAc)_2$	NaOAc	toluene	79	0
11	$Cu(OAc)_2$	NaOEt	toluene	trace	trace
12	$Cu(OAc)_2$	_	toluene	81	0
13	$Cu(OAc)_2$	_	H_2O	trace	trace
14	$Cu(OAc)_2$	_	PhCN	80	0
15	$Cu(OAc)_2$	_	1,4-Dioxane	23	0
16	$Cu(OAc)_2$	_	DMSO	78	0
17	**$Cu(OAc)_2$**	**_**	**DMF**	**87**	**0**
18	$Cu(OAc)_2$	_	AcOH	trace	trace
19[b]	$Cu(OAc)_2$	_	DMF	56	0

[a]Reaction conditions: 1a (1 mmol), 2a (3 mmol), catalyst (0.2 mmol), base (2 mmol), solvent (2 mL), 80°C, O_2 (O_2 balloon), 6 h, isolated yield. [b]Under air.

Considering the efficiency and selectivity of this conversion, $Cu(OAc)_2$ was chosen as the catalyst for further optimized condition to construct α-ketoamides **3aa**. To our delight, the yield of determine product was not decreased apparently without the addition of base (Table 1, entries 9-12). 80°C was the best choice for this transformation (see Table S2) and DMF was found to be a better solvent compared with DMSO, AcOH, dioxane, H_2O and PhCN (Table 1, entries 12-18). Moreover, further screening of catalyst and amine showed that 0.2 equiv. of catalyst and 2 equiv. of amine gave a desirable yield (see Table S3). As expected, a reduced yield was obtained when oxygen was replaced with air (56%). Finally, the optimal reaction conditions were **1a** (1 mmol), **1b** (2 mmol), $Cu(OAc)_2$ (0.2 mmol), in DMF (2 ml) at 80°C under O_2 balloon for 6 h based on the reaction parameters above.

V yde produced corresponding α-ketoamides to explore the substrate scope of this reaction (Table **2**). Firstly, the cyclic amines were investigated. Encouragingly, these amines (**2a-2f**) were successfully transformed into the corresponding products in 69~89% isolated yields (**3aa-3af**). Then, we explored the other secondary amine and primary amine including aliphatic amine, aniline, benzylamine. As expected, the aliphatic secondary amine could also be transformed into the desired product (**3ag, 3ah**), while the primary amine was failed to give the desired product (**3ak**). And no major product was detected when this reaction was applied to the aniline, benzylamine or pyrrole (**3i, 3j, 3l**). All the results above have clearly demonstrated that the secondary amine is essential for the success synthesis of α-ketoamide, and its structure may be a reasonable evidence for the mechanism of this reaction.

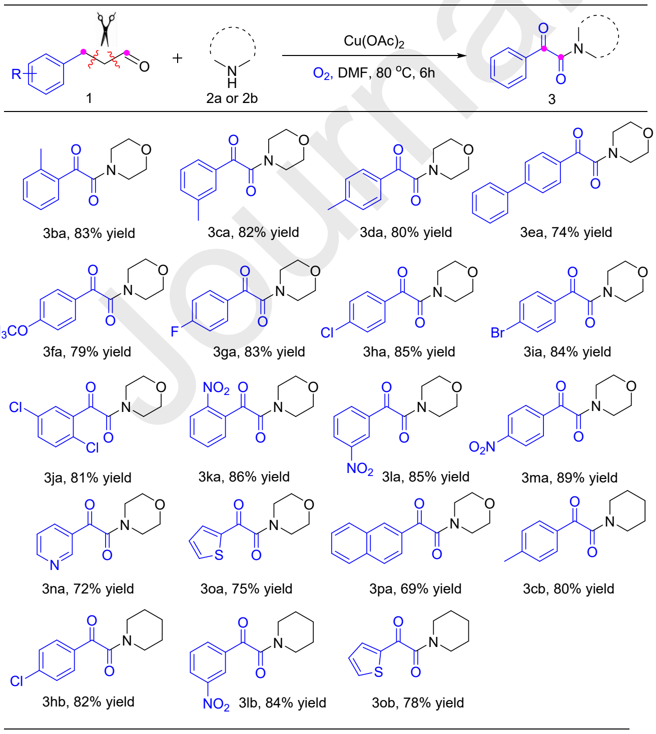
Table 2 Substrate scope for the cleavage of hydrocinnamaldehyde with variation of amines.



Reaction conditions: 1a (1 mmol), 2a-2j (2 mmol), $Cu(OAc)_2$ (0.2 mmol), DMF (2 mL), were heated under O_2 (O_2 balloon) at 80°C for 6 h, isolated yield.

To broaden the scope of this transformation, a variety of hydrocinnamaldehydes were applied under the standard conditions (Table 3). When the hydrocinnamaldehydes extended to some structure having electron donating groups on the aryl ring, this reaction afforded up to 74% yields of target product wherever the substituents at the *para*-, *meta*- or *ortho*-positions (**3ba-3fa**). To our delight, the yields of α-ketoamide increased when the substituents were halo groups (bromo, chloro, and fluoro) or electron-withdrawing groups (**3ga-3ma**, 81%~89%). It implies that the electron-withdrawing substituents are helpful for the efficiency of the oxidation reaction. Moreover, it is noteworthy that this reaction survived well when the phenyl groups were replaced by other heterocycles (**3na-3pa**, 69%~75%). Correspondingly, we examined the other secondary amines using hydrocinnamaldehyde with different substituents, and they were readily converted into the corresponding α-ketoamides in good yields (**3cb-3ob**, 78%~84%).

Table 3 Substrate scope for the cleavage of hydrocinnamaldehydes.

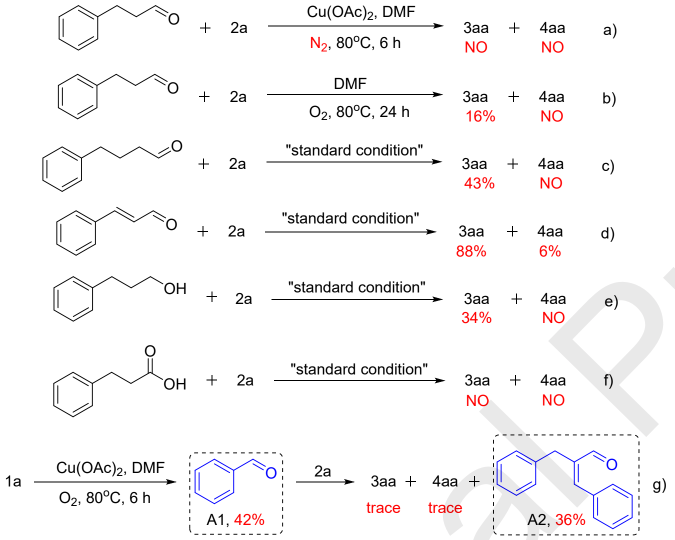


Reaction conditions: 1 (1 mmol), 2a-2b (2 mmol), $Cu(OAc)_2$ (0.2 mmol), DMF (2 mL), were heated under O_2 (O_2 balloon) at 80°C for 6 h. Isolated yield.

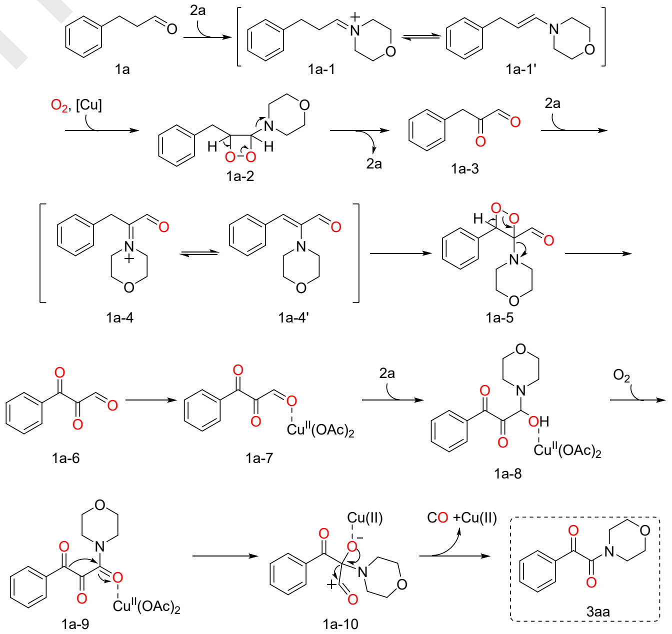
we performed the standard reaction condition under N_2 balloon, and no desired product was obtained, which indicated that molecular oxygen was necessary in the process of the C-C(CO) bond cleavage (Scheme 2a). Then, we noticed that this transformation was difficult to react without the copper salt (Scheme 2b). To gain more information, we tested some analogous substrates in standard conditions such as phenylbutyraldehyde, cinnamyl aldehyde, hydrocinnamyl alcohol, hydrocinnamic acid (Scheme 2c-2f). The desired product of **3aa** was generated in excellent yield (88%) when cinnamyl aldehyde was used (Scheme 2d). And, phenylbutyraldehyde or hydrocinnamyl alcohol was transformed into **3aa** with 43% or 34% isolated yield (Scheme 2c, 2e). While there were no **3aa** or **4aa** detected using hydrocinnamic acid as the starting material (Scheme 2f). The results above revealed that carbonyl was indispensable in the process of aerobic oxidative cleavage. Interestingly, the byproduct of **A1** and **A2** was generated when the **2a** was added 6 hours later (Scheme 2g). The generation of **A1** might involve the formation of benzyl radical, further aerobic oxidation to a four-membered intermediate and cleavage of C-C and O-O bonds. **A2** was obtained via Aldol reaction in the presence of weak base of **2a**.[16] However, no **A1** or **A2** was detected under the standard conditions, which indicated that a faster process existed in the presence of **1a** and **2a**.

On the basis of the control experiments and literature overview, a possible mechanism for the aerobic oxidative cleavage of hydrocinnamaldehydes was proposed (Scheme 3). Initially, imine intermediate **1a-1** was generated from the reaction of aldehyde **1a** and secondary amine **2a**, which could be converted into enamine **1a-1'** via intramolecular hydrogen shift. Addition reaction of O_2 to double bonds led to the formation of four-membered intermediate **1a-2** with the help of copper salt,[17] which gave the oxidation intermediate **1a-3** by the cleavage of O-O and C-N bonds.[18] Furthermore, **1a-6** was obtained by the same process above. Activation of carbonyl by Cu(II) led to the generation of addition product **1a-8**. Further oxidation gave intermediate **1a-9**, which underwent a 1, 2-Wagner-Meerwein-type rearrangement of a benzoyl group to electrophilic carbon resulting in the intermediate **1a-10**.[19] Finally, the desired product **3aa** was produced by liberation of carbon monoxide.

Scheme 2 Control experiments.



Scheme 3 Proposed mechanism.



In ydes using Cu-Catalyzed aerobic oxidative cleavage. The exclusivity of this strategy lies in the use of hydrocinnamaldehydes as a single substrate, which directly converts into primary α-ketoamides via muti-oxidation using O_2 as oxidation. The advantages of this methodology include high-efficiency transformation, straightforward operation, mild reacting condition and little contamination to the environment. Further synthetic application of this cleavage method is currently in progress in our laboratory.

Acknowledgments

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20. General procedure for the synthesis of 3 (3aa as an example):

Hydrocinnamaldehyde 1a (134 mg, 1 mmol) and morpholine 2a (174 mg, 2 mmol) were dissolved in DMF (2 mL). Then, $Cu(OAc)_2$ (36mg, 0.2mmol) was added to the reaction mixture. The reaction mixture was degassed 3 times by O_2 and stirred under O_2 balloon in a preheated oil batch at 80°C for 6h. After cooling down to room temperature, the reaction mixture was diluted with H_2O (30 mL) and extracted by ethyl acetate (30 mL) or dichloromethane (30 mL). The separated organic layers were dried over by anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residue was chromatographed on silica gel using hexane/ethyl acetate or dichloromethane/methanol to afford the desired product 3aa (85% yield).

Conflict of interest statement

The authors declared that they have no conflicts of interest to this work. We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

- A Cu-catalyzed aerobic oxidative cleavage method is developed.
- It involves two C(sp3)–C(sp3) bonds cleavage and C–N bond formation process.
- This reaction features simple starting materials and a broad substrate scope.
- Based on various control experiments, a reasonable mechanism is proposed.

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