VIP α-Ketoamides

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Copper-Catalyzed Aerobic Oxidative Coupling of Aryl Acetaldehydes with Anilines Leading to α-Ketoamides**

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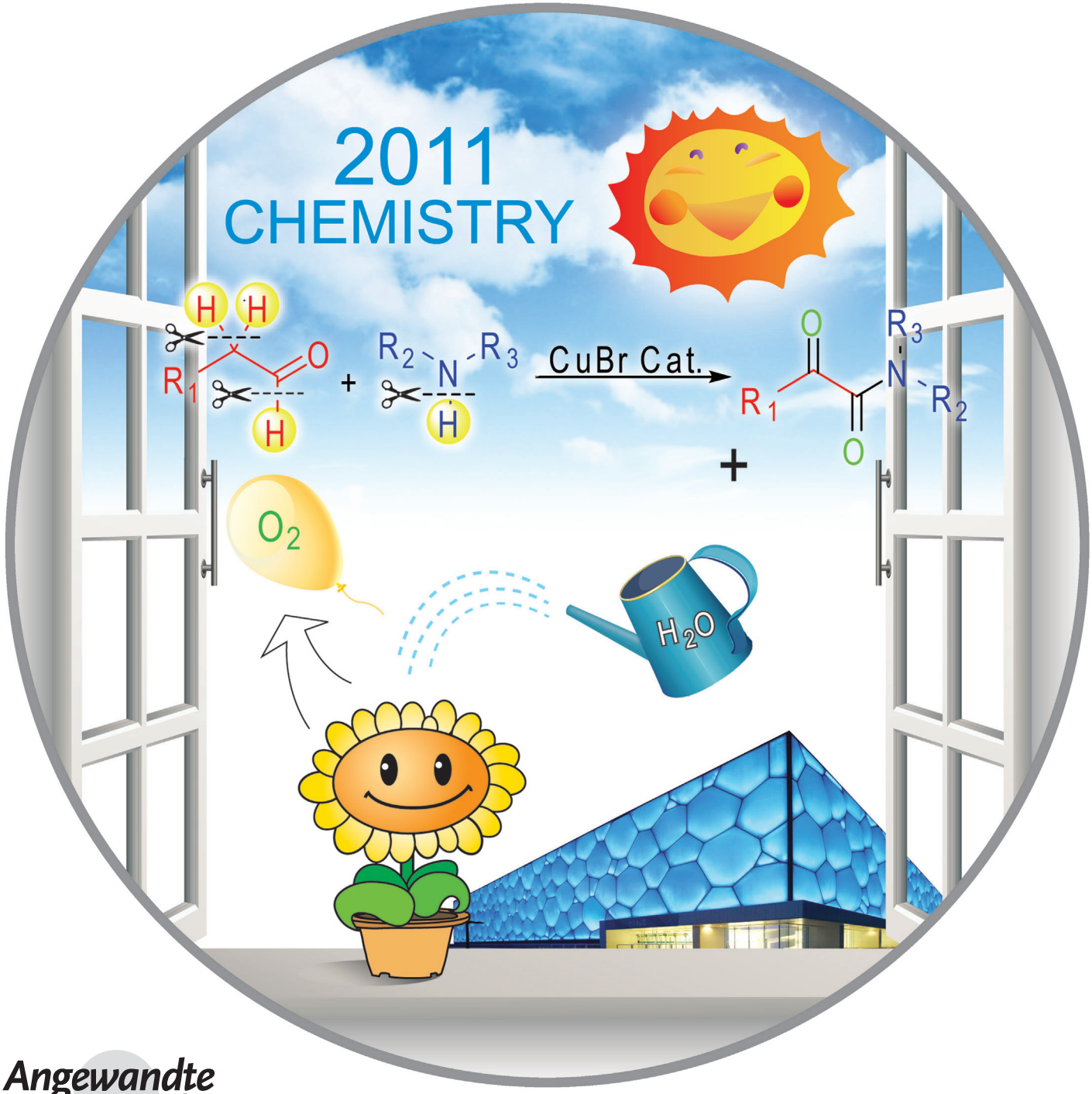
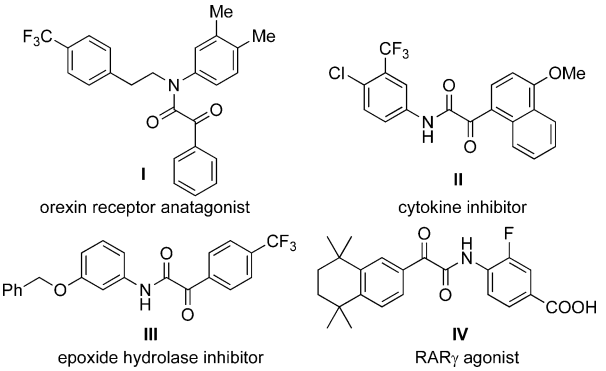
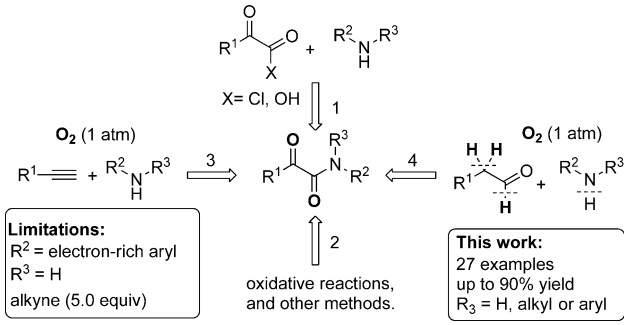


α-Ketoamides are important units in biologically active molecules, synthetic drugs, and drug candidates (Scheme 1).[1] Furthermore, they serve as useful precursors for a variety of functional group transformations.[2] Consequently, lots of effort has been made to construct α-ketoamides.[3–8] Among these methods, amidation of α-keto acids and α-keto acyl halides (Scheme 2, 1),[3] oxidation of α-hydroxyamides and α-aminoamides,[4] transition-metal-catalyzed double carbonylative amination of aryl halides,[5] oxidative coupling,[6a] and other methods[6] (Scheme 2, 2) have been widely used. Despite the numerous efforts toward the synthesis of α-ketoamides, the development of mild, efficient, and environmentally friendly methods is still desired: 1) Precursors should be easily prepared or handled; 2) Instead of stoichiometric oxidants, such as metal salts or peroxide, environmentally friendly molecular oxygen, as the ideal oxidant, is desirable.[7] 3) The reduction of the amount of environmentally unfriendly by-products should be given more attention. Recently, Cu-catalyzed oxidative amidation/diketonization of terminal alkynes leading to α-ketoamides was reported (Scheme 2, 3).[8] However, some drawbacks of this method may limit it applications. Firstly, the homocoupling of terminal alkynes is difficult to control, hence an excess of alkynes (5.0 equiv) must be employed. Secondly, the substrate scope is limited beacuse anilines that contain electron-withdrawing groups give only a trace amount of the desired products. Thirdly, N-substituted anilines did not react. Herein, we present a copper-catalyzed aerobic oxidative coupling of aryl acetaldehydes with anilines by a novel mechanistic process to give α-ketoamides; this reaction is highly efficient and has a broad substrate scope (Scheme 2, 4). Two C_{sp^3}–H, one C_{sp^2}–H, and one N–H bond cleavages are involved in this novel chemistry.



Scheme 1. Biologically active molecules.



Scheme 2. Methods for the synthesis of α-ketoamides.

With regard to sustainable chemistry, oxidative C–H bond functionalization is one of the most attractive and powerful strategies in organic synthesis.[9] For these transformations, molecular oxygen is an ideal oxidant. Significantly, the use of dioxygen activation for functionalization reactions represents one of the most ideal processes in organic synthesis.[7] Activation of dioxygen by copper enzymes has been observed in some biological oxygenase systems, such as monooxygenase tyrosinase and dopamine β-monooxygenase that effect hydroxylation of C–H bonds.[10] Recently, copper-catalyzed reactions that involve dioxygen activation and use rather simple models to realize biomimetic syntheses have been given considerable attention.[11] To the best of our knowledge, the aerobic oxidative transformation of adjacent C–H bonds to form α-ketoamides by dioxygen activation has not been reported.

Our study commenced with the reaction of 2-phenylacetaldehyde (**1a**) and 4-aminobenzonitrile (**2a**) catalyzed by copper salts. Interestingly, *N*-(4-cyanophenyl)-2-oxo-2-phenylacetamide (**3aa**) was produced in 68% yield when CuBr was used as the catalyst (Table 1, entry 1). The reaction in the absence of a Cu catalyst was not very successful (Table 1, entry 2). Other Cu catalysts including Cu^{II} salts gave lower reaction efficiencies (see, Table 1, entries 1, 3, and 4, and the Supporting Information). We then surveyed the effect of different solvents; the reactions proceeded with low yields in benzene, DMF, and other solvents (Table 1, entries 1, 5, and 6, and the Supporting Information). Further studies indicated that base can promote this transformation, and two equivalents of pyridine is optimal. The reaction efficiency decreased when using other bases, such as Na_2CO_3, and triethylamine (Table 1, entries 1, 7–10, and the Supporting Information). Both increasing and decreasing the temperature resulted in lower yields (Table 1, entries 11 and 12). Furthermore, various ligands were investigated, but the results were unsatisfactory (see the Supporting Information). Gratifyingly, the presence of molecular sieves (4 Å) resulted in an increase in the yield of **3aa** to 82% (Table 1, entry 13).

Under these optimized conditions (Table 1, entry 13), the scope of the substituted aldehydes (**1**) was investigated

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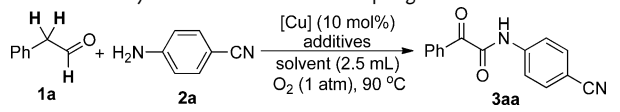
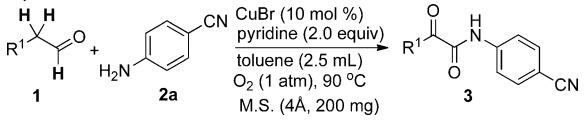
Table 1: Cu-catalyzed aerobic oxidative coupling of **1a** with **2a**.[a]



entry	[Cu]	solvent	Additives (equiv)	Yield [%][b]
1	CuBr	toluene	pyridine (2.0)	68
2	none	toluene	pyridine (2.0)	5
3	CuCl	toluene	pyridine (2.0)	55
4	CuOAc	toluene	pyridine (2.0)	43
5	CuBr	benzene	pyridine (2.0)	61
6	CuBr	DMF	pyridine (2.0)	29
7	CuBr	toluene	Na_2CO_3 (2.0)	trace
8	CuBr	toluene	triethylamine (2.0)	45
9	CuBr	toluene	pyridine (3.0)	66
10	CuBr	toluene	pyridine (1.0)	55
11[c]	CuBr	toluene	pyridine (2.0)	59
12[d]	CuBr	toluene	pyridine (2.0)	61
13	CuBr	toluene	4 Å MS (200 mg) pyridine (2.0)	82

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.25 mmol), cat. (0.025 mmol), solvent (2.5 mL), O_2 (1 atm), 90 °C, 12 h. [b] Yields of the isolated product. [c] The reaction was carried out at 60 °C. [d] The reaction was carried out at reflux. DMF = *N*,*N*′-dimethylformamide.

Table 2: Copper-catalyzed aerobic oxidative coupling of a range of aldehydes **1** with **2a**.[a]

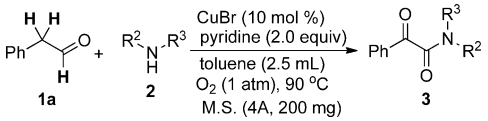


Entry	1	R^1	3	Yield [%][b]
1	**1a**	Ph	**3aa**	82
2	**1b**	4-$OMeC_6H_4$	**3ba**	83
3	**1c**	4-MeC_6H_4	**3ca**	77
4	**1d**	3-MeC_6H_4	**3da**	71
5	**1e**	2-MeC_6H_4	**3ea**	73
6	**1f**	4-FC_6H_4	**3fa**	84
7	**1g**	4-ClC_6H_4	**3ga**	78
8	**1h**	4-BrC_6H_4	**3ha**	75
9	**1i**	β-naphthyl	**3ia**	75
10	**1j**	nC_4H_9	**3ja**	0

[a] Standard reaction conditions: **1** (0.5 mmol), **2a** (0.25 mmol), CuBr (0.025 mmol), pyridine (0.5 mmol), toluene (2.5 mL), 90 °C, O_2 (1 atm), 12 h. [b] Yields of the isolated products. M.S. = molecular sieves.

(Table 2). Both electron-rich and electron-deficient aryl acetaldehydes could be smoothly transformed into the desired products. Furthermore, substituents at different positions on the arene group (*para*, *meta*, and *ortho* positions) did not affect the reaction efficiency. It is noteworthy that halo-substituted aryl acetaldehydes were tolerated well, thus leading to halo-substituted products, which could be used for further transformations (Table 2, entries 7 and 8). In addition, the naphthyl-substituted acetaldehyde, 2-(naphthalen-2-yl)-acetaldehyde (**1i**) was also tolerated in this transformation, thus generating **3ia** in 75% yield (Table 2, entry 9). However, an alkyl aldehyde did not afford the desired product (Table 2, entry 10).

Table 3: Copper-catalyzed aerobic oxidative coupling of **1a** with a range of anilines **2**.[a]

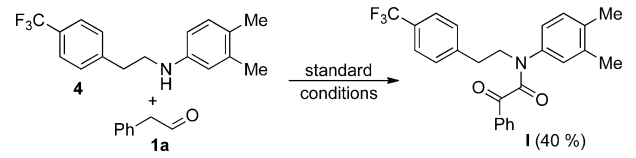


Entry	R^2	R^3	3	Yield [%][b]
1	4-CNC_6H_4	H	**3aa**	82
2	3-CNC_6H_4	H	**3ab**	70
3	2-CNC_6H_4	H	**3ac**	70
4	4-$COOEtC_6H_4$	H	**3ad**	60
5	4-$CF_3C_6H_4$	H	**3ae**	70
6	4-$NO_2C_6H_4$	H	**3af**	90
7	4-$CF_3OC_6H_4$	H	**3ag**	52
8	3,5-$(OMe)_2C_6H_3$	H	**3ah**	35
9	2,4,5-$F_3C_6H_2$	H	**3ai**	86
10	2,5-$F_2C_6H_3$	H	**3aj**	90
11	3,4,5-$Cl_3C_6H_2$	H	**3ak**	73
12	4-Br-3-$CF_3C_6H_3$	H	**3al**	75
13	Ph	Me	**3am**	65
14	4-ClC_6H_4	Me	**3an**	60
15	4-MeC_6H_4	Me	**3ao**[c]	41[c]
16	Ph	Et	**3ap**	40
17	Ph	$PhCH_2$	**3aq**	56
18	Ph	Ph	**3ar**	36
19	nC_5H_{11}	H	**3as**	0

[a] Standard reaction conditions: **1a** (0.5 mmol), **2** (0.25 mmol), CuBr (0.025 mmol), pyridine (0.5 mmol), toluene (2.5 mL), 90 °C, O_2 (1 atm), 12 h. [b] Yields of the isolated products. [c] **1a** (0.25 mmol), **2o** (0.5 mmol).

The scope of the copper-catalyzed aerobic oxidative coupling leading to α-ketoamides was further expanded to a range of substituted anilines **2** (Table 3). These results demonstrate that reactions of anilines with both electron-donating and electron-withdrawing groups proceed well with moderate to excellent yields. Notably, even when chloro- and bromo-substituted anilines were employed as substrates, they reacted with **1a** to produce the desired α-ketoamides **3ak**, **3al**, and **3an** in 73%, 75%, and 60% yield respectively. It is noteworthy that N-substituted anilines such as *N*-methyl-, *N*-ethyl-, *N*-benzyl-, and *N*-phenylaniline could be smoothly transformed into the desired products in moderate yields (Table 3, entries 13–18). However, an alkyl amine can not be converted into the desired product (Table 3, entry 19). The results show that anilines bearing electron-donating substitutents gave lower yields than those bearing electron-withdrawing substitutents. One important reason for this fact is that an electron-rich amine could form a radical cation, which could react to give an azo compound very easily,[12] thus suggesting a different reaction pathway leads to the formation of our target product in a low yield. At the same time, electron-poor amines would be unable to transform into an amine radical cation under our reaction conditions, so afford the target products in higher yields.

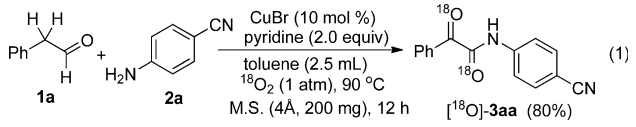
As α-ketoamides are ubiquitous structural motifs that can be found in many drugs and bioactive compounds,[1] the present method provides a simple and easily practical protocol for the construction of bioactive compounds from simple and readily available starting materials. For example, **I**, which is reported as an orexin receptor antagonist (Sche-



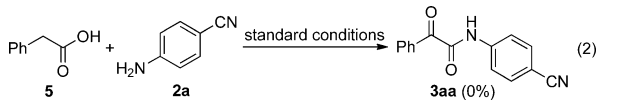
Scheme 3. The synthesis of orexin receptor antagonist **I**. Reaction conditions: **1a** (0.25 mmol), **4** (0.375 mmol), CuBr (0.025 mmol), pyridine (0.5 mmol), toluene (2.5 mL), 90 °C, O_2 (1 atm), 12 h. Yields are of the isolated products.

me 1),[1a] can be easily synthesized from the simple 2-phenylacetaldehyde (**1a**) and **4** in 40% yield (Scheme 3).

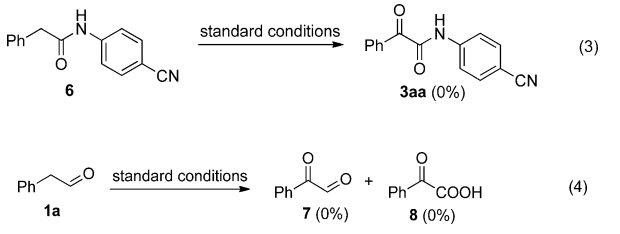
The reaction of **1a** and **2a** in the presence of $^{18}O_2$ (1 atm) generated the ^{18}O labelled product [^{18}O]-**3aa** in 80% yield [Eq. (1)], as determined by MS and HRMS (see the



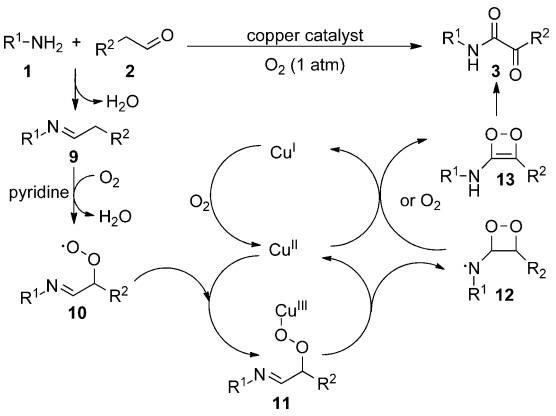
Supporting Information). This result indicates that both the oxygen atoms of the α-ketoamides originated from molecular dioxygen. Furthermore, the reaction of 2-phenylacetic acid (**5**) and **2a** under the standard reaction conditions was investigated. However, the desired product **3aa** was not obtained [Eq. (2)]. *N*-(4-Cyanophenyl)-2-phenylacetamide



(**6**) under the standard reaction conditions could not be converted into **3aa** [Eq. (3)]. Meanwhile, 2-oxo-2-phenylacetaldehyde (**7**) and 2-oxo-2-phenylacetic acid (**8**) were not detected in the reaction of **1a** under the standard reaction conditions [Eq. (4)]. These results indicate that **5**, **6**, **7**, and **8** are not intermediates of this copper-catalyzed aerobic oxidative transformation.



On the basis of the above results and EPR studies (see the Supporting Information), a plausible mechanism for the copper-catalyzed aerobic oxidative coupling is illustrated in Scheme 4. Aldehyde **1** and aniline **2** initially react to form imine **9**. Imine **9** could be oxidized to superoxide radical **10** by a radical pathway under O_2.[13] At the same time, the Cu^I salt is



Scheme 4. A proposed mechanism for the direct transformation.

oxidized by molecular oxygen to form the more-active Cu^{II} salt under these reaction conditions; this active Cu^{II} species can be detected by EPR (see the Supporting Information).[11,14] Then, Cu^{II} could combine with **10** to form Cu^{III} complex **11**.[15,16] Further intramolecular addition to the imine and N–Cu bond homolysis would form the radical intermediate **12**,[15] which could be oxidized by Cu^{II} or molecular oxygen, thus resulting in intermediate **13**.[17] Subsequent fragmentation[18] of **13** would produce the desired α-ketoamide **3**.

In conclusion, we have demonstrated a novel Cu-catalyzed aerobic oxidative coupling of aryl acetaldehydes with anilines leading to α-ketoamides, which are ubiquitous structural units in a number of biological active compounds; this reaction is highly efficient and has a broad substrate scope. Two C_{sp^3}–H, one C_{sp^2}–H, and one N–H bond are cleaved in this chemistry. It is noteworthy that N-substituted anilines are suitable substrates for this transformation. Oxidative C–H bond coupling and the use of molecular oxygen (1 atm) as the oxidant make this transformation sustainable and practical. A plausible mechanism is proposed on the basis of mechanistic studies. Further studies to clearly understand the reaction mechanism and the synthetic applications are ongoing in our laboratory.

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