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Cu(II)-catalyzed decarboxylative acylation of acyl C–H of formamides with α-oxocarboxylic acids leading to α-ketoamides†

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$CuBr_2$-catalyzed decarboxylative acylation of the acyl C–H of *N*-monosubstituted and *N*,*N*-disubstituted formamides with α-oxocarboxylic acids leading to α-ketoamides was developed, which generated the corresponding products in good yields.

In recent years, transition metal-catalyzed decarboxylative cross-coupling has been a rapidly growing area of research for carbon–carbon and carbon–heteroatom bond formations.[1] This method accesses reactive organometallic intermediates through the release of CO_2 from the metal carboxylates instead of toxic metal salts used in traditional cross-coupling methods. Meanwhile, protodecarboxylation achieves the site-specific generation of reactive organometallic species without requiring the use of directing groups, which is often necessary for regioselective formation of specific intermediates *via* C–H functionalization.

Moreover, carboxylic acid derivatives, as cross-coupling components, are non-toxic, low cost, structurally diverse and can be obtained both from natural and synthetic sources.[2] Since the decarboxylative Heck-type reactions reported by Myers *et al.*,[3] extensive studies on decarboxylative couplings of carboxylic acids (salts) have been carried out by Gooßen *et al.*,[4] Liu *et al.*,[5] Forgione *et al.*,[6] and Tunge *et al.*[7,8] In particular, the recently developed decarboxylative C–H bond functionalization, which combines decarboxylation and direct C–H bond (sp, sp^2 and especially sp^3 C–H bonds) functionalization, would allow chemists to exploit organic compounds in previously unimaginable ways.[9] Representative examples include the Pd-catalyzed reaction of carboxylic acids with saturated propiophenones by Su *et al.*,[9a] Cu-catalyzed reaction of cinnamic acids with benzylic molecules by Mao *et al.*,[9b] and Cu-catalyzed coupling of vinylic carboxylic acids with alcohols, ethers, and hydrocarbons by Liu *et al.*[9c] Most importantly, Ge's group has reported a Pd-catalyzed decarboxylative acylation of arenes with α-oxocarboxylic acids as acylating agents.[9d,e] Most recently, Kim *et al.* developed Pd-catalyzed decarboxylative acylation of *o*-methyl ketoximes and phenylacetamides with α-oxocarboxylic acids.[10] Meanwhile, Tan *et al.* also described Pd-catalyzed decarboxylative *ortho*-acylation of *o*-methyl oximes with phenylglyoxylic acids.[11]

α-Ketoamides are very important and frequently found in natural products, pharmaceuticals and synthetic intermediates.[12] The synthesis of α-ketoamides has been the subject of intense research, and several methods have been developed. These methods can roughly be divided into four categories with regard to substrates or reagents in the reactions; condensation reactions,[13] double carbonylation reactions,[14] oxidative reactions,[15] and others.[16] Among oxidative approaches, Cu-catalyzed oxidative amidation/diketonization of terminal alkynes with anilines,[15a] Cu-catalyzed oxidative coupling of aryl acetaldehydes,[15b] and aryl methyl ketones and amines[15c] have presented the most attractive strategies. Most recently, TBHP-promoted oxidative coupling of acetophenones with amines and dialkylformamides under metal-free conditions have been developed.[17]

Of course, formamides can be used as amide sources *via* acyl C–H activation of formamides.[18] Nevertheless, to the best of our knowledge, using formamides as amide sources for the preparation of α-ketoamides has not been reported. With regard to atom efficiency and environmentally benign features, and in our ongoing synthesis of α-ketoamides, herein, we wish to report a Cu(II)-catalyzed direct decarboxylative cross-coupling reaction between acyl C–H of formamides with α-oxocarboxylic acids using DTBP as the oxidant. The reactions generated α-ketoamides in good yields (Scheme 1).

At the beginning of our investigation, 2-oxo-2-phenylacetic acid (**1a**) and DMF (**2a**) were chosen as model substrates to optimize the reaction parameters and the results are summarized in Table 1. When the reaction of **1a** and **2a** was carried out in the *n*-Bu_4NI–TBHP or I_2–TBHP system,[17] the desired product **3aa** was not obtained. As listed in Table 1, among the tested catalysts, $CuBr_2$ was found to be the most effective together with 2 equiv. of DTBP (di-*tert*-butyl peroxide) and 2 equiv. of PivOH in toluene at 110 °C under an air atmosphere, and **3aa** was isolated in 81% yield (Table 1, entry 1). Other copper catalysts, including Cu(I) and Cu(II), were less effective (Table 1, entries 2–8). The attempts with other catalysts, such as $FeCl_3$ and $Pd(OAc)_2$, led to lower yields of **3aa** (Table 1, entries 9 and 10). **3aa** was not detected in the absence of a transition-metal catalyst (Table 1, entry 11).

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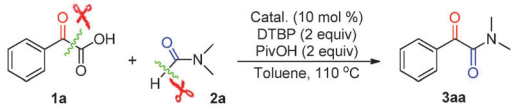
Scheme 1

Table 1 Optimization of the catalyst[a]



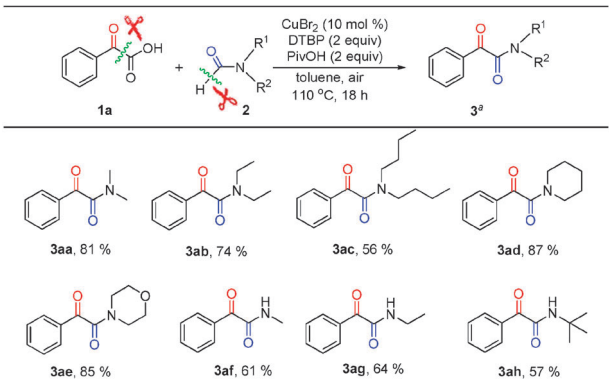
Entry	Catalyst	Oxidant	Additive	Yield[b] (%)
1	$CuBr_2$	DTBP	PivOH	81
2	$CuCl_2$	DTBP	PivOH	51
3	$Cu(acac)_2$	DTBP	PivOH	31
4	$CuSO_4$	DTBP	PivOH	29
5	CuI	DTBP	PivOH	25
6	CuCl	DTBP	PivOH	13
7	$Cu(OAc)_2$	DTBP	PivOH	<5
8	CuO	DTBP	PivOH	Trace
9	$FeCl_3$	DTBP	PivOH	34
10	$Pd(OAc)_2$	DTBP	PivOH	<5
11	—	DTBP	PivOH	NR

[a] Reaction conditions: **1a** (0.50 mmol), **2a** (5.0 equiv.), catalyst (10 mol%), DTBP (2.0 equiv.), PivOH (2.0 equiv.), toluene (1.5 mL), air atmosphere, 110 °C, 18 h. [b] Isolated yields.

The oxidant also plays an important role in the reaction and DTBP exhibited the highest reactivity among the tested oxidants, including H_2O_2, TBHP, TBPB, BQ, $K_2S_2O_8$ and O_2 (Table S1, ESI†). When the reaction was carried out under an air atmosphere without an additional oxidant, only 20% yield of **3aa** was obtained. Meanwhile, a significant influence of additive on the model reaction was observed. PivOH was the best additive because it can inhibit the side reactions and improve the yield of **3aa**.

Other additives, whether acids (TFA, HOAc, $PhCO_2H$, and CF_3SO_3H), or bases (pyridine, NEt_3, K_2CO_3, and K_3PO_4), were ineffective (Table S1, ESI†). The absence of additive resulted in a decreased yield of **3aa** to 43%. The solvent was also an important factor in this transformation and the results are shown in Table S1 (ESI†). Of the tested solvents, toluene was found to be the best choice. Other solvents, such as *t*-AmOH (tertiary amyl alcohol), dioxane, CH_2ClCH_2Cl, $CH_3OCH_2CH_2OCH_3$, CH_2Cl_2 and benzene, were less effective, and NMP, CH_3NO_2, DMSO, HOAc and H_2O shut down the reaction completely. During further investigation of the reaction conditions, the model reaction was completed at 110 °C for 18 h.

In order to study the potential and general applicability of this methodology, the representative formamides with 2-oxo-2-phenylacetic acid (**1a**) were screened. The results are shown in Scheme 2. Besides DMF, other dialkylformamides, such as *N*,*N*-diethylformamide and *N*,*N*-dibutylformamide, were well tolerated, and the product yield decreased along with the increase in chain length of formamides owing to the steric hindrance (**3ab** and **3ac**). However cyclic formamides, such as 1-formylpiperidine and 4-formylmorpholine, reacted smoothly with **1a**, furnishing high yields of the desired products (**3ad**, 87%; **3ae**, 85%). It is important to note that *N*-monosubstituted formamides were also well tolerated, providing

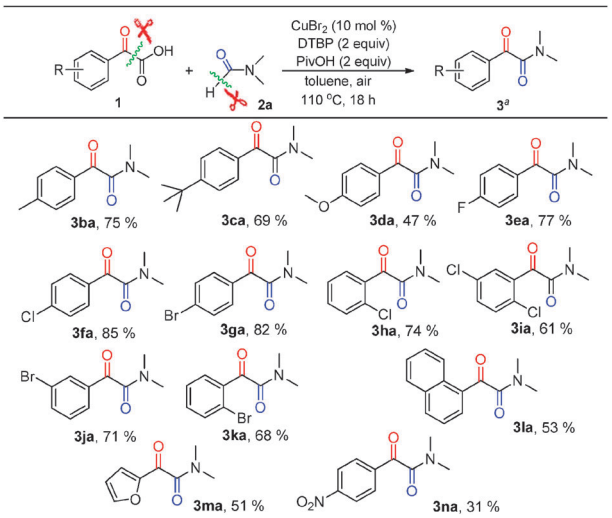


Scheme 2 The scope of formamides (**2**). Reaction conditions: **1a** (0.50 mmol), **2** (5.0 equiv.), $CuBr_2$ (10 mol%), DTBP (2.0 equiv.), PivOH (2.0 equiv.), toluene (1.5 mL), air atmosphere, 110 °C, 18 h. [a]Isolated yields.

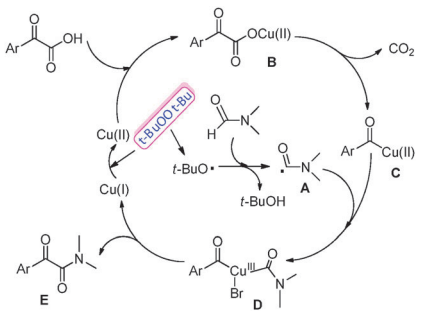
good yields of the corresponding products. *N*-Methylformamide, *N*-ethylformamide, and *N*-*tert*-butylformamide reacted with **1a** to generate the desired products (**3af**, **3ag** and **3ah**) in 61, 64, and 57% yields.

Next, the scope of α-oxocarboxylic acids was examined and a variety of 2-oxo-2-arylacetic acids bearing substituents on the benzene rings were well tolerated (Scheme 3). In general, 2-oxo-2-arylacetic acids possessing an electron-withdrawing group on the benzene ring gave better yields than those having an electron-donating group on the benzene ring. For example, 2-oxo-2-arylacetic acids with F, Br, and Cl on the *para*-positions of benzene rings reacted with DMF efficiently, and the corresponding products (**3ea**, **3fa** and **3ga**) were isolated in 77–85% yields. However, 2-oxo-2-arylacetic acids with Me, *t*-Bu, and MeO on the *para*-positions of benzene rings gave the desired products (**3ba**, **3ca** and **3da**) in 75%, 69%, and 47% yields respectively. But 2-(4-nitrophenyl)-2-oxoacetic acid is an exception, and only 31% yield of **3na** was obtained. Meanwhile, 2-oxo-2-arylacetic acids, bearing a sterically hindered group, such as Cl or Br on their *ortho*/*meta*-positions, also underwent decarboxylative coupling with DMF, providing the corresponding products (**3ha**, **3ia**, **3ja** and **3ka**) in slightly lower yields (61–74%) compared with their corresponding *para*-substituted ones. Additionally, 2-(naphthalen-1-yl)-2-oxoacetic acid and 2-(furan-2-yl)-2-oxoacetic acid also proceeded through the reaction smoothly with DMF to generate **3la** and **3ma** in 53% and 51% yields.

Although the reaction mechanism is not clear at this stage, on the basis of previous publications, it is believed that this transformation proceeds *via* a combination of C–H activation of formamide by a radical step[17,18a] and a transition-metal catalyzed decarboxylation of α-oxocarboxylic acid.[9d-f] As anticipated, the addition of a radical inhibitor blocked the reaction. The desired product **3aa** was not detected when 0.25 equiv. of TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl) was added to the model reaction. A plausible catalytic cycle is presented in Scheme 4. Firstly, homolysis of DTBP produces the *tert*-butoxy radical, which traps H from DMF to generate a radical intermediate **A**. On the other hand, 2-oxo-2-arylacetic acid reacts with Cu(II) catalyst to form a salt of Cu(II) carboxylate **B**, and then organometallic species **C** is produced *via* extrusion of CO_2 from **B**. The obtained intermediate **A** couples with organometallic species **C** to generate intermediate **D**, which was followed by a reductive elimination process to form the desired product and Cu(I).



Scheme 3 The scope of 2-oxo-2-arylacetic acids (**1**). Reaction conditions: **1** (0.50 mmol), **2a** (5.0 equiv.), $CuBr_2$ (10 mol%), DTBP (2.0 equiv.), PivOH (2.0 equiv.), toluene (1.5 mL), air atmosphere, 110 °C, 18 h. [a]Isolated yields.



Scheme 4 Proposed reaction mechanism.

Finally, oxidation of Cu(I) by DTBP regenerates Cu(II) to complete this catalytic cycle.

In conclusion, we have developed a $CuBr_2$-catalyzed decarboxylative acylation of acyl C–H of formamides with α-oxocarboxylic acids. The reactions of *N*-monosubstituted and *N*,*N*-disubstituted formamides with a variety of α-oxo-2-arylacetic acids proceeded smoothly to generate the corresponding α-ketoamides in good yields. This method can provide a useful strategy for the synthesis of α-ketoamides, which are key units of many biological active compounds, and it is the first example to use formamides as an amide source for the preparation of α-ketoamides. The reaction is highly efficient and has a broad substrate scope. Further investigation on the reaction is ongoing in our laboratory.

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