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Bu_4NI-catalyzed decarboxylative acyloxylation of an sp^3 C–H bond adjacent to a heteroatom with α-oxocarboxylic acids†

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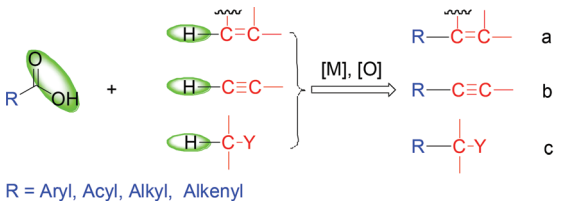
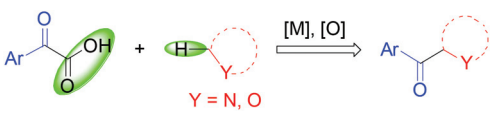
A novel metal-free decarboxylative acyloxylation of an sp^3 C–H bond in formamides and ethers has been explored. A variety of *N*-acyloxymethylamides and α-acyloxy ethers could be easily synthesized by this method. Preliminary mechanistic studies have shown that the reaction proceeded *via* a radical process.

Transition-metal-catalyzed decarboxylative cross-coupling reactions are of great interest in modern organic synthesis because the reactions show an advantage in using simple and readily available carboxylic acids as reactants compared to related cross-coupling with sensitive organometallic reagents.[1] For example, the direct olefination of arene carboxylates with olefins *via* decarboxylative cross-coupling has emerged as an attractive alternative to traditional Heck coupling methods.[2] In addition, the decarboxylative cross-coupling reactions of various carboxylic acids with organo halides also represented particularly powerful C–C bond formation strategies.[3] Very recently, more challenging decarboxylation/C–H activation of simple unactivated (hetero)arenes and alkenes has been developed, affording various biaryl or diaryl ketone products (eqn (1a)).[4] Additionally, the copper-catalyzed oxidative functionalization of unactivated C(sp)–H[5] and C(sp^3)–H[6] bonds through decarboxylative cross-coupling of carboxylic acids has also been reported (eqn (1b) and (1c)). Obviously, the direct decarboxylative dehydrogenative cross-coupling may provide a more appealing synthetic method because neither organohalides nor sensitive organometallics are required for these processes. Although some excellent pioneering progress has been made on this subject,[4–6] exploitation of the new catalytic decarboxylative/C–H functionalization reaction still remains a major challenge for synthetic chemists.



(1)

On the other hand, transition-metal-catalyzed oxidative functionalization of an sp^3 C–H bond is a challenging and powerful method to the formation of C–C and C–heteroatom bonds from simpler starting materials.[7] In this context, substrates which contain an sp^3 C–H bond adjacent to a heteroatom have been extensively examined in comparison with the analogous reactant.[7f–h] In addition, the metal-free oxidative functionalization of an sp^3 C–H bond adjacent to a nitrogen or an oxygen atom has also been reported.[8] However, to date, the metal-free decarboxylative functionalization of an sp^3 C–H bond adjacent to a heteroatom with stable carboxylic acids has been scarcely studied.[1] In connection with our recent efforts on transition-metal catalyzed decarboxylative C–H bond acylation,[4k] we envisioned that the use of readily available α-oxocarboxylic acids for catalytic decarboxylative sp^3 C–H bond acylation of formamides and ethers might be a useful method for the synthesis of various ketones (eqn (2)).



(2)

We first investigated the reaction of phenylglyoxylic acid (**1a**) with *N*,*N*-dimethylformamide (DMF, **2a**) in the presence of 20 mol% of CuO and 2 equiv. of di-*tert*-butyl peroxide (DTBP) as an oxidant at 80 °C for 3 h. Surprisingly, the expected product *N*-benzoylmethyl-*N*-methylformamide was not observed. Instead, a new product *N*-benzoyloxymethyl-*N*-methylformamide **3a** was obtained. Although Bamford and coworkers have found that DMF could be converted to **3a** in the presence of benzoyl peroxide, however, only this product was reported therein.[9] Given that *N*-acyloxymethylamides are valuable synthetic intermediates and important structural units

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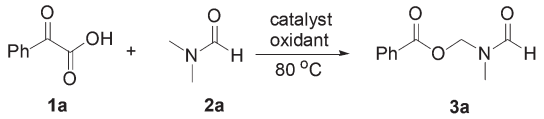
Table 1 Optimization of the direct decarboxylative C–H acyloxylation of DMF with phenylglyoxylic acid[a]



1a 2a 3a

Entry	Catalyst (mol%)	Oxidant (equiv.)	Yield[b] (%)
1	CuO (20)	DTBP (2)	<5[c]
2	TBAI (20)	DTBP (2)	12[c]
3	TBAI (20)	DCP (2)	18[c]
4	TBAI (20)	TBHP[d] (2)	30[c]
5	TBAI (20)	TBHP[e] (2)	48[c]
6	TBAI (20)	TBHP[e] (2)	62
7	TBAI (20)	TBHP[e] (2)	20[f]
8	TBAI (20)	TBHP[e] (1.2)	21
9	Bu_4NBr (20)	TBHP[e] (2)	Trace
10	KI (20)	TBHP[e] (2)	11
11	I_2 (20)	TBHP[e] (2)	Trace
12	—	TBHP[e] (2)	Trace

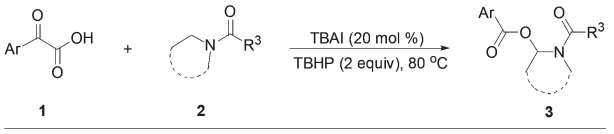
[a] Reaction conditions: 20 mol% of catalyst, **1a** (0.2 mmol, 1 equiv.), DMF (2 mL), oxidant (2 equiv.), 80 °C, 3 h. [b] Yield of the isolated product. [c] At 110 °C. [d] TBHP (70% aqueous). [e] TBHP (*tert*-butyl hydroperoxide, 5–6 M in decane). [f] At 60 °C.

found in numerous natural products and pharmaceuticals,[10] efforts were then made to improve the yield of this novel decarboxylative coupling reaction (Table 1). However, other metal catalysts did not show any catalytic activity for this decarboxylative acyloxylation reaction.[11] Very recently, tetrabutylammonium iodide (TBAI) catalyzed oxidative C–H activation reaction has attracted much attention in synthetic organic chemistry.[8c,12] However, when TBAI was used as a catalyst, only 12% yield of the desired product was obtained (Table 1, entry 2). The use of dicumyl peroxide (DCP) instead of DTBP has no significant influence on the yield (entry 3). When TBHP was employed as an oxidant, the yield could be improved to 48% (entry 5). Screening revealed that 80 °C was the optimal temperature, giving a moderate result (entry 6). Variation of the catalysts showed that TBAI was the best one (entries 9–11).

Table 2 summarizes the application of the optimized reaction conditions to a range of phenylglyoxylic acids. Phenylglyoxylic acids with *p*-substituted electron-rich or -poor groups proved to be good substrates for this transformation, affording the corresponding *N*-acyloxymethylamides in moderate yields (**3b–g**). Phenylglyoxylic acids bearing an *ortho*-substituent such as *o*-methylphenylglyoxylic acid also gave the desired product **3h** in moderate yield, but along with a small amount of inseparable byproduct, which indicated that steric hindrance disfavored this acyloxylation reaction. In addition, when β-naphthyloxoacetic acid and furoylformic acid were used, the desired products of **3i** and **3j** were obtained in 58% and 42% isolated yields, respectively. However, other *N*,*N*-disubstituted formamides, such as *N*-formylpiperidine, were inefficient for this decarboxylative coupling reaction (**3k**). The acetamide also gave the corresponding product in 63% yield (**3l**).

To further expand the scope of this acyloxylation reaction to other substrates, we next investigated the decarboxylative

Table 2 Decarboxylative C–H acyloxylation of amides with various phenylglyoxylic acids[a]



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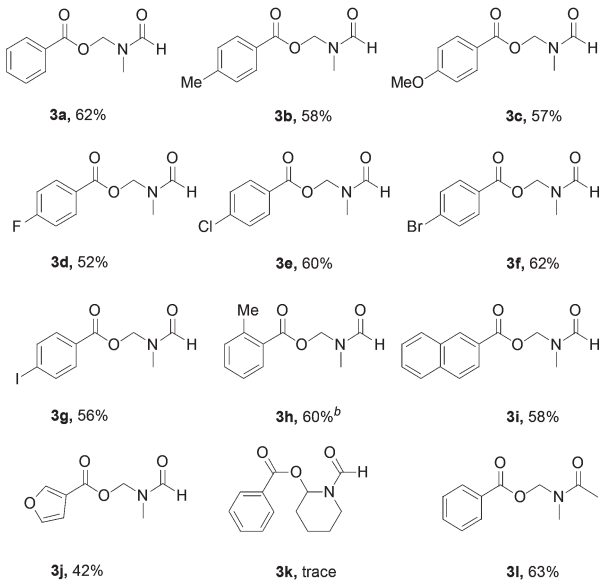
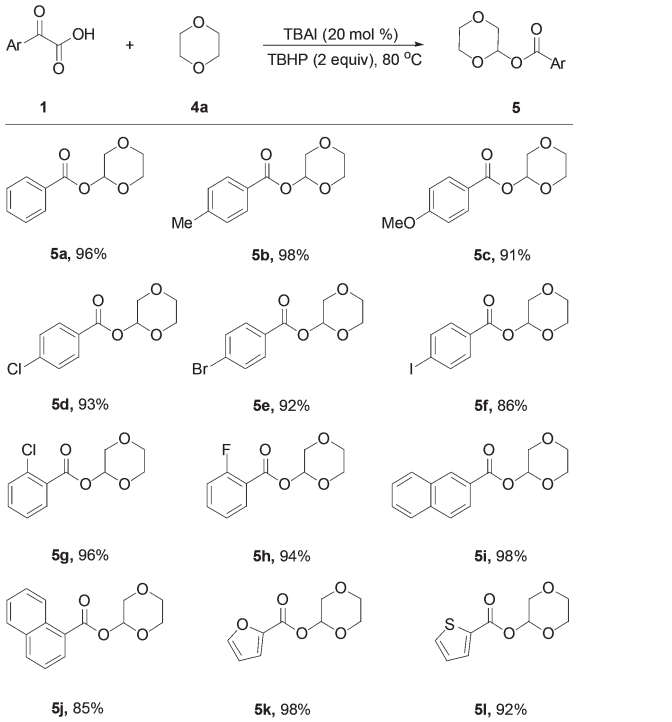


[a] All reactions were performed with 1 (0.2 mmol) and formamides **2** (2 mL), under standard conditions (Table 1, entry 6) at 80 °C, 3 h. Yields are of the isolated products. [b] An inseparable byproduct was observed.

coupling of α-oxocarboxylic acids with ethers. As expected, the various phenylglyoxylic acids reacted with 1,4-dioxane leading to the desired α-acyloxy ethers **5** in good to excellent yields (Table 3). A variety of electron-donating and electron-withdrawing groups could be tolerated in this reaction (**5b–h**). Additionally, the furoylformic acid and 2-thienylglyoxylic acid also proceeded smoothly to give the desired products **5k** and **5l** in 98% and 92% yields, respectively.

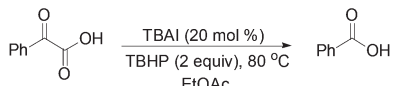
For the TBAI-catalyzed decarboxylative acyloxylation reaction reported above, the corresponding arenecarboxylic acids were also observed in some cases. The result suggested that arenecarboxylic acid might be a potential intermediate in this reaction. It is known that the α-oxocarboxylic acids could easily undergo oxidative decarboxylation to homologous carboxylic acids in the presence of various oxidants.[13] In fact, when ethyl acetate was used instead of DMF, under the same conditions the benzoic acid **6** was isolated in 97% yield, which indicated that phenylglyoxylic acid also oxidatively degraded to **6** under the TBAI/TBHP (eqn (3)). On the other hand, the reaction of **6** with DMF **2a** also gave the *N*-acyloxymethylamide **3a** in 62% isolated yield (eqn (4)). So, we proposed that the benzoic acid should be the key intermediate of this oxidative decarboxylative C–H acyloxylation reaction.[14] Furthermore, the reaction was also suppressed by addition of a radical scavenger, such as TEMPO. Thus, we speculated that the reaction proceeds *via* a

Table 3 Decarboxylative C–H acyloxylation of 1,4-dioxane with various phenylglyoxylic acids[a]

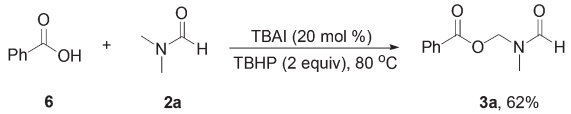


[a] Reaction conditions: 20 mol% of TBAI, **1** (0.2 mmol, 1 equiv.), 1,4-dioxane **4a** (1 mL), TBHP (70% aqueous, 2 equiv.), 80 °C, 4 h. Yields are of the isolated products.

radical process, which was similar to the cross-dehydrogenative coupling of ethers with benzoic acid,[8c] whereas an imine-type intermediate was formed when DMF was used.[8b] The imine-type intermediate reacts with a benzoate anion, which is generated *in situ* from phenylglyoxylic acid, to furnish the target product **3a**. However, the formamide *N*-methyl radical[8a] and acyloxy radical[12g] were also reasonable intermediates to consider for this reaction.[15]



(3)



(4)

In summary, we have demonstrated that the C(sp^3)–H bond acyloxylation of formamides and ethers with α-oxocarboxylic acids can be achieved using metal-free catalytic systems. This operationally simple and efficient method provides a new approach toward the synthesis of *N*-acyloxymethylamides and α-acyloxy ethers with a wide range of substrate scopes. In these transformations, the C–O bond was easily constructed by the decarboxylative coupling of α-oxocarboxylic acids with formamides and ethers under an inexpensive catalyst–oxidant system, respectively. Both the starting materials are simple and easily available.

Acknowledgements

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11 A variety of copper catalysts were screened, in all the cases, only a very small amount of the desired product **3a** was detected.

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14 Treatment of benzaldehyde with DMF under TBAI/TBHP, only a trace amount of the **3a** was detected. The major product was *N*,*N*-dimethylbenzamide which indicated that aldehyde was not the intermediate in this acyloxylation reaction, also see ref. 12*h*.

15 We gratefully acknowledge valuable suggestions by the reviewers for the reaction mechanism.