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Iron-catalyzed Cleavage Reaction of Keto Acids and Aliphatic Aldehydes for the Synthesis of Ketone/Ketone Esters

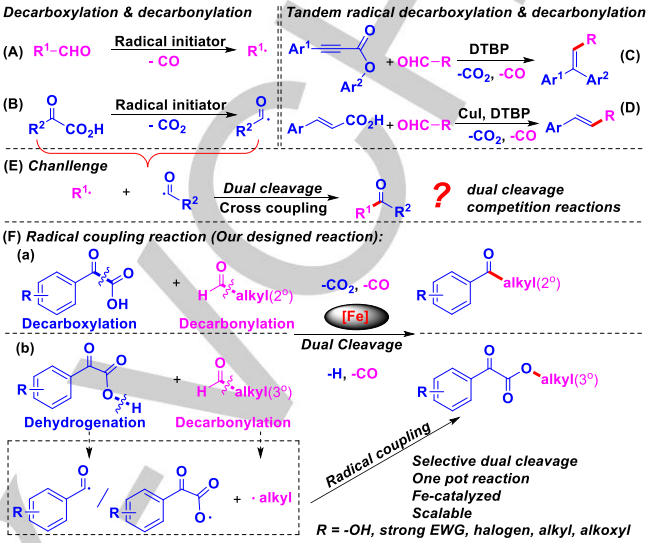
Fangyuan Zhou, Lesong Li, Kao Lin, Feng Zhang, Guo-Jun Deng, and Hang Gong*

Abstract: The radical-radical coupling reaction is an important synthesis strategy. In this study, the iron-catalyzed radical-radical cross-coupling reaction based on the decarboxylation of keto acids and decarbonylation of aliphatic aldehydes to obtain valuable aryl ketones is reported for the first time. Remarkably, when tertiary aldehydes were used as carbonyl sources, ketone esters were selectively obtained instead of ketones. The gram-scale preparation of aryl ketone *via* this strategy was easily achieved using only 3 mol% of the iron catalyst. As a proof-of-concept, the bioactive molecule flurprimidol was synthesized in two steps by this strategy.

Radical reaction is one of the most basic and important synthetic tools available in organic chemistry. It has been widely used as a powerful strategy for the synthesis of pharmaceutical molecules, natural products and functional materials[1]. As an important component of radical reactions, the formation of a C-C bond through a radical process has received increasing attention over the past decade. The key step of these reactions is the formation of the carbon radical. Aldehyde is a kind of safe, inexpensive and readily available reagent, and could be served as a carbon radical source *via* a decarbonylation reaction (Scheme 1, **A**)[2]. Various C-C bonds, such as C(SP^2)-C(SP^2) [3], C(SP^2)-C(SP^3)[4],C(SP)-C(SP^3)[5] and C(SP^3)-C(SP^3)[6] etc. have been constructed based on the decarbonylation reaction. In addition, decarboxylation of carboxylic acids to obtain the carbon radical and then achieve the chemo- and regioselective conversion has also been widely investigated[7]. Among them, the decarboxylation of α-keto acid in the presence of a radical initiator has been attractive for preservation of the carbonyl skeleton (Scheme 1, **B**)[8].

There are only two reports about the construction of C–C *via* tandem radical decarboxylation and decarbonylation (Scheme 1, **C** & **D**)[9]. Despite the vigorous development of research on decarboxylation and decarbonylation, the radical-radical coupling reaction *via* decarboxylation and decarbonylation remains challenging. In particular, the simultaneous cleavage of carboxylic acid and aldehyde, and the competition coupling reactions of multiple radicals (Scheme 1, **E**).

In this paper, the iron-catalyzed decarboxylative and decarbonylative radical cross-coupling reactions between keto acids and aliphatic aldehydes are reported for the first time (Scheme 1, **F**). This strategy is significant since the corresponding aromatic ketones would be achieved when secondary aldehydes are used as alkyl source (Scheme 1, **F**, **a**). Traditionally, aromatic ketones are synthesized through the Friedel-Crafts acylation



Scheme 1. The strategies of decarboxylation vs. decarbonylation and our designed reaction.

reaction. However, besides having limited tolerance of functional groups, such reaction consumes large amounts of Lewis acid, and produces a large amount of by-products[10].

Aromatic ketones can also be prepared by the reaction of acid chlorides or esters with organometallic species, such as organolithium[11], Grignard[12], organoaluminum[13], organotin[14], organozinc[15], organoindium[16] reagents, etc[17]. However, the stoichiometric consumption of metal reagents and the ready generation of tertiary alcohols as side-products are unfavorable to the organic synthesis [18]. Compared with these conventional methods, our strategy does not consume large amounts of Lewis acid, does not require pre-preparation of stoichiometric metal reagents, is compatible with substrates containing active hydrogen and strong electron-withdrawing group, and its influence on the environment is greatly reduced. More importantly, when tertiary aldehydes were used as carbonyl sources, ketone esters were selectively obtained instead of ketones (Scheme 1, **F**, **b**).

Our study began with the reaction of phenylglyoxylic acid with isobutyraldehyde using $Fe(OTf)_3$ (15 mol%) as the catalyst, di-tert-butyl peroxide (DTBP) as the oxidant, and toluene as the solvent, at 120 °C under an atmosphere of air (Table 1). Gratifyingly, the yield of the desired radical coupling product isobutyrophenone was 22% (entry 1). Motivated by this result, various reaction conditions, including catalysts (entries 1–7, 22), the ratio of reactants (entries 8–9), oxidants (entries 10-11, 23–26), reaction temperature (entries 12–13), reaction time (entries 14–15) and solvents (entries 16–21) were optimized (More details of the optimization reactions are given as supporting information). The optimized reaction conditions were as follows: 30 mol% $Fe(OTf)_3$ as catalyst, 2 equiv DTBP and 1.5 equiv $K_2S_2O_8$ as

[*] Mr. F. Zhou, Mr. L. Li, Mr. K. Lin, Prof. Dr. G.-J. Deng, Dr. H. Gong, The Key Laboratory of Environmentally Friendly Chemistry and Application of the Ministry of Education; The Key Laboratory for Green Organic Synthesis and Application of Hunan Province; College of Chemistry, Xiangtan University, Xiangtan 411105 (China)
E-mail: hgong@xtu.edu.cn
Ms. F. Zhang
College of Science, Hunan Agricultural University, Changsha 410128, China

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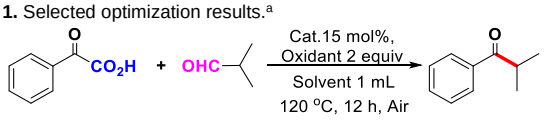
Table 1. Selected optimization results.[a]



1a (0.2 mmol) **2a** (5 equiv) **3a**

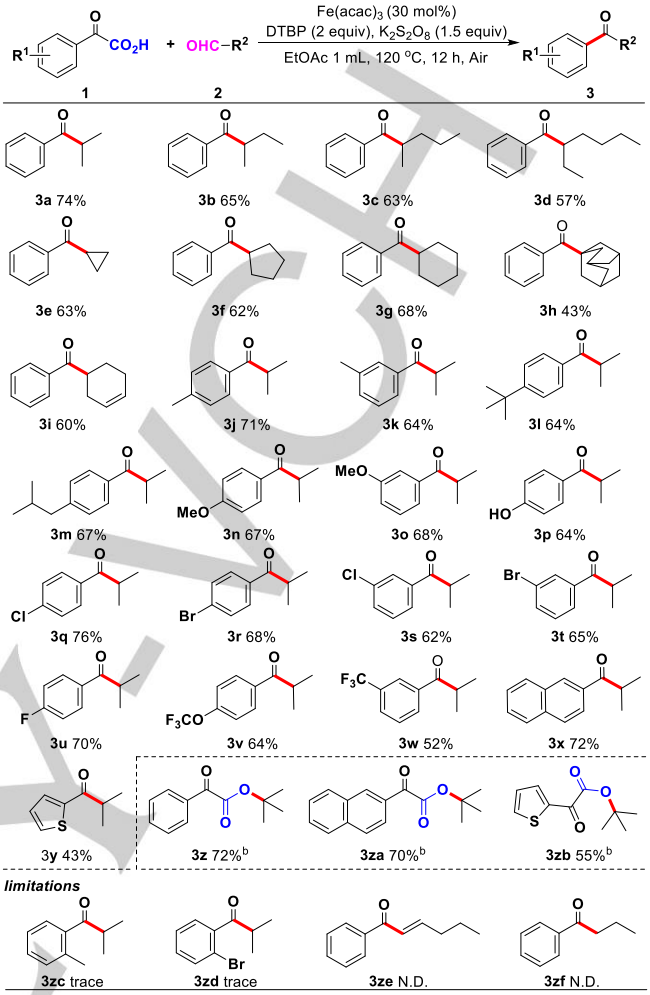
Entry	Cat. (mol%)	Oxidant	Solvent	T (°C)	Time (h)	**3a** (%)
1	$Fe(OTf)_3$	DTBP	toluene	120	12	22
2	$Fe(OTs)_3$	DTBP	toluene	120	12	18
3	$FeBr_3$	DTBP	toluene	120	12	21
4	$Fe(acac)_2$	DTBP	toluene	120	12	45
5	$Fe(acac)_3$	DTBP	toluene	120	12	53
6	DPPF	DTBP	toluene	120	12	24
7	DTBPF	DTBP	toluene	120	12	36
8[b]	$Fe(acac)_3$	DTBP	toluene	120	12	44
9[c]	$Fe(acac)_3$	DTBP	toluene	120	12	47
10[d]	$Fe(acac)_3$	DTBP	toluene	120	12	47
11[e]	$Fe(acac)_3$	DTBP	toluene	120	12	53
12	$Fe(acac)_3$	DTBP	toluene	100	12	29
13	$Fe(acac)_3$	DTBP	toluene	150	12	47
14	$Fe(acac)_3$	DTBP	toluene	120	10	50
15	$Fe(acac)_3$	DTBP	toluene	120	18	51
16	$Fe(acac)_3$	DTBP	dioxane	120	12	23
17	$Fe(acac)_3$	DTBP	DMSO	120	12	25
18	$Fe(acac)_3$	DTBP	DMF	120	12	12
19	$Fe(acac)_3$	DTBP	$CHCl_3$	120	12	12
20	$Fe(acac)_3$	DTBP	EtOAc	120	12	52
21	$Fe(acac)_3$	DTBP	CH_3CN	120	12	41
22[f]	$Fe(acac)_3$	DTBP	EtOAc	120	12	67
23[f]	$Fe(acac)_3$	$K_2S_2O_8$	EtOAc	120	12	17
24[f,g]	$Fe(acac)_3$	DTBP+$K_2S_2O_8$	EtOAc	120	12	68
25[f,h]	$Fe(acac)_3$	DTBP+$K_2S_2O_8$	EtOAc	120	12	76
26[f,i]	$Fe(acac)_3$	DTBP+$K_2S_2O_8$	EtOAc	120	12	77
27[i]	——	DTBP+$K_2S_2O_8$	EtOAc	120	12	15
28[f]	$Fe(acac)_3$	——	EtOAc	120	12	trace

[a] Unless otherwise noted, all reactions were conducted on a 0.2 mmol scale in a sealed tube under the atmosphere of air; NMR yields were given using CH_3NO_2 as internal standard; DPPF = 1,1'-Bis(diphenylphosphino)ferrocene; DTBPF = 1,1'-Bis(di-tert-butylphosphino)ferrocene. For other results from the optimization of the reaction conditions please see the *Supporting Information*; [b] 2 equiv aldehyde was used; [c] 3 equiv aldehyde was used; [d] 1.5 equiv DTBP was used; [e] 2.5 equiv DTBP was used; [f] $Fe(acac)_3$ 30 mol%; [g] 2 equiv DTBP and 1 equiv $K_2S_2O_8$ were used; [h] 2 equiv DTBP and 1.5 equiv $K_2S_2O_8$ were used; [i] 2 equiv DTBP and 2 equiv $K_2S_2O_8$ were used.

oxidants, 1 mL ethyl acetate (EtOAc) as solvent, reaction temperature of 120 °C and reaction time of 12 h (entry 24). Control experiments were also conducted and the results revealed that both the iron catalyst and oxidant play an important role for this reaction (entries 27–28).

With the optimized reaction conditions in hand, the generality of this strategy was investigated (Table 2). First, various secondary aldehydes for use as alkyl source were scanned. When aliphatic aldehydes with short or long chains were used, moderate to good yields were obtained (**3a**–**d**). Gratifyingly, this reaction is also compatible with cyclo-aliphatic aldehydes, and the corresponding aromatic ketones were obtained in good yields (**3e**–**g**). Additionally, the sterically hindered adamantane moiety, which is frequently found in pharmaceutical, nanomaterials and supramolecular assemblies[19], was successfully introduced into the aryl ketone (**3h**). The vinyl bond in the aliphatic ring could be preserved after this reaction, and a good yield could also be obtained (**3i**). Subsequently, the substitutes on the aromatic ring of the keto acid were explored. It was determined that some of the substituents were electron-donating groups (**3j**–**p**) while others were electron-withdrawing groups (**3q**–**w**), and good yields were obtained. Importantly, this reaction is compatible with substrates containing active hydrogen such as hydroxyl group (**3p**). α-Naphthyl and α-heteroaryl keto acids also followed this rule well, and the corresponding ketones were obtained with acceptable

Table 2. Scope of decarboxylation and decarbonylation radical coupling reaction.[a]



[a] Unless otherwise noted, all reactions were carried out with phenylglyoxylic acid (0.2 mmol), isobutyraldehyde (1.0 mmol), $Fe(acac)_3$ (30 mol%), DTBP (2 equiv) and $K_2S_2O_8$ (1.5 equiv) in a sealed tube in 1 mL EtOAc at 120 °C for 12 hrs under the atmosphere of air; Isolated yields were given; [b] Without $K_2S_2O_8$.

yields (**3x**, **y**). In particular, when tertiary aldehydes were used as carbonyl sources in the reaction with phenylglyoxylic acid, ketone esters, instead of ketones, were selectively obtained in good yields (**3z**–**zb**). This is probably caused by the rapid generation of tertiary carbon radicals, which were then coupled with carboxyl radicals rather than carbonyl radicals after decarboxylation. When 1-adamantane carboxaldehyde (**1h**) was used, a bridgehead carbon radical with less stability would be formed, thus ketone **3h** is achieved instead of ketone ester. In addition, in the case of using **1z-1zb** as reactants, $K_2S_2O_8$ were not benifite for this reaction. However, this reaction is sensitive to steric hindrance and when the substituent is present in the ortho-position almost no desired products could be found (**3zc**, **zd**). Primary aldehydes and alkenyl substituted aldehydes were also incompatible with this reaction due to the poor stability of the radical after decarbonylation (**3ze**, **zf**).

To investigate the reaction mechanism, a radical inhibition experiment was conducted using 2 equiv of TEMPO as inhibitor, and almost no desired aromatic ketone **3a** was detected (Scheme 2, **A**). Remarkably, when the reaction was performed in the presence of 1,1-diphenylethylene, besides the desired ketone **3a**,

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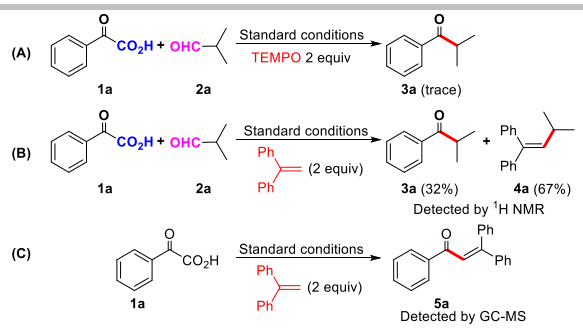
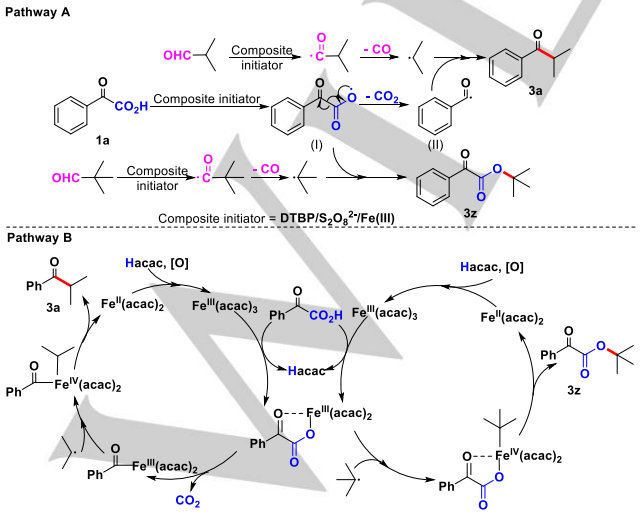


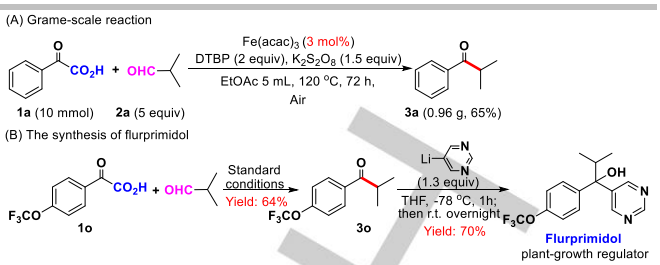
Scheme 2. Radical inhibition/capture experiments.

the radical-capturing product **4a** was obtained with a yield of 67% (Scheme 2, **B**). In addition, when phenylglyoxylic acid (**1a**) was treated with 1,1-diphenylethylene under the standard condition, the radical-capturing product **5a** was detected (Scheme 2, **C**). These results revealed that this reaction is a radical process, and the alkyl radical and acyl radical were formed through decarbonylation and decarboxylation reactions, respectively.

Based on these control experiments, a plausible mechanism is depicted in Scheme 3. For payway A, the aryl ketonic acid **1a** loses a hydrogen atom, which in the presence of the composite initiator and is transferred to carboxyl radical (**I**). Subsequently, the decarboxylation process occurs and the corresponding carbonyl radical (**II**) is generated. In addition, aldehyde is converted to the carbonyl radical, which is followed by decarbonylation to form the alkyl radical. When the secondary aldehyde is used, the derived alkyl radical couples with the carbonyl radical (**II**) to generate the desired product aryl ketone **3a**. Instead, when tertiary aldehydes are used, the derived alkyl radical couples with carboxyl radical (**I**) and the ketone esters **3z** are obtained. This is probably caused by the rapid generation of tertiary carbon radicals, which leads to the occurrence of the radical-radical coupling reaction before the decarboxylation of the carboxyl radical (**I**). In pathway B, Fe(III) species interact with the α-keto acid, and followed by decarboxylation (for tertiary aldehydes, this process was skipped) and radical addition and reduction elimination to give the corresponding products.



Scheme 3. The proposed mechanism.



Scheme 4. Gram-scale reaction and the synthesis of flurprimidol.

To prove the feasibility of this method, a gram-scale synthesis of aryl ketone **3a** was conducted and a good yield also obtained using only 3 mol% of the iron catalyst with a longer reaction time (72 h) (Scheme 4, **A**). The convenient decarboxylation and decarbonylation radical coupling reaction can be readily applied in the synthesis of bioactive molecules. As a proof-of-concept, the plant-growth regulator flurprimidol was effectively synthesized from **1o** and isobutyraldehyde in two steps (Scheme 4, **B**). The key intermediate **3o** could be obtained by a one-step reaction with a good yield of 64%.

In conclusion, in this study for the first time the iron-catalyzed decarboxylative and decarbonylative radical-radical cross-coupling reactions between keto acids and aliphatic aldehydes were shown to produce valuable aryl ketones. Compared with traditional methods of preparing aryl ketones, our strategy does not consume large amounts of Lewis acid, does not require pre-preparation of stoichiometric metal reagents, is compatible with substrates containing active hydrogen and strong electron-withdrawing group, and its influence on the environment is greatly reduced. Additionally, the gram-scale reaction was easily achieved with a much lower iron catalyst loading (3 mol%). As an example, the rapid synthesis of bioactive molecules, such as flurprimidol was successfully performed by this strategy.

Acknowledgements

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Experimental Section

A typical experimental procedure: A solution of aryl keto acid (0.2 mmol), Fe(acac)$_3$ (21.2 mg, 0.06 mmol), aldehyde (1.0 mmol), DTBP (79.5 μL, 0.4 mmol) and $K_2S_2O_8$ (81.1 mg, 0.3 mmol) in EtOAc (1 mL) is prepared by stirring in a sealed tube under an atmosphere of air at 120 °C for 12 h. Subsequently, the reaction mixture is cooled to room temperature, and the solid residue is filtered through a short silica gel column, and washed with 10 mL EtOAc. Afterwards, the solvent is evaporated in vacuo. The residue is then purified by preparative thin-layer chromatography

(TLC) on silica gel with petroleum ether/EtOAc to obtain the pure product.

Keywords: Radical-radical cross-coupling • decarboxylation • decarbonylation • iron-catalyzed reaction • synthetic methods

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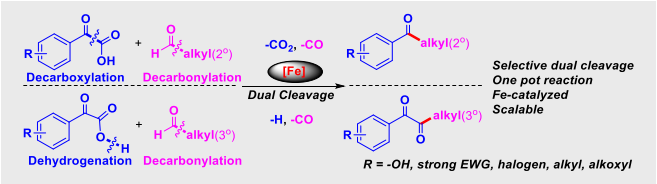

The iron-catalyzed radical-radical cross-coupling reaction based on the decarboxylation/dehydrogenation of keto acids and decarbonylation of aliphatic aldehydes to obtain the valuable aryl ketones/ketone esters were reported.

*Fangyuan Zhou, Lesong Li, Kao Lin, Feng Zhang, Guo-Jun Deng, and Hang Gong**

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Iron-catalyzed Cleavage Reaction of Keto Acids and Aliphatic Aldehydes for the Synthesis of Ketone/Ketone Esters