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Iron-catalyzed domino decarboxylation-oxidation of α,β-unsaturated carboxylic acids enabled aldehyde C–H methylation†

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A practical and general iron-catalyzed domino decarboxylation-oxidation of α,β-unsaturated carboxylic acids enabling aldehyde C–H methylation for the synthesis of methyl ketones has been developed. This mild, operationally simple method uses ambient air as the sole oxidant and tolerates sensitive functional groups for the late-stage functionalization of complex natural-product-derived and polyfunctionalized molecules.

The methyl group, the smallest alkyl motif in nature, is very important in modulating biological activity, selectivity, solubility, metabolism and pharmacokinetic/pharmacodynamic properties of biologically active molecules.[1] Using a methyl group to replace a hydrogen atom of a bioactive compound can result in profound potency enhancement mainly owing to the methyl group's capacity to cause stereoelectronic changes, to fill a hydrophobic pocket of the protein, and/or to induce a propitious conformational change of the molecule.[2] Less than 5% of the top 200 best-selling pharmaceuticals of 2018, contained a CF_3 group, whereas more than 44% of these drugs bear a methyl group bound to a carbon atom.[3] In contrast, the CF_3 group has attracted much attention among the researchers in the synthetic community in the past few decades, while the methyl group is underrepresented in recent synthetic chemistry.[4] Hence, the development of a direct and practical strategy for the introduction of a methyl group into a molecule has a significant impact on drug discovery.[1]

Aryl methyl ketone is a privileged scaffold in medicinal chemistry and pharmaceutical agents.[5] A selection of drugs containing acetophenone skeletons are presented in Fig. 1. Typically, aryl methyl ketones are prepared by Friedel–Crafts acylation of arenes with acetyl halides.[6] Unfortunately, this transformation requires overstoichiometric amounts of Lewis acid, which is limited to electron-rich arenes and affords *ortho* and *para* isomers. Other synthetic strategies rely on the addition of methyl organometallic reagents to aryl aldehydes followed by oxidation.[7] However, the methyl organometallic reagents readily cause the issue of functional group tolerance. Recently, aldehyde C–H functionalization has emerged as a robust method for the preparation of ketones,[8] albeit remaining an unmet challenge for the synthesis of aryl methyl ketones. The development of one-step methylation of aryl aldehyde C–H bonds for the construction of aryl methyl ketones is highly desirable, as this is an atom-, and step- economic transformation, and aryl aldehydes are inexpensive, stable, and widely available feedstocks.[9] However, the similar polarities of the starting material and the methylated product lead to the difficulty of isolation and purification of the product when unreacted starting material remains.[10] With this in mind, our ultimate strategy involved the use of an intermediate readily available from an aryl aldehyde, which clearly differentiates the product from the starting material in terms of polarity, while being easily transformed to aryl methyl ketone. Cinnamic acid, which is easily prepared from Knoevenagel reaction of aryl

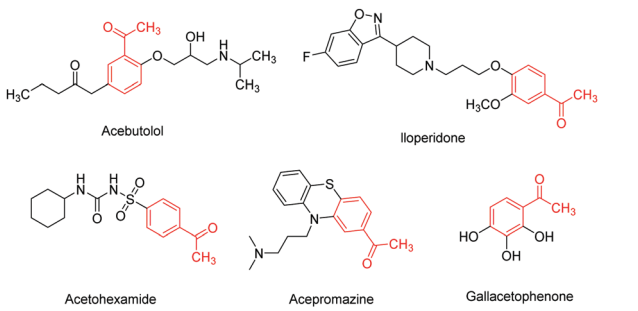

Fig. 1 Small-molecule drugs containing acetophenone skeletons.

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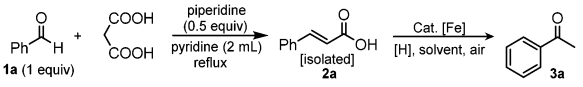
aldehyde and malonic acid can undergo decarboxylation to give olefin.[11] Recently, our group reported a highly efficient iron-catalyzed Wacker-type oxidation, which is suitable for late-stage oxidation.[12] Collectively, it is possible to realize the oxidation of cinnamic acid to form an aryl methyl ketone through decarboxylation and then oxidation under iron catalysis. Herein we demonstrate an iron catalyzed aerobic oxidation of α, β-unsaturated carboxylic acids from Knoevenagel transformation of aldehydes and malonic acid to produce methyl ketones. It features inexpensive and nontoxic reagents, excellent functional group tolerance, and application to late-stage oxidation of complex small molecules.

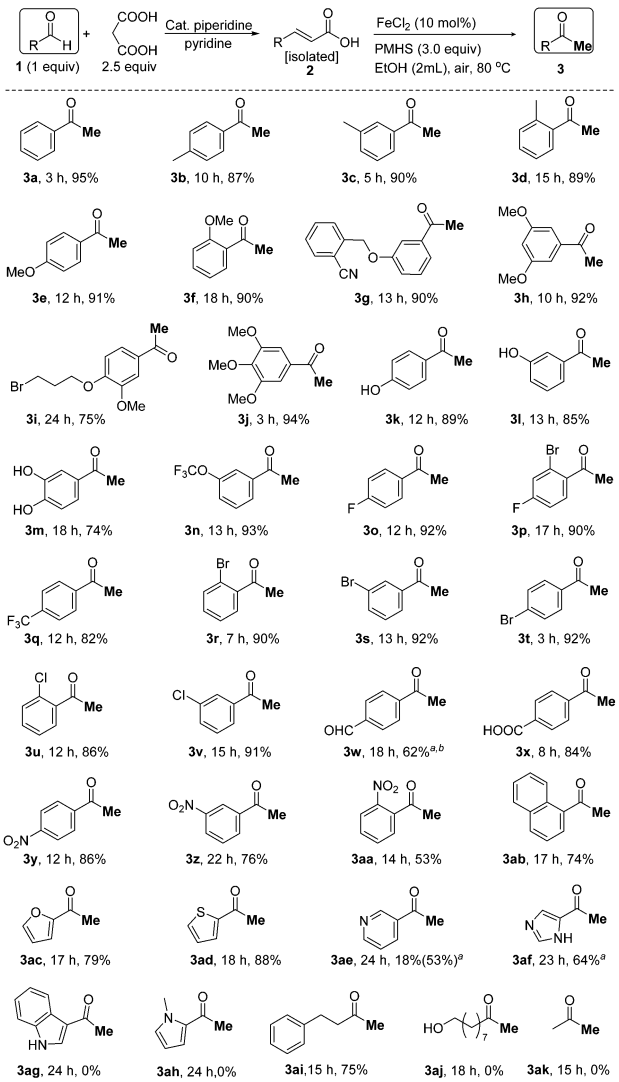
Inspired by our recent studies on bioinspired iron catalysis,[12,13] we first studied the reaction of cinnamic acid **2a** (from benzaldehyde **1a**). To our delight, the desired product acetophenone **3a** was obtained in 45% yield in ambient air and at 80 °C in the presence of 10 mol% $FeCl_3$ and 3 equiv. PMHS (polymethylhydrosiloxane) in EtOH (Table 1, entry 1). Encouraged by this result, we tested a series of other iron catalysts [$FeCl_2$, $Fe(acac)_2$, ferrocene, FePc and $FeSO_4{\cdot}7H_2O$], and found that $FeCl_2$ resulted in a much better yield (95%) (entries 1–6). No desired product was observed when the reaction was carried out under N_2 atmosphere or in the absence of either the iron catalyst or of PMHS (entries 7–9). The use of $(EtO)_3SiH$, TMDSO (1,1,3,3-tetramethyldisiloxane), DEMS (diethoxymethylsilane) or Et_3SiH instead of PMHS gave a much poorer result (entries 10–13). Replacing EtOH with ^{i}PrOH, ^{t}BuOH, DMF, 1,4-dioxane or MeCN led to a much lower yield (entries 14–18). The yield significantly diminished when the reaction temperature was decreased from 80 °C to 50 °C (entry 19).

Table 1 Aerobic oxidation of **2a**[a]



Entry	[Fe]	[H]	Solvent	Yield of **3a**[b] (%)
1	$FeCl_3$	PMHS	EtOH	45
2	**$FeCl_2$**	**PMHS**	**EtOH**	**95**
3	$Fe(acac)_2$	PMHS	EtOH	11
4	Ferrocene	PMHS	EtOH	10
5	FePc	PMHS	EtOH	0
6	$FeSO_4{\cdot}7H_2O$	PMHS	EtOH	0
7	—	PMHS	EtOH	0
8	$FeCl_2$	—	EtOH	0
9[c]	$FeCl_2$	PMHS	EtOH	0
10	$FeCl_2$	$(EtO)_3SiH$	EtOH	34
11	$FeCl_2$	TMDSO	EtOH	38
12	$FeCl_2$	DEMS	EtOH	32
13	$FeCl_2$	Et_3SiH	EtOH	0
14	$FeCl_2$	PMHS	^{i}PrOH	6
15	$FeCl_2$	PMHS	^{t}BuOH	18
16	$FeCl_2$	PMHS	DMF	45
17	$FeCl_2$	PMHS	1,4-Dioxane	0
18	$FeCl_2$	PMHS	MeCN	0
19[d]	$FeCl_2$	PMHS	EtOH	5

[a] Reaction conditions (unless otherwise stated): **2a** (0.25 mmol), [Fe] (0.025 mmol, 10 mol%), [H] (0.75 mmol), solvent (2.0 mL), 80 °C, 3 h, and air. [b] Isolated yields. [c] Under N_2 atmosphere. [d] 50 °C.



Scheme 1 Oxidation of α,β-unsaturated carboxylic acids compounds **2** from aryl aldehydes **1** into aryl methyl ketones **3** by air. Reaction conditions (unless otherwise stated): **2** (1 equiv.), $FeCl_2$ (10 mol%), PMHS (3 equiv.), EtOH (2.0 mL), 80 °C, and air. [a]$FeCl_2$ (30 mol%). [b]*t*BuOH. (2.0 mL)

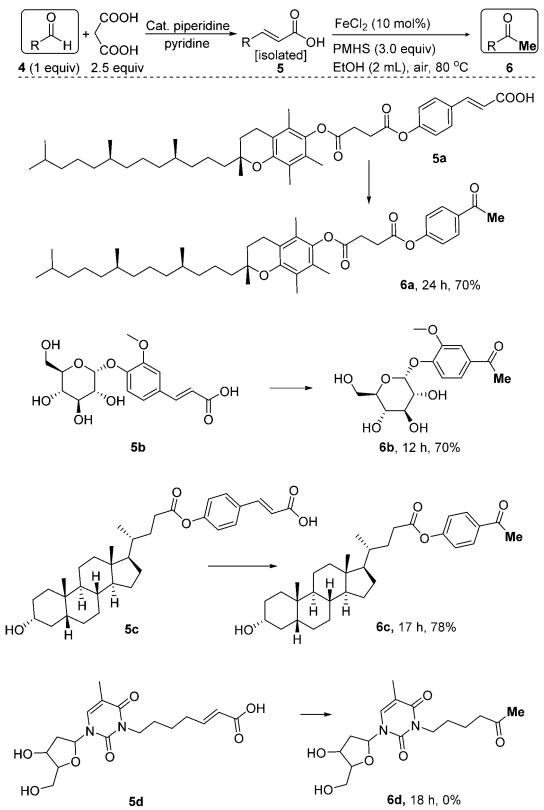
Under the optimized reaction conditions, we assessed the scope of the methodology (Scheme 1). Electron-neutral (**2a**), electron-rich (**2b–2n**), and electron-withdrawing (**2o–2aa**) cinnamic acid compounds were competent substrates and were found to provide desired products in good to excellent yields. The positions of the substituents such as methyl, methoxy, bromine, chloro and nitro, on the phenyl ring almost did not affect the reactivity (**3b–3f**, **3r–3v**, **3y–3aa**). In particular, it is noteworthy that the reactive groups like phenolic hydroxy, aldehyde, and carboxyl (**3k–3m**, **3w**, and **3x**) did not reduce the efficacy of the reaction, which is rare in oxidation reactions. Furthermore, the reaction can move beyond the simple phenyl group. For instance, substrates containing naphthalene, furan, thiophene, pyridine, and imidazole (**3ab–3af**) proceeded well. Gratifyingly, under the same reaction conditions, aliphatic acrylic acid also afforded the desired product in good yield (**3ai**, 75%). However, 3-indoleacrylic acid (**2ag**), (*E*)-3-(1-methyl-1*H*-pyrrol-2-yl)acrylic acid (**2ah**),

(*E*)-10-hydroxy-2-decenoic acid (**2aj**), and crotonic acid (**2ak**) failed to undergo the decarboxylation-oxidation.

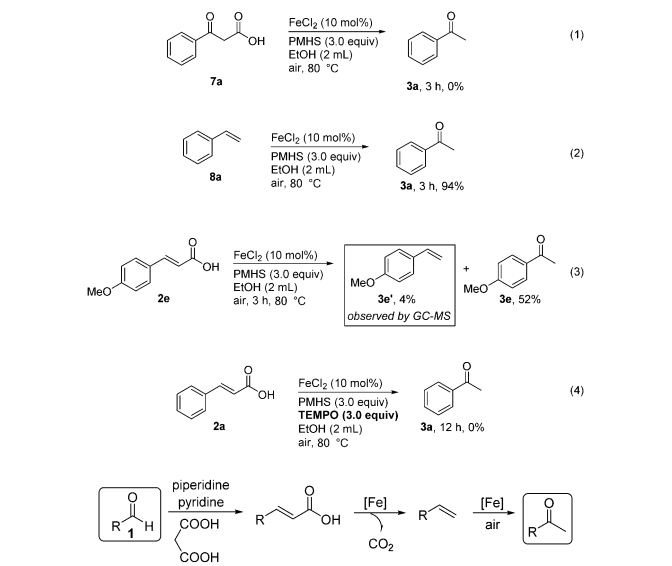
Furthermore, the robustness of this protocol was evaluated in the late-stage oxidation of an array of complex bioactive molecules (Scheme 2). Bioactive compound **5a** containing a vitamin E fragment[14] was selectively oxidized to the corresponding ketone **6a** in 70% yield. Notably, an unprotected carbohydrate fragment[15] in **5b** was compatible with the reaction conditions and produced ketone **6b** in a satisfactory yield (70%). Lithocholic acid-derived substrate **5c** bearing a hydroxy group[16] was also easily oxidized to the desired product **6c** in high yield. These examples revealed the potential and modularity of our protocol in bioactive molecule late-stage functionalization to quickly generate diverse bioactive aryl methyl ketones, which will surely facilitate the related structure–activity relationship (SAR) investigations in drug discovery.[1h,17] Unfortunately, a complex aliphatic α,β-unsaturated carboxylic acid **5d** did not give the desired product **6d**.

To gain a preliminary insight into the process of the transformation, control experiments were carried out. Recently, we demonstrated the iron-catalyzed Wacker-type oxidation.[12] This work implied that the present transformation may proceed through Wacker-type oxidation of α,β-unsaturated carboxylic acids into β-keto acids, which readily undergo thermal decarboxylation to give methyl ketones.[18] To check this mechanism in our case, β-keto acid **7a** was employed as the substrate but did not give the desired product (eqn (1)), thus indicating that the process of oxidation and then decarboxylation is not involved in the reaction. It is well-known that α,β-unsaturated carboxylic acids can undergo decarboxylation to form olefins.[11] Furthermore, we performed the reaction of styrene **8a** under the standard reaction conditions (eqn (2)) and observed that the desired acetophenone **3a** was produced in 94% yield, consistent with the result of the reaction of cinnamic acid **2a**. We further conducted oxidation of (*E*)-3-(4-methoxyphenyl) acrylic acid (**2e**) under normal reaction conditions. Minor 4-methoxystyrene was observed using GC-MS (see the ESI†) when the reaction is quenched before full conversion (eqn (3)). CO_2 was also detected using GC (see the ESI†). The decarboxylation of α,β-unsaturated carboxylic acids proceeded well at a relatively low temperature (80 °C), suggesting that a radical pathway may be involved in the decarboxylation process.[11] When a radical inhibitor, TEMPO, was added to the model reaction system, the reaction was completely inhibited (eqn (4)), supporting the radical process. These results suggest that the transformation proceeds *via* decarboxylation of α,β-unsaturated carboxylic acids to the olefins and subsequent oxidation of the olefins to methyl ketones (Scheme 3). The role of PMHS is demonstrated in our previous study and acts as a hydride donor and a reducing agent in the step of iron-catalyzed oxidation of olefins.[12]

Although styrenes can be used as the substrates in the present reaction and are available from Wittig reactions of aryl aldehydes, they easily undergo polymerization and oxidative cleavage; and the Wittig transformation often requires a strong base, such as RLi, *t*BuOK or $NaNH_2$, thus leading to a tedious operation caused by using air-free techniques and dry solvent. In contrast, cinnamic acids are more stable and inexpensive, and easily prepared from Knoevenagel transformation of aldehydes and malonic acid, and readily removed from a reaction mixture.



Scheme 2 Late-stage functionalization of complex molecules. Reaction conditions (unless otherwise stated): **5** (1 equiv.), $FeCl_2$ (10 mol%), PMHS (3 equiv.), EtOH (2.0 mL), 80 °C, and air.



Scheme 3 Reaction process.

In conclusion, we have developed an operationally simple and efficient iron catalyzed domino decarboxylation-oxidation of α,β-unsaturated carboxylic acids enabled aldehyde C–H methylation for preparing diversified methyl ketones. This two-stage methylation, rather than direct methylation, is helpful for product purification. This method is compatible with sensitive functional groups, which will be damaged in oxidation, ionic or polar reactions. Importantly, this toolbox can be applied to the late-stage modification of complex small molecules. Further work will be dedicated to the use of the method for the synthesis of complex molecules and to study the detailed mechanism.

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Conflicts of interest

There are no conflicts to declare.

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