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Decarboxylative chlorination of α,β -unsaturated acids

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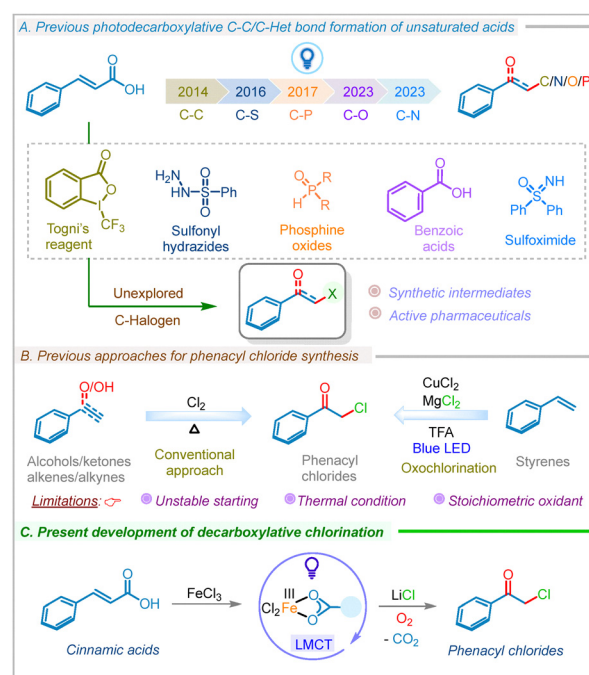
Herein, an unprecedented oxidative decarboxylative chlorination of α,β -unsaturated acids for α -chloroketones is reported. This green and sustainable approach employs Fe(III)-catalyzed LMCT to generate a chloride radical from non-hazardous LiCl under violet light irradiation. Molecular oxygen serves as the oxygen source for the ketone group, while naturally abundant unsaturated acids replace unstable alkenes or alkynes, enabling efficient and eco-friendly synthesis of α -phenacyl chlorides.

Visible light induced decarboxylative functionalization of carboxylic acids and their derivatives has emerged as a powerful and versatile approach for small molecule activation.¹ This strategy unveiled unprecedented chemical conversion in diverse carbon-carbon (C-C) and carbon-heteroatom (C-Het) bond-forming reactions under mild conditions with CO₂ as a traceless byproduct. These radical-relay processes often help to overcome the stringent reaction parameters and stoichiometric oxidant usage in classical and conventional catalytic decarboxylation trials.² Among the diverse carboxylic acids, α,β -unsaturated carboxylic acids have garnered significant interest from organic chemists for their versatility as synthetic analogs for alkyl, alkene, or keto-methyl sources, along with their abundant feedstock availability.³

In 2014, the Zhu group pioneered a photo-decarboxylative C-C bond-forming reaction for unsaturated acids, employing Togni's reagent to synthesize fluoromethylated alkene moieties (Scheme 1A).⁴ In the following years, different groups, including ours, have reported diverse C-C cross-coupled alkylation, arylation and fluoromethylated products from biomass derived unsaturated acids under photocatalytic conditions.^{5,6} Beyond C-C cross-coupling, subsequent development on several decarboxylative C-Het strategies have also been reported in recent years (Scheme 1A).⁷ Photo-decarboxylative cross-coupling of α,β -unsaturated acids with heteroatoms such as sulfur, phosphorus,

oxygen, and nitrogen predominantly yields alkenyl or β -keto systems. Despite these significant advancements in decarboxylative C-C and C-Het bond-forming methodologies for α,β -unsaturated acids, the photocatalytic cross-coupling of unsaturated acids with halides to generate C-halogen bonded products remains unexplored.

Halides, especially chloride atoms, are present in at least 50% of industrial chemicals and polymers, as well as in 20% of pharmaceutical compounds.⁸ Among the various possible chloride systems derived from α,β -unsaturated acids, α -chloroketones serve as essential building blocks in synthetic chemistry, with significant applications in agrochemicals, pharmaceuticals, and synthetic precursors.⁹ Conventional synthetic approaches for



Scheme 1 Photo-decarboxylation of α,β -unsaturated acids.

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α -chloroketones, including direct halogenation of ketones and oxidative halogenation of alcohols, alkenes, or alkynes, are hindered by thermal conditions, reliance on elemental chlorine and the intrinsic instability of alkene and alkyne substrates (Scheme 1B).¹⁰

In 2020, the Zhu group pioneered visible-light-irradiated α -haloketone synthesis using non-hazardous KCl as a chloride source, while the Zhang group demonstrated a similar transformation of α -haloketones from styrenes employing ruthenium photocatalysis.¹¹ Most recently, the Cai group introduced a copper-catalyzed ligand-to-metal charge transfer (LMCT) strategy for synthesizing α -chloroketones from alkenes (Scheme 1B).¹² In spite of significant advancements in photocatalytic methodologies, their utility is often hindered by the multi-step syntheses and the inherent instability of alkene substrates. Therefore, the direct synthesis of α -chloroketones from readily available and bench-stable α,β -unsaturated acids remains a challenging and largely unexplored area (Scheme 1C). Herein, we present the halogenation of α,β -unsaturated acids through a photo-decarboxylative oxychlorination pathway using non-hazardous LiCl and the sustainable FeCl₃ catalyst.

We initially optimized the reaction parameters for the photo-decarboxylative chlorination of unsaturated acids, using commercially available cinnamic acid (**1a**) as the model substrate (Table S1; see the SI). The abundant and inexpensive FeCl₃ photocatalyst (10 mol%), along with a stoichiometric amount of LiCl as the chloride source and KH₂PO₄ as the buffering agent in acetonitrile, was employed for the transformation. Under 40 W of 390 nm violet LED irradiation in ambient conditions, this setup afforded the desired phenacyl chloride (**2a**) in 51% yield, along with 28% of benzaldehyde (**2aa**) as a by-product (Table 1, entry 1). Screening of different solvents under iron photocatalytic conditions diversified oxychlorination reactivity and acetonitrile was found to be the best solvent to yield the desired α -chloroketone (see the SI, Table S1). Other commercially available iron, cobalt, and copper salts failed to demonstrate catalytic superiority under similar conditions and remain ineffective (Table 1, entries 2–4; see the SI for details). Remarkably, the

catalytic combination of tetrabutylammonium chloride (TBACl, 10 mol%) with LiCl led to a significant enhancement in the yield of α -chloroketone (**2a**) up to 82% (Table 1, entry 5). Various control experiments highlighted the crucial roles of the FeCl₃ photocatalyst, the phase-transfer agent TBACl, the KH₂PO₄ additive, molecular oxygen, and violet LED irradiation in facilitating the present decarboxylative C–Cl cross-coupling reaction (Table S1, see the SI). After scrupulous exploration, 1 equiv. of cinnamic acid (**1a**), 1 equiv. of LiCl, 10 mol% of FeCl₃, 10 mol% of TBACl and 1 equiv. of KH₂PO₄ in MeCN under irradiation with 390 nm 40 W violet LED light under ambient atmosphere were found to be the optimal conditions for the synthesis of the desired α -chloroketone product (**2a**; Table 1, entry 5).

The substrate scope of this reaction was investigated using a range of α,β -unsaturated acid (**1**) derivatives under the optimized conditions (Table 2). Cinnamic acid derivatives bearing electron donating *para* substituents (e.g., Me, ^{*i*}Pr, ^{*t*}Bu, OMe; **1a–1e**) were well tolerated, delivering the corresponding α -chloroketones (**2a–2e**) in good to high yields (58–76%). Halogen-substituted acid derivatives (–F, –Cl, –Br; **1f–1h**) also underwent efficient

Table 1 Optimization of the chlorination reaction (**2a**)^a

Entry	Condition	Yield (%) (2a / 2aa) ^b
1	FeCl ₃ , LiCl, KH ₂ PO ₄ , MeCN	51/28
2	FeCl ₂ instead of FeCl ₃	39/25
3	Fe(acac) ₃ instead of FeCl ₃	7/0
4	CuCl ₂ instead of FeCl ₃	17/08
5	FeCl₃, LiCl, TBACl, KH₂PO₄, MeCN	82/05
6	Without FeCl ₃	NR
7	Without LiCl	8/trace
8 ^c	Dark reaction	NR

^a Conditions: 0.25 mmol **1a**, 10 mol% photocatalyst, 0.25 mmol LiCl, 10 mol% TBACl, 0.25 mmol additive, and solvent (1.5 mL) for 12 h under ambient atmosphere. ^b GC yield.

Table 2 Scope of decarboxylative chlorination^a

Substrates variation	
2a ; 76%	2b ; 63%
2c ; 66%	2d ; 65%
2e ; 58%	2f ; 82%
2g ; 78%	2h ; 77%
2i ; 84%	2j ; 81%
2k ; 82%	2l ; 62%
2m ; 62%	2n ; 81%
2o ; 76%	2p ; nr
2q ; 47%	2r ; 77%
2s ; 60%	2t ; 78%
2u ; 46%	2v ; 70%
2w ; 73%	2x ; 8% ^b
2y ; 46%	2z ; 51%
2za ; 62%	2zb ; trace
2zc ; nr	2zd ; trace
2ze ; trace	2zf ; nr

^a Conditions: 0.25 mmol **1**, 10 mol% FeCl₃, 0.25 mmol LiCl, 10 mol% TBACl, 0.25 mmol KH₂PO₄, and MeCN (1.5 mL) for 12 h under ambient atmosphere. ^b All yields are isolated (**2x** is GC yield).

decarboxylative C–Cl coupling to furnish phenacyl chloride products (**2f–2h**, 77–82% yields). Furthermore, electron-withdrawing *para* substituents (–CF₃, –OCF₃, –CN, –NO₂) showed excellent reactivity, delivering the desired products (**2i–2l**) in up to 86% yields. We also evaluated electron rich and halogen substituents at the *meta* and *ortho* positions of cinnamic acid under standard conditions (**1m–1r**). Electron-withdrawing groups demonstrated superior reactivity, while substrates bearing a free hydroxyl group (**1p**) proved inefficient for the present transformation (**2m–2r**, 47–81% yield). Gratifyingly, di- and tri-substituted as well as bicyclic α,β -unsaturated acids were well tolerated under the reaction conditions, affording the desired products (**2s–2w**) in moderate to good yields (46–78%). Interestingly, α -methyl-cinnamic acid (**1x**) afforded the desired secondary halide product **2x** in very low yield (8%). Additionally, sulfur-containing thiopheneacrylic acid derivatives were well tolerated under the standard conditions, affording the desired chlorinated products (**2y–2za**) in moderate to good yields (46–62%). In contrast, oxygen and nitrogen containing heterocyclic unsaturated acids (**1zb–1zc**) remained unreactive under the same conditions. Meanwhile, a series of aliphatic conjugated acrylic acids (**1zd–1zf**) remained dormant under the standard conditions.

The present iron-catalyzed photo-decarboxylative α -chloroketone synthesis was successfully tested on a 5 mmol scale, yielding **2f** and **2i** with excellent isolated yields of 67% and 68%, respectively (Fig. 1a). Furthermore, to highlight the synthetic utility of this method, the chlorinated products were transformed into structurally complex and bioactive molecules (Fig. 1b). The base-promoted nucleophilic dehydroxylative annulation of phenacyl chloride (**2a**) with 2-aminopyridine (**3**) led to the formation of 2-arylimidazo[1,2-*a*]pyridine (**4**), a pharmaceutically active anticancer agent (Fig. 1b-i).¹³ Similarly, the reaction with 2-aminopyrimidine (**5**) afforded 2-phenylimidazo[1,2-*a*]pyrimidine (**6**), a compound relevant to the treatment of CNS disorders (Fig. 1b-ii).¹³ Subsequently, we expanded the modification of **2a** to a bioactive α -ketoamide (**8**) and an antibacterial 2-phenylquinoxaline (**10**) from aniline (**7**) and *o*-phenylenediamine (**9**), respectively (Fig. 1b-iii, iv).¹⁴

We then explored the mechanistic details of the photo-decarboxylative oxychlorination reaction by performing a series

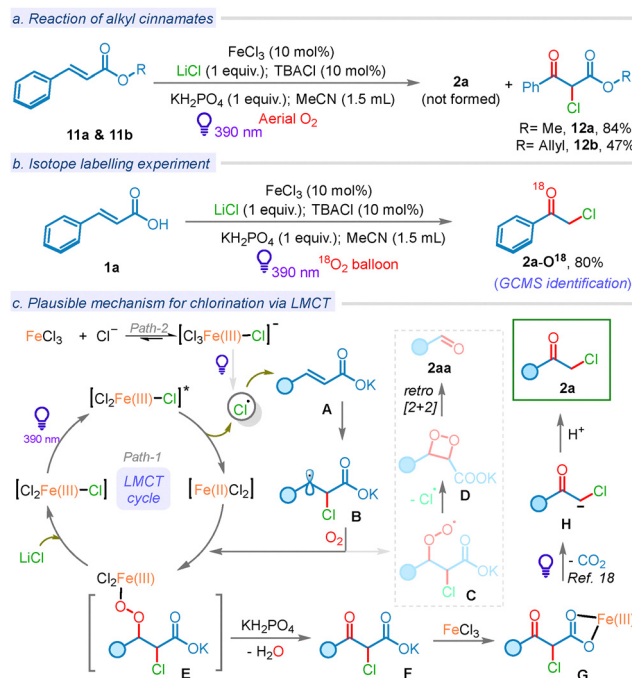


Fig. 2 Mechanistic insight and photocatalytic cycle.

of control experiments (Fig. 2). The reactions of cinnamate esters (**11a** and **11b**) were initially carried out under standard conditions, yielding oxidative chlorinated products (**12a** and **12b**) (Fig. 2a). This result suggested that the olefinic moiety of esters reacts similarly to that of acids; however, the decarboxylation step requires the presence of a free carboxylic acid group. The reaction proceeded smoothly under an atmosphere of O¹⁸-labelled oxygen, with the formation of an O¹⁸-labelled product (**2a–O¹⁸**) and H₂O¹⁸ as the sole byproduct, indicating atmospheric oxygen plays a key role in the reaction mechanism (Fig. 2b).^{6,7g,7i} UV-visible spectra in MeCN showed enhanced absorption of photoexcited FeCl₃ (λ_{max} = 237 nm) upon the addition of LiCl and TBACl, indicating inner-sphere LMCT involvement under 390 nm violet LED irradiation (see the SI).¹⁵

Based on the experimental evidence and literature reports, a radical mechanism is proposed in Fig. 2c.^{11a,16,17} The reaction is initiated by the photolytic cleavage of excited FeCl₃ under violet light *via* a LMCT process, generating FeCl₂ and a chloride radical (Cl[•]) (Path-1). A similar radical species could also be generated from FeCl₄[–], followed by the regeneration of the metal catalyst (Path-2).¹⁵ The generated Cl[•] radical adds to the double bond of the potassium cinnamates **A**, forming intermediate **B**, which is subsequently trapped by O₂ either to generate benzaldehyde **2aa** *via* peroxo intermediates **C** and **D**, or to propagate towards FeCl₂ to form intermediate **E**. In the presence of LiCl and KH₂PO₄, intermediate **E** is dehydroxylated to convert the β -ketone intermediate **F** with the restoration of FeCl₃. Species **F** attaches with FeCl₃ to generate the chelated adduct **G**. Subsequent photo-decarboxylation of intermediate **G** generates anionic species **E**, which is readily protonated to yield the desired oxychlorinated product **2a**.¹⁸

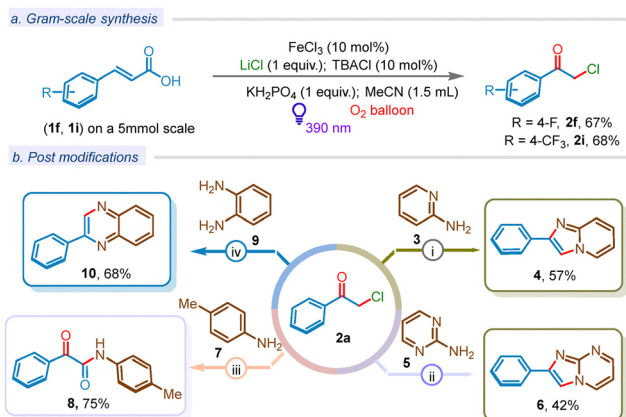


Fig. 1 Applications of decarboxylative chlorination.

In summary, we present a novel oxidative decarboxylative iron-photocatalyzed C–Cl cross-coupling strategy for the efficient synthesis of α -chloroketones from α,β -unsaturated acids. This green and sustainable approach leverages abundant and cost-effective FeCl_3 as a photocatalyst, non-toxic LiCl as the chlorine source, and molecular oxygen as the ketone oxygen donor. Mechanistic studies revealed that decarboxylation is an essential step for free carboxylic acids and O^{18} -labelling experiments identifying atmospheric oxygen as the ketone source. UV-vis spectroscopy further supports LMCT activation of FeCl_3 in the presence of LiCl and TBACl under violet LED light irradiation. The broad substrate scope, including electron donating and withdrawing groups, as well as bicyclic and heterocyclic systems, highlights the versatility and efficiency of the present synthetic methodology.

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Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the SI.

Detailed reaction optimization, NMR, HRMS, GC-MS *etc.* See DOI: <https://doi.org/10.1039/d5cc03038b>.

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