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Copper-catalyzed photoinduced carbonylation of C1-C3 gaseous alkanes

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The catalytic conversion of carbon monoxide (CO) provides an enormous opportunity to construct carbonyl-containing molecules. Among them, the direct carbonylation of C-H bonds on gaseous hydrocarbon feedstocks provides a straightforward approach to access industrially important short-chain carboxylic acid derivatives. Here, we report a general and mild direct carbonylation of methane, ethane, and propane under blue LED irradiation at ambient temperature, enabling the direct formation of short-chain carboxylic acid derivatives. Notably, the direct carbonylation of ethane offers the potential for a more cost-efficient route to produce MMA. The combination of copper reduction and chlorine radical released via a ligand-to-metal charge transfer (LMCT) process facilitates the activation of gaseous hydrocarbon in a mild and atom-economical mode.

As a versatile C1 feedstock, the transformation of carbon monoxide (CO) provides a potent approach to accessing carbonyl-containing fine chemicals.[1–4] Especially, due to their important applications in chemical industry and organic chemistry, the production of short-chain carboxylic acids is of great significance. Millions of tons of industrially important short-chain carboxylic acids and their derivatives are produced each year. Among these, most of the world's acetic acid production is based on methanol carbonylation, one of the most successful industrial applications of homogeneous transition metal catalysis.[5,6] In addition, methyl methacrylate (MMA) is a monomer produced on a large scale for the production of poly(methyl methacrylate) (PMMA), with the annual global MMA market reaching approximately 4 million tonnes. Currently, ethylene carbonylation has gained attention due to its cost-effectiveness and high atom-economy (Fig. 1a).[7] Moreover, these processes often rely on the rarest transition metal catalysts (e.g., rhodium, iridium, or palladium) on the planet. Conventionally, the production of carboxylic acid derivatives through homogeneous catalysis carbonylation predominantly originates from commercial alcohols,[5,6] organic halides,[8–13] or olefins.[14–18] From the perspective of developing new synthetic methodologies, it is crucial to find more economical and readily available starting materials. In contrast, substantial advantages can be foreseen in the prospective by using simple gaseous hydrocarbon feedstocks as carbonylation substrates to produce carboxylic acids and their derivatives. For example, ethane presents clear cost-effectiveness advantages compared to other C2 carbon-based feedstocks (Fig. 1b).

Gaseous alkanes are abundant in nature and play an indispensable role as one of the most vital carbon-based resources in both the global chemical industry and research laboratories (Fig. 1c).[19–22] With the soaring production of natural gas, these gaseous alkanes have become more economically attractive as basic raw materials.[23,24] In recent years, the direct conversion of gaseous alkanes into high value-added bulk chemicals using various efficient catalytic processes has been a key objective and attracted widespread attention.[25–29] Despite the numbers methodologies established for the carbonylation of liquid alkanes,[30–33] the carbonylation of gaseous alkanes to short-chain carboxylic acid derivatives is still limited.

A major obstacle arises from the lower reactivity of gaseous alkanes, which is caused by their stronger C-H bonds (bond dissociation energy (BDE) = 99–105 kcal/mol), compared to most liquid alkanes (Fig. 1d). Additionally, gaseous alkanes have very low polarity, due to the similar electronegativity values of carbon and hydrogen ($\chi_C = 2.1$; $\chi_H = 2.5$). Traditionally, gaseous alkanes are converted into more reactive alkyl electrophiles to release their reactivity via halogenation at elevated temperatures (>500 °C) or light irradiation conditions.[34,35] Furthermore, the direct functionalization of gaseous alkanes typically occurs under extreme conditions (e.g., high temperature, superacids, or powerful oxidants)[36–38] or noble metal catalysts.[39,40] However, these processes are limited by factors such as

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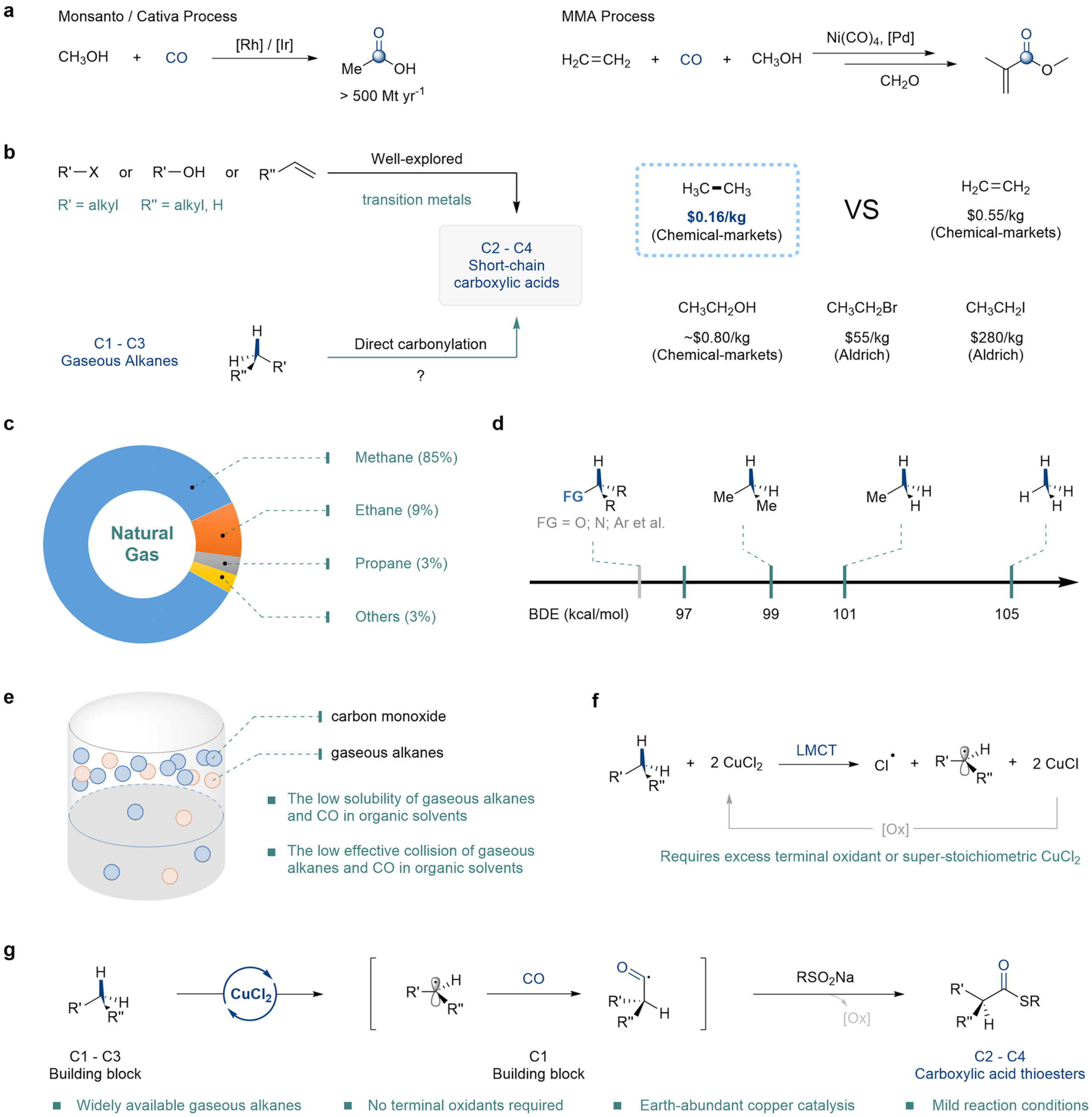


Fig. 1 | Background and introduction of C1-C3 gaseous alkanes carbonylation. **a** Application examples of CO in industrial synthesis. **b** General strategies for the synthesis of short-chain carboxylic acid derivatives by carbonylation. **c** Distribution of C1-C3 gaseous alkanes in natural gas. **d** Bond dissociation energy (BDE) of various gaseous alkanes. **e** The low solubility and competition of gaseous starting materials in organic solvents. **f** A net oxidative process in photoinduced ligand-to-metal charge of $CuCl_2$. **g** This work, a copper-catalyzed C1-C3 gaseous alkanes carbonylation via photoinduced ligand-to-metal charge transfer. MMA, methyl methacrylate, production volume not yet announced.

poor economic feasibility, harsh reaction conditions, environmental concerns, and harmful halogen emissions. In addition, the limited gas-liquid mass transfer of gaseous reagents (e.g., gaseous alkanes and carbon monoxide) in organic solvents significantly reduces effective collision with suitable catalysts and reaction partners (Fig. 1e). When multi-component gaseous reagents are involved in carbonylation reactions, these challenges are exacerbated due to the competitive dissolution and uneven distribution of gaseous molecules. In recent years, continuous-flow reactors have helped advance gas-liquid mass transfer technology to some extent.[41–44] Moreover, the chemoselective activation of various C-H bonds in solvents, carbonyl products, and gaseous alkanes adds another layer of complexity to the reaction.

In the past few decades, photoredox catalysis has rapidly developed and impacted various fields of scientific inquiry.[45–49] Considering potential photocatalysts, we turned our attention to 3d-metal chlorides, which can undergo photoinduced ligand-to-metal charger transfer (LMCT) to produce a chlorine radical.[50,51] We anticipated that $CuCl_2$ could promote alkanes C(sp^3)-H carbonylation; however, this is a net oxidative process that still requires a terminal oxidant (Fig. 1f).[52,53] In this article, we discovered that $CuCl_2$ can catalyze the C(sp^3)-H carbonylation of gaseous alkanes with sulfinate salts in the absence of any additional stoichiometric oxidants. This enables the selective C(sp^3)-H carbonylation of feedstock gaseous alkanes, such as methane, ethane, and propane, to synthesize value-added chemicals. Sulfinate salts were chosen as substrates for two key reasons. First, we hypothesized that the corresponding acyl radical could be intercepted by *S*-arylsulfonothioates to generate sulfonyl radical, which could act as a stoichiometric oxidant and regenerate as a substrate to participate in the next catalytic cycle. Additionally, sulfinate salts are readily available[54,55] and provide a simple entry to thioesters without the use of odorous sulfur-containing reagents.[56] Therefore, the advantages of gaseous alkanes and sulfinate salts make them both accessible and practical in organic chemistry.

Regarding the reaction design, we first hypothesized that the $CuCl_2$ complex could generate a highly active chlorine radical species, which undergoes a hydrogen atom transfer (HAT) process with gaseous alkanes, releasing a key carbon-centered radical intermediate.[52,53,57] The resulting highly reactive alkyl radicals, with nucleophilic properties, could then participate in radical addition to carbon monoxide at higher pressures,[30,41,58] which inhibits the formation of sulfides. A subsequent radical capture and single-electron oxidation complete the desired carbonylation process. Importantly, the current carbonylation protocol enables the coupling of two C1 fragments (CH_4 and CO), effectively combining them into C2 structural units, which offers great potential for future synthetic transformations. However, methane, among all gaseous alkanes, is the most difficult to activate due to its high bond energy and similar electronegativity between carbon and hydrogen. The reforming of methane typically requires elevated temperature, and its room-temperature functionalization remains a significant challenge.[59] In this protocol, the strong C-H bonds (BDE = 105 kcal/mol) of methane can be successfully cleaved, allowing carbonylation to generate acetic acid derivatives,[21,60,61] albeit in lower yields. We speculate that another factor could be the mass difference between methane and carbon monoxide, leading to methane's tendency to remain at the surface, reducing its interaction with the catalyst. Our protocol provides a general and mild carbonylative strategy for synthesizing short-chain carboxylic acid thioesters using gaseous alkanes as carbon-based feedstocks. Furthermore, the practicality of this protocol extends to the one-pot, two-step synthesis of methyl propionate, a precursor to methyl methacrylate (MMA), offering a more cost-efficient route for MMA production.

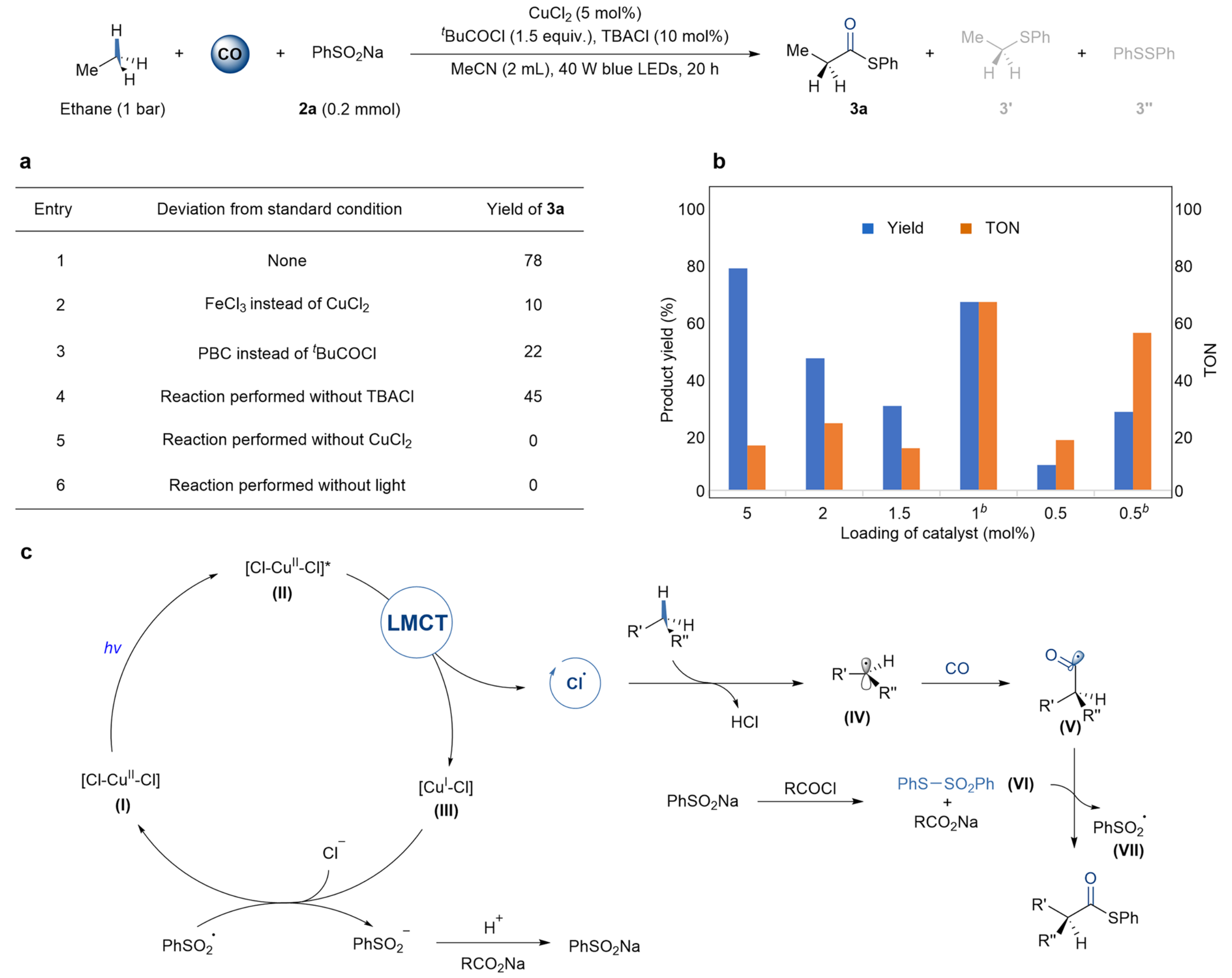
Results

To validate our hypothesis, we initiated the optimization of a model reaction between ethane (**1a**) and benzenesulfinic acid sodium salt (**2a**) in the presence of a catalyst cupric chloride and an acid chloride under blue LEDs irradiation conditions (Fig. 2a). Through systematic investigation of various reaction parameters, the optimal reaction conditions have been determined for the carbonylation of gaseous alkanes (see Supplementary Fig. 3 and Supplementary Table S1 for more details). Fortunately, the desired carbonylated product *S*-phenyl propanethioate **3a** was obtained in 78% yield when using $CuCl_2$ as a photocatalyst, pivaloyl chloride as an activating reagent for sulfinate salt, MeCN as a solvent, and under the irradiation of 40 W blue LEDs (Fig. 2a, entry 1). The common 3d-metal chlorides iron can also catalyze the carbonylation of ethane to access the target product, but only in 10% yield (Fig. 2a, entry 2). Alternative acid chloride, such as 4-bromobenzoyl chloride (PBC), gave a lower yield (Fig. 2a, entry 3). A moderate situation was reflected when performing this reaction in the absence of tetrabutyl ammonium chloride (TBACl) (Fig. 2a, entry 4). Afterwards, in the absence of light or photocatalyst, the desired reaction cannot be carried out, and a large amount of byproduct **3”** was detected (Fig. 2a, entries 5 and 6). Finally, reducing the catalyst loading to 1 mol% under 20 bar ethane resulted in a decreased yield of **3a** (68%) but with an increased turnover number (67 turnovers) relative to the standard conditions (Fig. 2b, entry 6).

Based on our experimental results and relevant literature,[50,53] a plausible photoinduced C-H carbonylative mechanism was proposed (Fig. 2c). Under light irradiation, the copper(II) complex **I** is excited to generate its excited state species **II**, which undergoes a single-electron oxidation of chloride and intramolecular LMCT process to afford the reduced copper(I) complex **III** and a highly active chlorine radical species. The resulting chlorine radical then undergoes a HAT process with the C-H bond of alkane to give a carbon-centered radical intermediate **IV**. Afterwards, the carbon radical will capture CO to produce acyl radical intermediate **V**. Meanwhile, the activation of sulfinate salt with pivaloyl chloride in situ delivers the key thiosulfonate intermediate **VI,**[55] which would react with the generated acyl radical to give the target product and a sulfonyl radical species **VII**. From the control experiment, it can be inferred that the sulfonyl radical could undergo a single-electron oxidation with the reduced copper(I) complex **III**, and then regenerate sulfinate salts.

Having successfully established the optimal reaction conditions, we further explored the versatility of this carbonylation methodology by using a variety of sulfinate salts and representative gaseous alkane feedstocks under standard conditions (Fig. 3). First, when using ethane as a C-H substrate, the current protocol was adaptable to various sulfinate salts with either electron-withdrawing substituents or electron-donating group on the benzene rings, delivering the desired carbonylated products **3a**-**3i** in moderate to good yields (50-80%). In particular, when the *para*-position of the benzene ring contained an iodine substitution, the reaction proceeded smoothly and iodine was retained (**3f**). This is disadvantageous in traditional transition-metal-catalyzed carbonylation reactions for synthesizing thioesters. Next, a variety of *ortho*- and *meta*-substituted sulfinate salts were prepared and employed for this reaction, as expected, they could successfully react with ethane and gave the corresponding products **3g**–**3p** in moderate yields. Among them, the introduction of *ortho*-substituents (-F, -OMe) on the benzene ring resulted in slightly lower yields due to steric hindrance effect (**3o**, 51%; **3p**, 43%). For heterocyclic sulfinate salt, sodium thiophene-2-sulfinate (**2r**), was also a suitable substrate for this transformation and the target product **3r** was isolated in 54% yield. To our delight, this catalytic protocol was also applicable to alkyl sulfinate salt, and the carbonylated product **3s** was obtained in 59% yield. As far as we know, alkyl substituted sulfinate salts are not preferred in the conversion of sulfinate salts to thiosulfonates. Additionally, methylsulfinate salt and ethylsulfinate salt were also tested here, but the corresponding products were not detected most likely due to their low boiling point. Subsequently, for less effective coupling partners, such as **3f, 3o, 3p**, and **3r**, significant improvements were observed by simply increasing the ethane pressure to 10 bar.

To further extend the versatility of the present carbonylation process, our interest then shifted to other gaseous alkanes. First, we turned our attention to propane, and a variety of similar isolated yields were obtained under standard conditions. Various sulfinate salts, such as phenyl, naphthyl, and thienyl, were all viable substrates to deliver the corresponding products **4a**–**4e** in moderate to good yields with two regioisomers (52–81%). Relevant literature indicated that the regioselectivity of alkyl radical generation by chlorine radicals from alkanes is generally dictated by the C-H bond energy, thus following a reaction trend of tertiary >secondary >primary.[62] However, no obvious advantage in the secondary carbon radical was observed in this carbonylation process, which may due to that terminal radical has steric advantage for CO capture. After successfully testing C2 and C3 gaseous alkanes, we shifted our focus to the carbonylation of methane. Methane is a prevalent gas and one of the most abundantly available carbon-based resources. To our delight, this $CuCl_2$-catalyzed photoredox system could enable the carbonylation of methane with sulfinate salts with separable yield. Both electron-withdrawing or electron-donating substituents on the *para* positions of the benzene rings



Entry	Deviation from standard condition	Yield of **3a**
1	None	78
2	FeCl$_3$ instead of CuCl$_2$	10
3	PBC instead of ^{t}BuCOCl	22
4	Reaction performed without TBACl	45
5	Reaction performed without CuCl$_2$	0
6	Reaction performed without light	0

Fig. 2 | Exploration of reaction conditions. a Optimization of the reaction conditions with ethane and substrate **2a** under blue light irradiation in the presence of CO, (**b**) Investigating the effect of catalyst loading on yield and TON, (**c**) Proposed mechanisms. ^{a} Ethane (1 bar), **2a** (0.2 mmol), CuCl$_2$ (5 mol%), ^{t}BuCOCl (1.5 equiv.), TBACl (10 mol%), MeCN (0.1 M), CO (49 bar), 40 W blue LEDs, r.t., 20 h. ^{b} Ethane (20 bar), CO (40 bar). TON turnover numbers, TBACl tetrabutyl ammonium chloride, PBC 4-bromobenzoyl chloride.

(**5a**–**5d**) could effectively provide acetyl sulfide products in our catalytic system. This exciting result highlighted the practicality of the protocol and provided an idea for efficient carbonylation of methane in the future. It's also been important to mention that low reaction efficiency and regioselectivity was observed when pentane and hexane was tested as the substrate here which require additional efforts to solve this challenge in the future.

To demonstrate the synthetic utility of this carbonylative reaction, scale-up and related transformation were performed (Fig. 4). Gratifyingly, the current protocol could be carried out on a 1 mmol scale with ethane and 5 mol% catalyst loading, giving the target product **3b** in a similar yield (74%, 133 mg; Fig. 4a). Subsequently, a strong electron acceptor diethyl azodicarboxylate (DEAD) was subjected to the standard conditions, and the corresponding target product **6** could also be obtained successfully in 43% yield (Fig. 4b). Next, we performed a one-pot, two-step, room-temperature protocol for the conversion of ethane to methyl propionate (Fig. 4c). Then, methyl propionate can condensate with formaldehyde followed by dehydration to deliver methyl methacrylate (MMA).[63] In addition, methyl propionate is used as a solvent for nitrocellulose and varnish, as well as a starting material for the production of other chemicals such as paints and varnishes.[64] The global demand for MMA is expected to reach 4 million tonnes in 2024. We further identified that installing C1 carbon monoxide gas on widely available gaseous alkanes is one of the most cost-effective strategies, and we believe it would bring enormous value.

To gain some insight into the generation of chlorine radicals in this photoinduced carbonylative reaction. First, 1-(*tert*-butyl)-4-vinylbenzene **9** was directly employed in the photoinduced copper-catalyzed LMCT system to produce vicinal dichlorination product **10** in 4% yield (Fig. 4d). Additionally, when several chloride-containing compounds were added to the transformation, the corresponding vicinal dichlorination product **10** were obtained in 9% (with 1 equiv. ^{t}BuCOCl), 20% (with 1 equiv. CuCl$_2$), and 14% (with 20 mol% TBACl) yields, respectively. In addition, it has been reported that photoinduced LMCT excitation of metal chlorides promotes the release of chlorine radical species, which can react with olefins to produce 1,2-dichloro products. It has been proven that the visible light-induced LMCT process promotes the release of chlorine radical species, and the reaction of chlorine radical with alkenes to produce 1,2-dichloride products is evidence of this.[57]

Next, we performed a variety of control experiments to capture the key intermediates in the copper-catalyzed C(sp^3)-H carbonylation

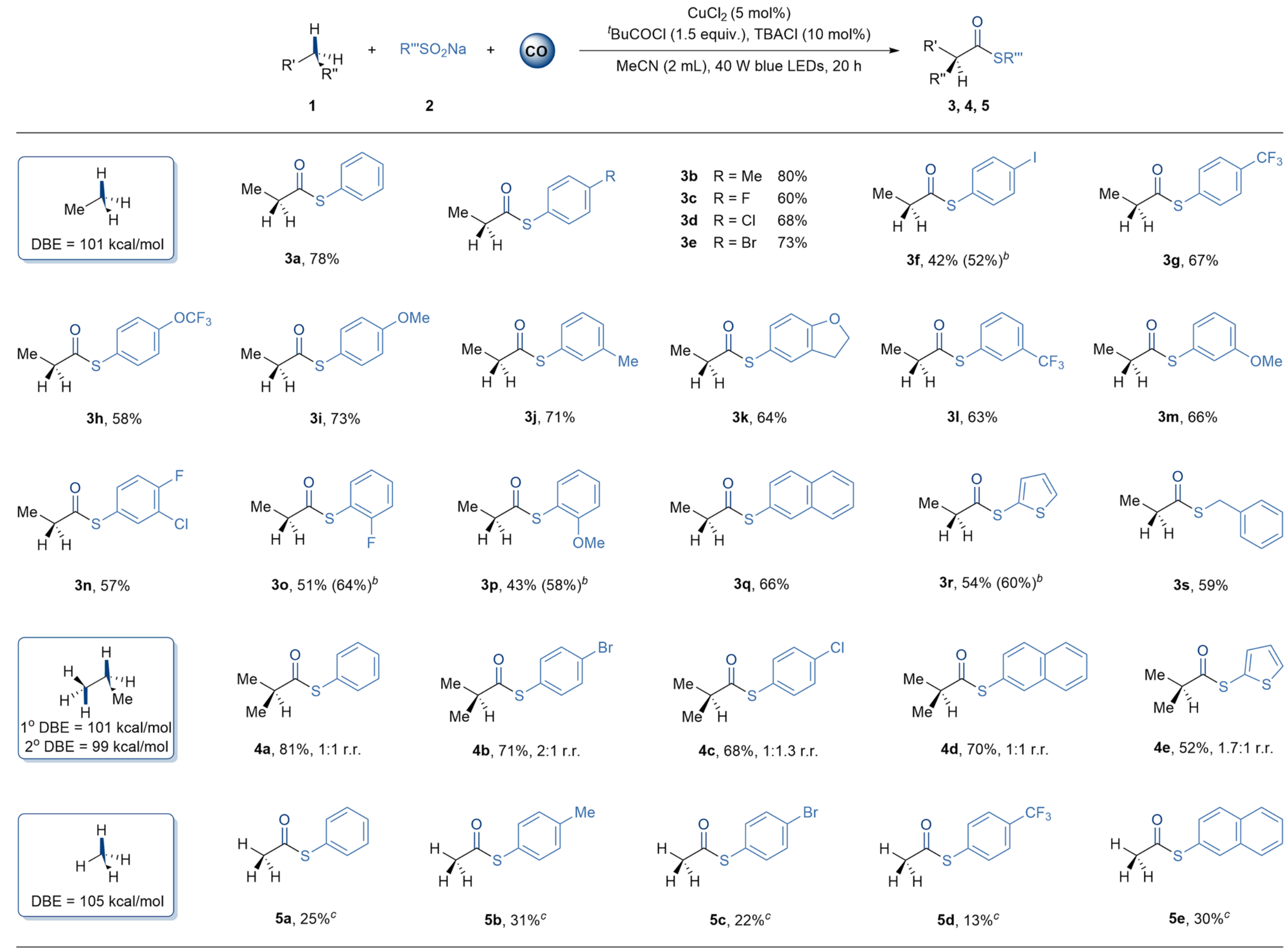


Fig. 3 | Evaluating the reaction scope.^{a} ^{a} General reaction conditions: **1** (1 bar), **2a** (0.2 mmol), CuCl$_2$ (5 mol%), ^{t}BuCOCl (1.5 equiv.), TBACl (10 mol%), MeCN (0.1 M) at r.t. for 20 h under CO (49 bar), irradiated by 40 W blue LEDs. ^{b} CuCl$_2$ (10 mol%), ethane (10 bar). CO (50 bar). ^{c} 0.1 mmol scale, CuCl$_2$ (10 mol%), methane (30 bar), CO (40 bar), MeCN (0.05 M). The regioisomeric ratios (r.r.) were determined by ^{1}H NMR analysis. All yields are isolated yields.

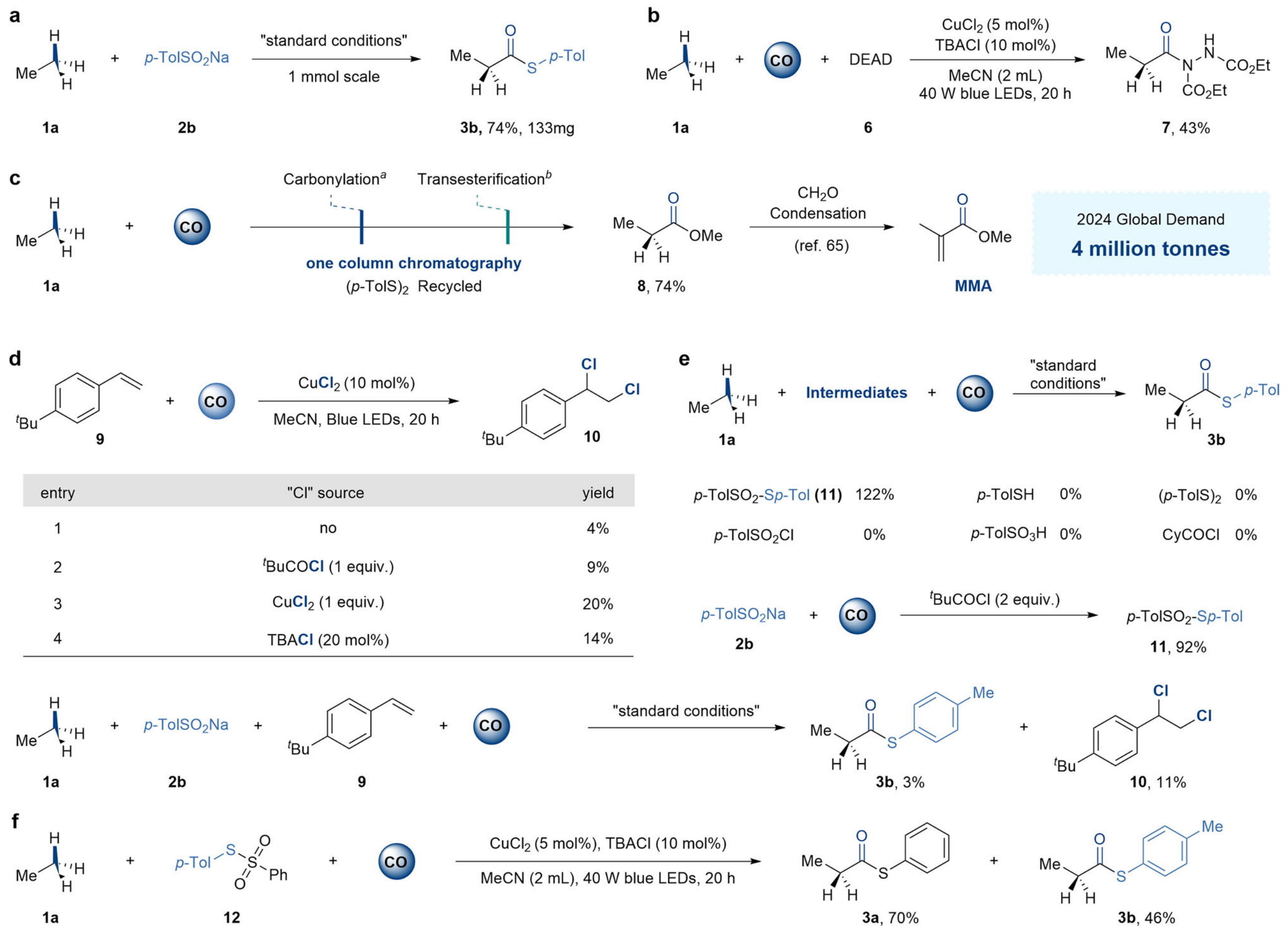
(Fig. 4e). The direct employment of thiosulfonate **11** with ethane and CuCl$_2$ into the current transformation under blue LEDs irradiation delivered the target product in 122% yield (based on 1 equiv. thiosulfonate **11**). In contrast, when other possible intermediates such as thiophenol, disulfide, sulfonyl chloride, and sulfonic acid, were used in this reaction, no target product was detected. Moreover, we also ruled out the possibility of generating acyl chlorides in the reaction. Interestingly, two equivalents of sulfinate salts could undergo a fast reaction under CO atmosphere to produce thiosulfonate **11** in 92% yield. Finally, to verify our hypothesis that sulfonyl radical could undergo single-electron reduction and regenerate into an active substrate to participate in the next catalytic cycle. *S*-(*p*-Tolyl) benzenesulfonothioate **12** was prepared and employed into the reaction, to our delight, it could react smoothly with ethane and delivered the corresponding products **3a** and **3b** in 70 and 46% yields, respectively, which confirmed our hypothesis above (Fig. 4f).

Discussion

We have developed a direct carbonylation protocol with CO as C1 source and C1-C3 gaseous alkanes as carbon-based feedstocks via photoinduced ligand-to-metal charge transfer. Given the abundance and low cost of the copper catalyst and starting materials, as well as the mild reaction conditions, we believe that this carbonylation process is highly attractive from a feedstock perspective. Gaseous alkanes represent some of the most cost- and atom-efficient reagents for producing high-value chemicals. However, they also pose unique challenges, including strong C-H bond dissociation energies (BDEs), limited gas-liquid mass transfer, competition, and chemoselectivity. In this process, the CuCl$_2$ catalyst undergoes LMCT to generate an active chloride radical, which acts as a HAT reagent, abstracting hydrogen atoms from alkanes. The resulting sulfonyl radical undergoes single-electron oxidation with the reduced copper(I) complex, regenerating the sulfinate salts. Finally, a one-pot, two-step, room-temperature protocol was successfully developed for the conversion of ethane to the industrially important compound methyl propionate (a precursor to methyl methacrylate, MMA).

Methods

General procedure for the carbonylation. A 4 mL screw-cap vial was charged with sulfinate salt (0.2 mmol), TBACl (10 mol%), CuCl$_2$ (5 mol%) and an oven-dried stirring bar. The vial was closed with a Teflon septum and cap and connected to the atmosphere via a needle. Then MeCN (2 mL) and ^{t}BuCOCl (1.5 equiv.) were added with a syringe under nitrogen atmosphere. The closed autoclave was flushed two times with nitrogen (~5 bar) and carbon monoxide (~5 bar). Subsequently, gaseous alkanes and carbon monoxide were charged at the required pressure for the experiments. The autoclave was then placed on a magnetic stirrer. The reaction mixture was stirred while being irradiated with 40 w blue light at room temperature for 20 h. After irradiation, the light was turned off and the pressure was released carefully. The mixture was concentrated under vacuum. The crude product was purified by column chromatography (PE/EA = 10/1 to 100/1) on silica gel to afford the



entry	"Cl" source	yield
1	no	4%
2	^{t}BuCOCl (1 equiv.)	9%
3	CuCl$_2$ (1 equiv.)	20%
4	TBACl (20 mol%)	14%

Fig. 4 | Synthetic applications and Mechanistic studies. **a** 1 mmol scale-up reaction. **b** Cu-catalyzed carbonylation of ethane with DEAD. **c** Synthetic methyl methacrylate (MMA). **d** Capture of chlorine radical species. **e** Key intermediates of this carbonylation. **f** *S*-(*p*-tolyl) benzenesulfonothioate experiment. ^{a} 1 mmol Scale-up carbonylation. ^{b} Added KOH (1 equiv.), MeOH (10 equiv.), r.t., 4 h.

corresponding products. Note: Because of the high toxicity of carbon monoxide, all the reactions should be performed in an autoclave. The laboratory should be well-equipped with a CO detector and alarm system.

Data availability

The data supporting the findings of this study are available within the paper and its Supplementary Information. All data are available from the corresponding author upon request.

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Author contributions

L.-C.W. designed and carried out most of the reactions and analyzed the data. X.-F.W. designed and supervised the project. X.-F.W. and L.-C.W. wrote and revised the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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