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Model study on photoinduced direct activation of cyclohexane for carbonylation reaction

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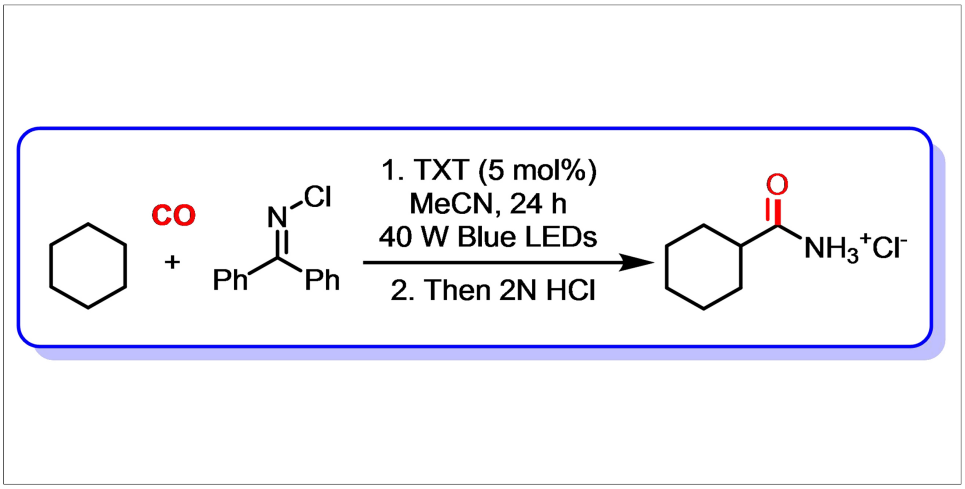

Abstract

C(sp³)–H bond activation is widely recognized as a key area for the development of organic chemistry in the 21st century. However, its activation has long been a challenge for scientists. The advent of photochemistry has offered hope for addressing this challenge. Various radicals generated under light irradiation have emerged as versatile hydrogen atom transfer (HAT) agents, streamlining the C–H activation process while enabling excellent regioselectivity. Herein, we present a chlorine radical-mediated hydrogen atom abstraction approach conducted under pressurized carbon monoxide (40 bar), which successfully achieves the C–H bond activation and carbonylation of cyclohexane.

C(sp³)–H bond activation plays a pivotal role in pharmaceutical molecule optimization, natural product editing, and related fields[1]. It has facilitated a paradigm shift in traditional organic chemistry from a functional group interconversion model to a direct transformation approach, thereby promoting the two core objectives of synthetic methodology: step economy and atom economy[2]. From the perspective of resource chemistry, C(sp³)–H activation enhances the conversion efficiency and utilization of natural gas, long-chain alkanes, fatty acids,

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sugars, and other C(sp^3)–H-rich compounds[3]. It bridges the gap between fundamental theory and industrial application and serves as a core driving force in advancing organic chemistry from a molecular construction art toward precision molecular engineering. Nevertheless, its development still faces several challenges. For instance, the bond dissociation energies of C(sp^3)–H bonds are about 90-100 kcal/mol, significantly higher than those of unsaturated bonds, making them difficult to activate[4]. Moreover, their low highest occupied molecular orbital (HOMO) and high lowest unoccupied molecular orbital (LUMO) energies render C(sp^3)–H bonds resistant to both electrophilic and nucleophilic attack, resulting in high reaction barriers [Supplementary Scheme 1A]. In addition, achieving selectivity often requires the pre-installation of directing groups, which contradicts the original intent of C–H activation.

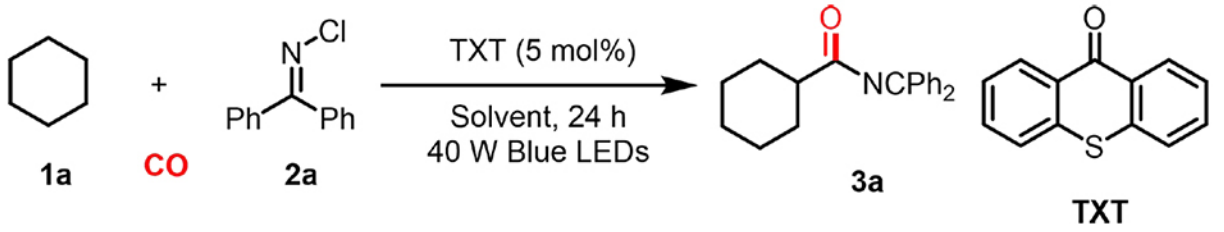
Photochemistry has developed rapidly in recent years. The simplicity of its reaction pathways and reduced reliance on catalysts make organic synthesis more sustainable and efficient[5]. In addition to undergoing self-coupling, various radicals generated under light irradiation can participate in reactions such as hydrogen atom transfer (HAT) and single-electron transfer (SET)[6]. These reactions proceed under mild conditions (room temperature, visible-light irradiation), exhibit excellent functional group tolerance, and complement traditional transition-metal catalysis, making them indispensable tools in pharmaceutical synthesis, materials chemistry, and chemical synthesis. Photocatalytically generated radicals-including halogen-centered, oxygen-centered, sulfur-centered, nitrogen-centered, and carbon-centered radicals, can serve as highly efficient hydrogen abstraction reagents. Oxygen-centered radicals have found widespread applications in thermal reactions, requiring only heating to release radicals for hydrogen abstraction, whereas halogen radical-mediated HAT is typically employed in photochemical reactions[7]. Among halogen ions, chloride and bromide are most commonly used. Bromide is usually generated via photoredox catalysis and exhibits higher selectivity than chloride, enabling precise abstraction of benzylic hydrogen[8]. Chloride is typically produced through ligand-to-metal charge transfer (LMCT) photocatalysis of $FeCl_3$ or $CuCl_2$, as well as photooxidation of Cl^-, and possesses strong electrophilic character, preferentially abstracting hydrogen from electron-rich C–H sites [Supplementary Scheme 1B][9]. Overall, halogen radical-mediated hydrogen abstraction provides a convenient and reliable pathway for the functional group transformation of organic compounds.

Carbonylation reactions represent an important class of transformations for constructing carbonyl compounds. Traditional carbonylation reactions have primarily relied on noble metal catalysts. In recent years, carbonylation reactions catalyzed by earth-abundant metals have also been developed. Additionally, metal-free carbonylation involving radicals has gradually emerged[10]. In 2025, the Wu group reported the C(sp^3)–H activation and carbonylation of gaseous alkanes and cyclohexane, bringing new insights to the advancement of carbonylation chemistry[11]. Herein, we present a novel hydrogen abstraction strategy in which imine species generate chlorine radicals under light irradiation to abstract hydrogen, followed by carbon monoxide insertion, while another portion directly couples with the acyl radical, ultimately affording an imide compound [Supplementary Scheme 1C].

To validate the feasibility of this strategy, we screened reaction conditions (see Supplementary Materials for more details). First, we screened several solvents, because solvent choice often play a decisive role in the reaction. Various solvents such as MeOH, DCE, DMF, and MeCN were tested [Table 1]. Gas chromatography results indicated that acetonitrile performed relatively well, affording a yield of 61%. Ethyl acetate also gave a yield of 45%. However, in the presence of methanol, only 11% yield was obtained.

Next, the effects of different photosensitizers on this reaction were evaluated, including both metal-based and organic photosensitizers. The results showed that iridium-based photosensitizers $Ir(dtbbpy)[dF(CF_3)ppy]_2]PF_6$, $Ir(ppy)_3$ were not applicable to this reaction. Carbazole-based photosensitizers such as 4CzIPN gave the desired product in 45% yield, while 9-thioxanthone exhibited the best catalytic

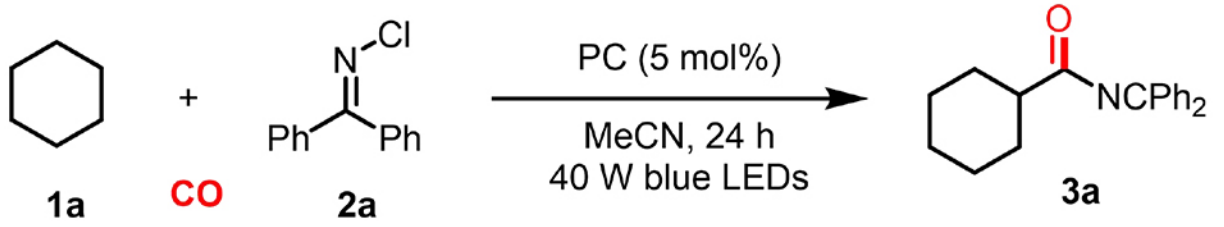
Table 1. Optimization of solvent[a]



Entry	Solvent	Yield (%)
1	Ethyl acetate	45
2	DCE	32
3	MeCN	61
4	DMF	trace
5	MeOH	11
6	DME	trace

[a]Reaction conditions: **1a** (1 mmol), **2a** (0.1 mmol), CO (40 bar), TXT (5 mol%), 40 W blue LEDs, solvent (1.5 mL), rt, 24 h. GC yield of **3a**, with dodecane as the internal standard. LEDs: Light-emitting diodes; GC: gas chromatography.

Table 2. Optimization of photocatalyst[a]



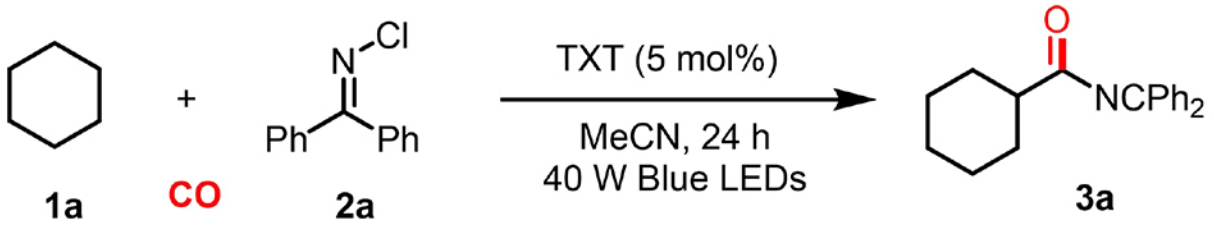
Entry	Photocatalyst	Yield (%)
1	TXT	61
2	$Ir(dtbbpy)[dF(CF_3)ppy]_2]PF_6$	Trace
3	4CzIPN	45
4	$Ir(ppy)_3$	0
5	Xanthone	0
6	Eosin Y	0

[a]Reaction conditions: **1a** (1 mmol), **2a** (0.1 mmol), PC (5 mol%), 40 W blue LEDs, CO (40 bar), MeCN (1.5 mL), rt, 24 h. GC yield of **3a**, with dodecane as the internal standard. LEDs: Light-emitting diodes; GC: gas chromatography.

performance, delivering the target product in 61% yield as determined by gas chromatography (Table 2, entry 1).

Subsequently, we attempted to further improve the reaction efficiency by varying the stoichiometric ratios of the substrates, but without success [Table 3]. Reducing the cyclohexane loading lowered the yield of the desired product. We then attempted to increase the reaction concentration by raising the amounts of reactants, but this did not improve the yield. During screening of solvent loading, we found that decreasing or increasing the solution concentration all resulted in decreased yield (Table 4, entries 1-5). Additionally, either increasing or decreasing the carbon monoxide pressure inhibited the reaction and failed to improve the yield. Notably, the yield drops dramatically when the reaction was performed under lower pressure of CO. As the imine product decomposed during the purification process, we treated the reaction mixture with 2N HCl, and the corresponding primary amide salt was isolated in 55% yield.

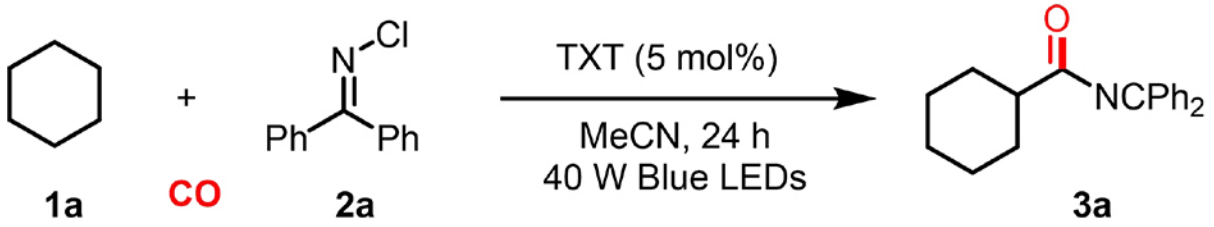
Table 3. Optimization of the ratio of reactants[a]



Entry	1a:2a	Yield (%)
1	10:1	61
2	5:1	37
3	2:1	31
4	1:1	17
5	1:2	Trace

[a]Reaction conditions: **2a** (0.1 mmol), TXT (5 mol%), CO (40 bar), 40 W blue LEDs, MeCN (1.5 mL), rt, 24 h. GC yield of **3a**, with dodecane as the internal standard. LEDs: Light-emitting diodes; GC: gas chromatography.

Table 4. Optimization of solvent usage[a]



Entry	Usage of MeCN (mL)	Yield (%)
1	0.5	11
2	1	52
3	1.5	61
4	2	31
5	2.5	24

[a]Reaction conditions: **1a** (1 mmol), **2a** (0.1 mmol), CO (40 bar), TXT (5 mol%), 40 W blue LEDs, rt, 24 h. GC yield of **3a**, with dodecane as the internal standard. LEDs: Light-emitting diodes; GC: gas chromatography.

Based on previous reports and our mechanistic experimental studies, we propose a plausible mechanism for this transformation [Supplementary Scheme 2][11]. First, substrate **2a** undergoes N–Cl bond homolysis under light irradiation to generate two radical species. The chlorine radical abstracts a hydrogen atom from cyclohexane **1a** to afford a cyclohexyl radical **B**. Radical **B** then inserts a molecule of carbon monoxide, and the resulting acyl radical couples with radical **A** to furnish the final product.

In summary, we have developed a chlorine radical-mediated hydrogen abstraction/carbonylation pathway. Under blue light irradiation, the desired product can be obtained with only catalytic amounts of thioxanthone. The reaction proceeds under mild conditions with a simple operation, providing a new strategy for the C(sp^3)–H activation and carbonylation of cyclohexane.

DECLARATIONS

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Authors' contributions

Project supervision and manuscript revision: Wu, X. F.

Data collection, data analysis, and original manuscript preparation: Li, Q.

Availability of data and materials

The data supporting the findings of this study are available within this Article and its Supplementary Materials. Further data are available from the corresponding author upon request.

AI and AI-assisted tools statement

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

Wu, X. F. is a Guest Editor of the Special Issue "C1 for Fine Chemicals" of the journal *Chemical Synthesis*. Wu, X. F. was not involved in any stage of the editorial processing, notably including reviewers selection, manuscript handling, and decision-making. The other author declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Supplementary Materials

Supplementary Materials

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