Visible light-mediated 1,3-acylative chlorination of cyclopropanes employing benzoyl chloride as bifunctional reagents in NHC catalysis

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KEYWORDS: 1,3-acyl chlorination, cyclopropanes, NHC/PC dual-catalysis, benzoyl chloride, γ-chlorinated ketones

ABSTRACT: Chlorine-substituted ketones are essential intermediates in organic synthesis, and commercially available benzoyl chloride participated acyl chlorination provides a atom and step economic route for their synthesis. While atom-transfer radical addition (ATRA) is an efficient method for 1,2-acyl chlorination, achieving efficient 1,3-acyl chlorination remains a significant challenge. In this work, we developed an NHC/PC dual-catalyzed system for the 1,3-acyl chlorination of cyclopropanes using benzoyl chloride as a bifunctional reagent. Furthermore, it enables the synthesis of acyl-cyclopropanes featuring quaternary carbon centres through nucleophilic annulation process. The practical utility of the approach is demonstrated by large-scale synthesis, product derivatization, and the preparation of analogs to antipsychotics such as haloperidol and melperone.

Chlorine-substituted ketones are highly valuable building blocks in organic synthesis, playing a crucial role as intermediates in the synthesis of numerous natural products, pharmaceutical molecules, and biologically active compounds.[1] Significant progress has been made in the synthesis of α- and β-chlorinated ketones[2]; however, the development of γ-chlorinated ketones has been comparatively limited[3]. Acyl chlorides are readily available and widely used as chemical raw materials. They are traditionally employed in Friedel-Crafts type[4] acylation, including 1,2-chloroacylation of olefins, however, due to the harsh conditions, dehydrochlorination may occur, resulting in formal β-aroylation [4b, 5] (Scheme 1Aa). As an alternative approach, atom-transfer radical addition (ATRA) using acyl chloride as a bifunctional reagent, presents an attractive route for synthesizing chlorinated ketones by simultaneously incorporating chlorine and acyl groups into carbon-carbon multiple bonds under mild conditions.[6] In 2019, Liu and Ngai group[6a] developed a photocatalyzed radical 1,2-acyl chlorination of olefins via ketyl radical addition followed by 1,3-chlorine atom shift. Very recently, the Ritter group[6d] and Guin group[6e] independently realized inverse regioselectivity through a Ni/PC dual-catalyzed chlorine radical addition followed by acyl group transfer (Scheme 1Ab). Despite the significance, strategy for 1,3-acyl chlorination of hydrocarbons remains elusive (Scheme 1Ac), highlighting the need for innovative reaction modes and catalytic strategies for acyl chloride.

On the other hand, since the groundbreaking work of Ohmiya[7], Studer[8], and Chi[9] et al., N-heterocyclic carbenes (NHCs)[10] have proven effective in stabilizing acyl radicals to persistent Breslow intermediate-driven radicals (BIRs)[11], opening novel avenues for radical acylation chemistry.[12] In 2020, the Studer[13a] and Scheidt[14a] groups independently reported single-electron reduction of NHC-acyl adducts to generate BIRs combined with photocatalysis. In this area, various carboxylic acid derivatives, such as benzoyl fluoride[13], benzimidazole[14], aryl benzoate[15], and benzoic acid anhydride[16], have been developed as efficient radical acylating agents. However, benzoyl chloride has not to be efficiently applied in radical NHC catalysis[14e, 16a]. The main issue lies in the reduction quenching mechanism in the NHC/PC co-catalytic system, which leads to the formation of highly reducing PC^{-}, that undergo single-electron transfer (SET) with NHC adducts to generate persistent BIRs (Scheme 1B). However, the oxidation potential of benzoyl chloride (E_{red} = −1.26 V vs SCE)[6c] may lead to competitive quenching with PC* or PC^{-}, disrupting the reductive quenching cycle[6]. Moreover, the high electrophilicity of benzoyl chloride[3,4] limits its compatibility with substrate, complicating controllable transformations.

We recognized that these challenges could be effectively addressed by selecting an appropriate photocatalyst (PC)[17], modulating the photo-redox cycle towards the oxidative quenching pathway[13h, 16b], and employing benzoyl chloride as a bifunctional reagent[6] (Scheme 1C, Right). Cyclopropane[18], for instance, can undergo photooxidation[19] to generate radical cations[20], which can be opened by nucleophiles, leading to

novel radical species and enabling 1,3-functionalization[13e, 14m, 19-21]. Continuing our efforts in NHC catalysis[13h, 14m, 22, 23], we present the NHC/PC dual-catalyzed 1,3-acyl-chlorination of cyclopropane, utilizing benzoyl chloride as a bifunctional reagent (Scheme 1C, Left). To the best of our knowledge, this nucleophilic chlorination/acyl radical transfer cascade represents the first acyl chlorination at the 1,3-position of feedstocks, complementing the well-established FC-type acylation and ATRA strategy, providing a versatile platform for synthesizing γ-chlorinated ketones and acyl-cyclopropanes.

Scheme 1 Motivation for radical 1,3-acylative chlorination employing benzoyl chloride as bifunctional reagents

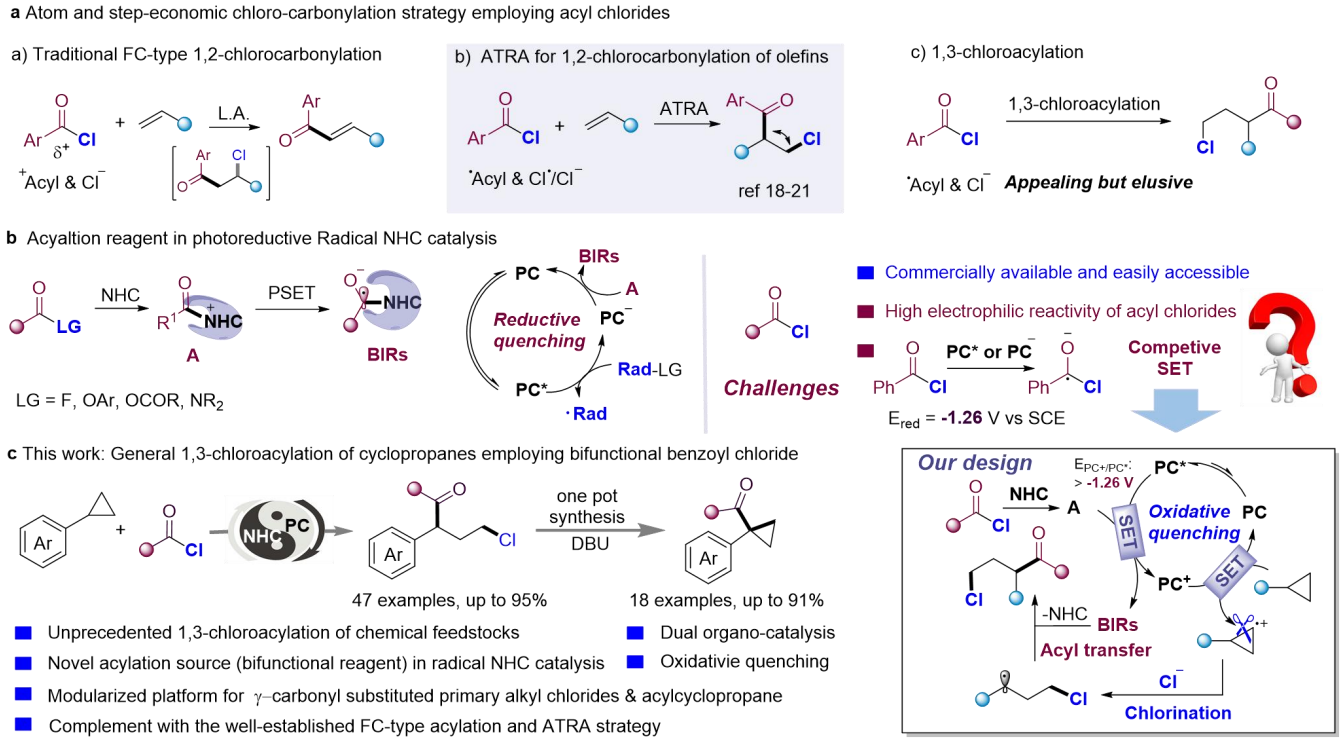
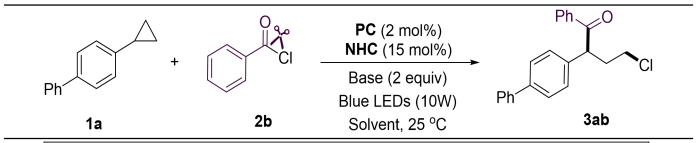
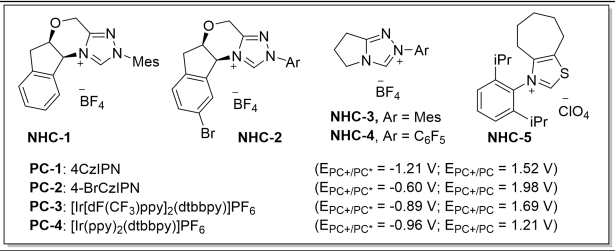


Table 1 Optimization of the reaction conditions.[a]





Entry	PC	NHCs	Base	Solvent	Yields
1	PC-1	NHC-1	K_3PO_4	DCM	77%
2	PC-2	NHC-1	K_3PO_4	DCM	94%
3	PC-3	NHC-1	K_3PO_4	DCM	80%
4	PC-4	NHC-1	K_3PO_4	DCM	trace
5	PC-2	NHC-2	K_3PO_4	DCM	93%
6	PC-2	NHC-3	K_3PO_4	DCM	79%
7	PC-2	NHC-4	K_3PO_4	DCM	28%
8	PC-2	NHC-5	K_3PO_4	DCM	47%
9	PC-2	NHC-1	K_3PO_4	$PhCF_3$	37%
10	PC-2	NHC-1	K_3PO_4	DCE	71%
11	PC-2	NHC-1	K_3PO_4	CH_3CN	40%
12	PC-2	NHC-1	K_3PO_4	$CHCl_3$	88%
13	PC-2	NHC-1	K_3PO_4	THF	n.d.
14	PC-2	NHC-1	K_2CO_3	DCM	77%
15	PC-2	NHC-1	K_2HPO_4	DCM	72%
16	PC-2	NHC-1	Cs_2CO_3	DCM	83%

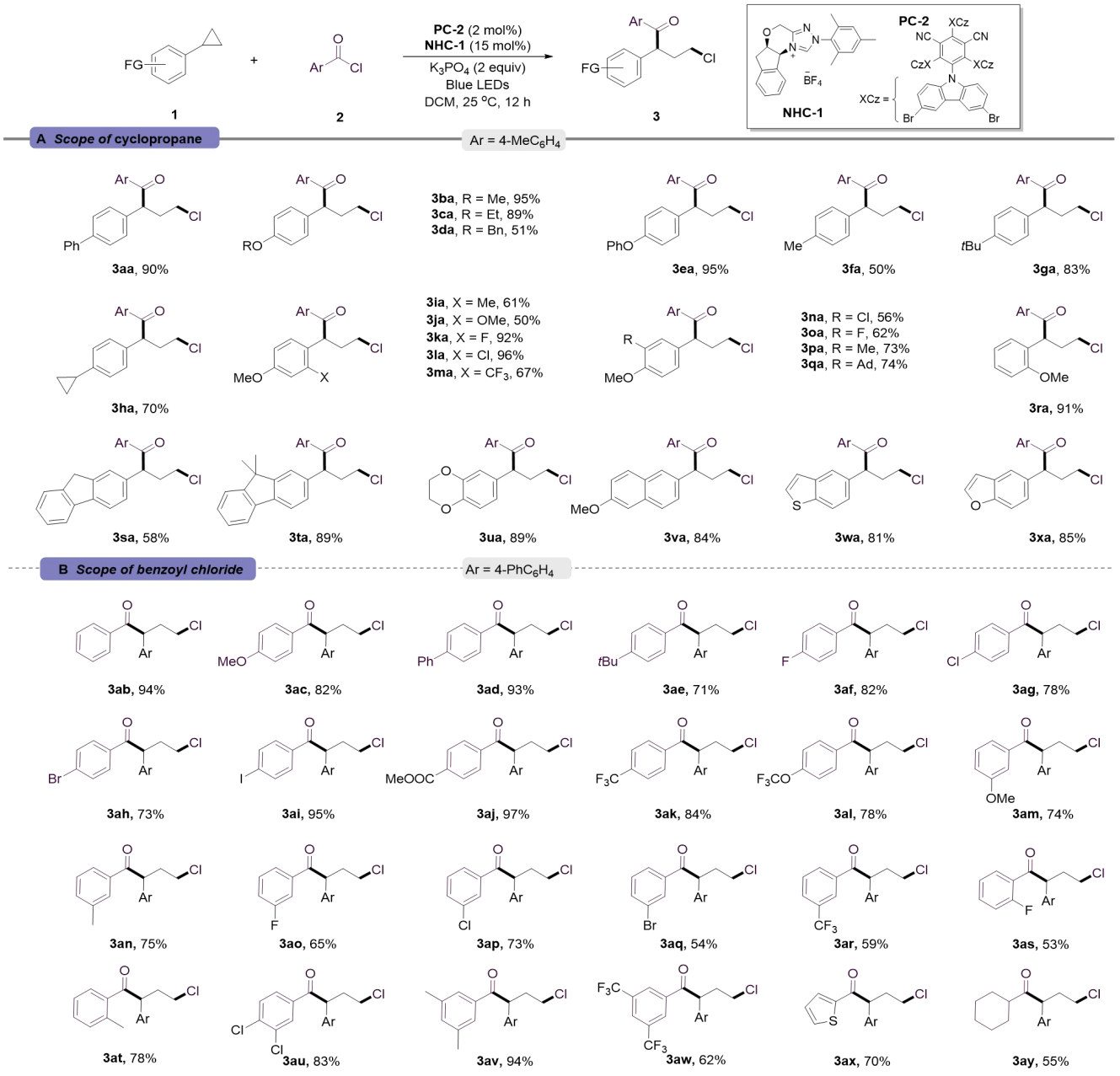
[a] Unless otherwise noted, all the reactions were carried out with **1** (0.1 mmol), **2** (0.2 mmol), NHCs (0.015 mmol), K_3PO_4 (0.2 mmol), and PC (0.002 mmol) in solvent (2 mL), with 40 W blue LEDs at 25 °C for 12 h.

The principle of concept chlorination/acylation was conducted using cyclopropane **1a** (0.1 mmol) and benzoyl chloride **2b** (0.2 mmol) as starting materials, 4CzIPN (2 mol%) as the photosensitizer, **NHC-1** (15 mol%) as the catalyst, K_3PO_4 (2.0 equiv) as the base, DCM (2 mL) as the solvent under blue light irradiation for 12 h, and the desired γ-chlorinated ketone **3** was isolated with 77% yield (Table 1, Entry 1). Encouraged by this result, we further screened photosensitizers (Entries 1-4), and the reaction is more suitable for more oxidizing photosensitizers, with **PC-2** (4-BrCzIPN) able to obtain the target product **3ab** at 94% yield (Entry 2). In contrast, **PC-4** can only obtain trace amount of **3ab** (Entry 4). Other NHC catalysts were tested (Entries 5-8), and N-mesityl substituted triazolium **NHC-2** (93%), **NHC-3** (79%) deliver comparable results. The substitution of the mesityl group in **NHC-3** with a polyfluoroaryl moiety (**NHC-4**) significantly diminishes the yield of **3ab** to 28% (Entry 7), underscoring the pivotal role played by the *N*-substituent in determining reaction efficiency. The conversion can be promoted by *N*-2,6-di-iPrC_6H_3-substituted seven-membered ring fused thiazolium salt **NHC-5**, albeit with moderate yield (Entry 8). Other solvents ($PhCF_3$, DCE, CH_3CN, $CHCl_3$) also promoted this transformation with

https://doi.org/10.26434/chemrxiv-2024-2pd87 **ORCID:** https://orcid.org/0000-0003-0201-6279

37-88% yields, however THF was failed to give the desired products (Entries 9-13). Replacing K_3PO_4 with other bases, such as K_2HPO_4, K_2CO_3, Cs_2CO_3 exhibit comparable reactivity, but not improve the yield. Thus, conditions in Entry 2 was identified as Conditions A for further investigations.

Scheme 2. Scope of the substrate for 1,3-acylative chlorination.[a]

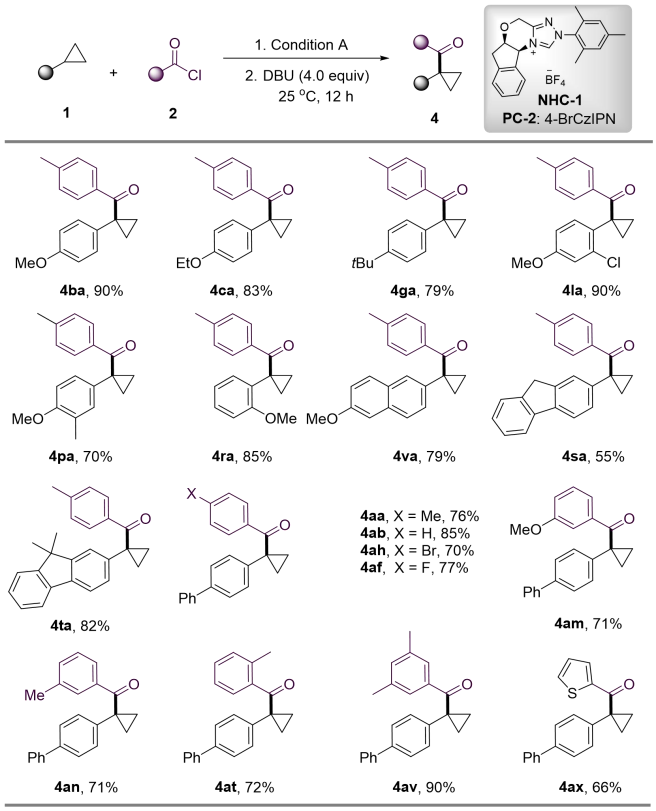


Substrate scope for 1,3-Aminoacylation of Cyclopropane.[a] [a]Conditions A: Unless otherwise noted, all the reactions were carried out with **1** (0.1 mmol), **2** (0.2 mmol), NHCs (0.015 mmol), K_3PO_4 (0.2 mmol), and PC (0.002 mmol) in dichloromethane (2 mL), with 10W blue LEDs at 25 °C for 12 h.

The scope in terms of aryl cyclopropane was initially investigated under the established optimized reaction conditions (Table 1, entry 2). As summarized in Scheme 2A, a wide range of aryl cyclopropane with different substituents at different sites of the aryl ring could be tolerated and deliver γ-chlorinated ketones **3aa-3xa** in 50-96% yields. The reactivity of aryl cyclopropane with strong electro-donating alkoxy and phenoxyl substituents was found to be excellent, resulting in the formation of compounds **3ba**, **3ca**, and **3ea** with yields ranging from 89% to 95%; however, **3da** (51%) bearing benzyloxy group provides only moderate yield. Interestingly, aryl cyclopropanes bearing alkyl groups (methyl, tertiary butyl, cyclopropyl) at the para position exhibited excellent tolerance and yielded acyl chlorination products **3fa-3ha** in yields ranging from 50% to 83%. The aforementioned observation indicates the successful expansion of cyclopropane's application range in photoredox reactions to encompass moderate electron-donating substrates. The system exhibited excellent tolerance towards various functional groups and steric hindrance for aryl cyclopropane, as

evidenced by the well-tolerated presence of electron-donating (alkyl and alkoxy), halogen (fluorine, chlorine), and electron-withdrawing groups (trifluoromethyl) at the *ortho*-(**3ia-3ma**) or *meta*-position (**3na-3qa**) of the 4-methoxyphenyl ring. Additionally, the substitution of cyclopropane with 9*H*-fluorene (**3sa**) resulted in a moderate yield of 58%, while the employment of 9,9-dimethyl-9*H*-fluorene (**3ta**) and 2,3-dihydrobenzo[b][1,4]dioxine (**3ua**) led to high yields of 89% and 89% respectively. This strategy can be expanded to encompass fused aryl-cyclopropane and heteroaryl-cyclopropane, resulting in compounds **3va-3xa** with 81-85% yield.

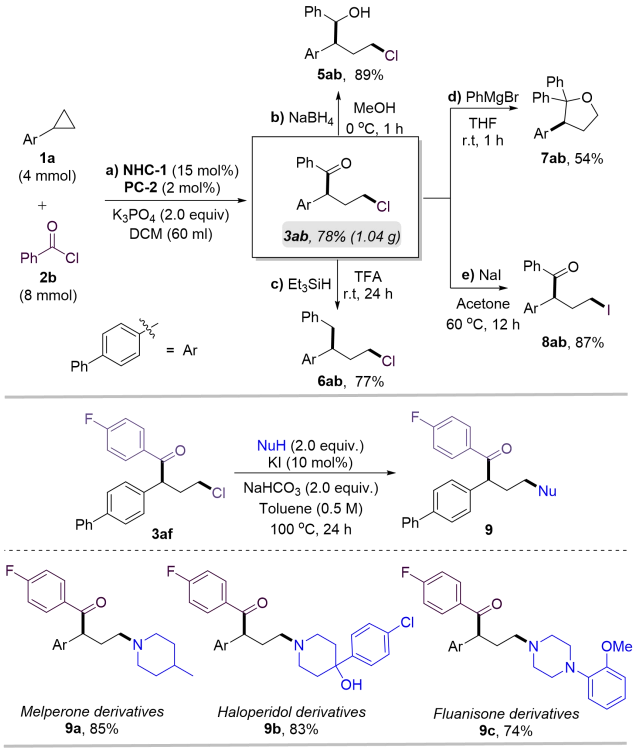
Scheme 3. Scope of the substrate for formal C-H acylation aryl-cyclopropane.[a]



Scope of the substrate for formal C-H acylation aryl-cyclopropane.[a] [a]Conditions B: Unless otherwise noted, all the reactions were carried out with **1** (0.1 mmol), **2** (0.2 mmol), NHCs (0.015 mmol), K_3PO_4 (0.2 mmol), and PC (0.002 mmol) in dichloromethane (2 mL), with 10W blue LEDs at rt. for 12 h, then DBU (0.4 mmol) at 25 °C for 12 h.

The scope concerning the acyl chlorines was subsequently investigated (Scheme 2B). A diverse range of commercially available acyl chlorines can be efficiently transformed into target products **3ab-3ay** with moderate to high yield. The para position of benzoyl chlorides exhibits excellent tolerance towards various electron-donating (OMe, tBu, Ph), halogen (F, Cl, Br, I), and electron-withdrawing (COOMe, CF_3, OCF_3) groups with successful conversion to **3ab-3al** in yields ranging from 71-97%, showcasing compatibility towards electronic effects. The good reactivity of acyl chlorides towards different substitution patterns at *meta*- (**3am-3ar**, 54-75%) or *ortho*-(**3as**, 53%; **3at**, 78%) sites demonstrated a remarkable tolerance for steric hindrance. The employment of di-substituted benzoyl chloride (**3au-3aw**, 62-94%) is also applicable for this conversion. Furthermore, thiophenyl chloride can also be converted into the target product **3ax** in 70% yield. Finally, cyclohexane carbonyl chloride is also applicable for this conversion despite its moderate yield (**3ay**, 55%). The transformations exhibited excellent compatibility with various functional groups. Halogens, particularly iodine, which is sensitive in metal catalysis, were maintained, offering the potential for subsequent cross-coupling reactions. Fluorine, trifluoromethyl, and trifluoromethoxy groups have found significant applications in drug discovery.

Scheme 4. Large-scale synthesis and follow-up transformations.

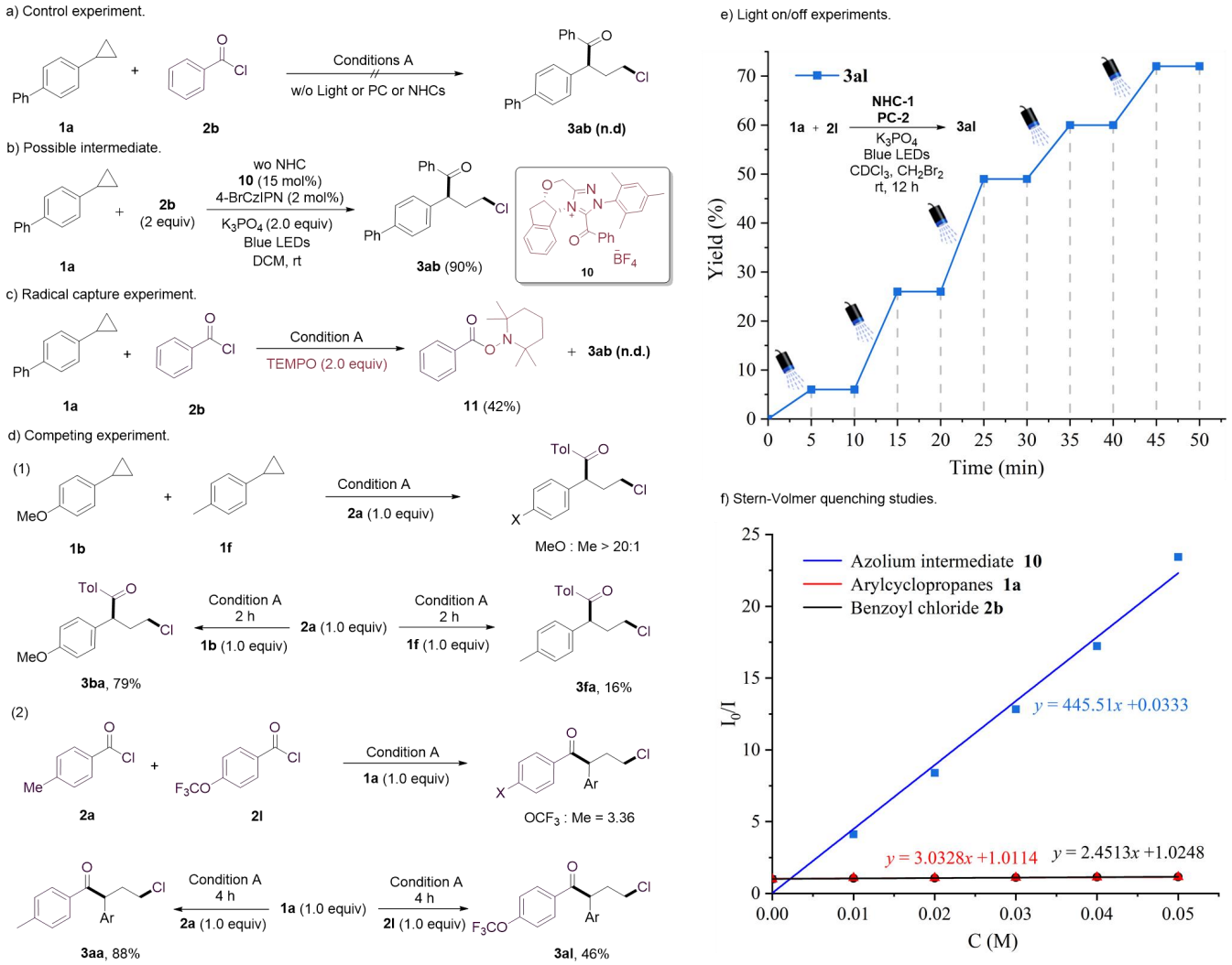


Reaction conditions: b) **3ab** (0.1 mmol), $NaBH_4$ (2.0 equiv), MeOH (1.0 ml), 0 °C, 1 h. c) **3ab** (0.1 mmol), Et_3SiH (2.5 equiv), TFA (1.0 ml), rt. 24 h. d) **3ab** (0.2 mmol), PhMgBr (0.1 ml), THF (2.0 ml), rt. 1 h. e) **3ab** (0.2 mmol), NaI (3.0 equiv), Acetone (2.0 ml), 60 °C, 12 h.

Cyclopropanes are a privileged structural motif in natural products and bioactive compounds, and they serve as valuable building blocks in organic synthesis.[19] Functionalizing the C-H bond in cyclopropanes is an ideal strategy for accessing functionalized derivatives; however, the inherent ring strain of cyclopropanes presents significant challenges for achieving ring-maintaining functionalization.[24] In this study, formal C-H acylation of aryl-cyclopropane was successfully achieved via a chlorination-mediated cut-and-sew strategy. As shown in Scheme 3, a wide range of α-acylated aryl-cyclopropanes (**4ba-4ax**) were synthesized in 55-90% total yields by simply adding DBU (4.0 equiv) to the acyl chlorination system without the need for intermediate separation, followed by an additional 12 hours of reaction. This modular strategy provides a versatile platform for the targeted synthesis of acyl-substituted aryl-cyclopropanes[25], broadening the scope of cyclopropane functionalization.

Gram-scale synthesis and several derivatization reactions were performed to demonstrate the synthetic utilities. The coupling of **1a** and **2b**, as depicted in Scheme 4a, was successfully conducted at a scale of 4 mmol with excellent efficiency, resulting in the formation of compound **3ab** (1.04g, 78%) without any significant loss in yield (Scheme 4a). γ-Chlorinated ketone **3ab** could serve as a versatile building block for organic synthesis. The reduction of **3ab** by $NaBH_4$ yields δ-chlorinated alcohol **5ab** in 89% yield with excellent diastereoselectivity (Scheme 4b). Haloalkane **6ab** can be obtained in a 77% yield in TFA solution by employing Et_3SiH as the reductant (Scheme 4c). The chloride atom, serving as a leaving group, enables nucleophilic substitution reactions and facilitates the incorporation of other significant functional groups. Interestingly, the Grignard reagent can undergo nucleophilic addition to the carbonyl group and cascade nucleophilic cyclization, thereby constructing a substituted tetrahydrofuran skeleton (Scheme 4d). **3ab** undergo SN_2 type nucleophilic iodination delivering γ-iodinated ketone **8ab** in 87% yield. Furthermore, γ-chlorinated ketone **3af** could serve as a critical intermediate for synthesizing derivatives of melperone (**9a**), haloperidol (**9b**), and fluanisone (**9c**), which are employed as antipsychotics.[26]

Scheme 5 Mechanistic investigations.



The mechanism of this acyl chlorination system was investigated through a series of experiments. Control experiments demonstrate the indispensability of NHCs, photocatalysts and light irradiation in facilitating the reaction (Scheme 5a). Without additional NHCs, **10** can catalyse the acyl chlorination reaction efficiently (Scheme 5b). The reaction was effectively inhibited by the addition of TEMPO, a free radical scavenger, and subsequent isolation of the acylation products provided evidence for the potential involvement of a free radical intermediate (Scheme 5c). We conducted a series of competitive experiments, as illustrated in Scheme 5d. The electron density of cyclopropane was found to play a pivotal role in the reaction rate, with highly electron-donating aryl cyclopropanes exhibiting higher reactivity compared to moderately donating ones under both competitive and parallel conditions (Scheme 5d1). Interestingly, in competitive conditions, electron-deficient acyl chloride **2l** exhibited enhanced reactivity compared to electron-rich counterparts **2a** (Scheme 5d2, upper). However, contrasting outcomes were observed for parallel reactions (Scheme 5d2, lower), providing support for the hypothesis that the C–Cl cleavage step may be involved in the product-determining step but not the rate-determining step. The radical chain mechanism is not preferred, according to the

Light on/off experiment (Scheme 5e). Finally, fluorescence quenching experiments were conducted, revealing a higher propensity for the excited photosensitizer to be quenched by NHC-acyl adduct compared to arylcyclopropane and benzoyl chloride (Scheme 5f). The inertness of benzoyl chloride towards excited photosensitizers is also crucial for achieving selective acyl chlorination cascade.

In summary, we have successfully developed a visible light-mediated NHC-catalyzed 1,3-acyl chlorination of cyclopropanes, enabling the direct synthesis of γ-chlorinated ketones that are otherwise challenging to access. In addition, a series of acyl-cyclopropanes with quaternary carbon were obtained via one-pot two-step synthesis. Commercially available benzoyl chloride was first employed as acyl radical precursors in radical NHC catalysis. The synthetic utility has been further demonstrated through the large-scale synthesis, product derivatization, and the synthesis of analogues of antipsychotics haloperidol, melperone, and fluanisone. The mechanistic studies point to the oxidative quenching mechanism in the photo redox process. The inertness of benzoyl chloride towards PC in our reaction system, along with the incorporation of chloride anion, plays a pivotal role in facilitating controllable radical transformation. This nucleophilic chlorination/acyl transfer cascade offers a promising solution for 1,3-acyl chlorination, which complements the well-established FC-type acylation and ATRA strategy, and provides a modularized platform for synthesizing γ-chlorinated ketones, acyl-cyclopropanes, and their derivatives.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at http://pubs.acs.org.

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ACKNOWLEDGMENT

We acknowledge the NSFC (22471034, 22193012, and 22201033), Natural Science Foundation of Jilin Province (20230101047JC, YDZJ202201ZYTS338), and the Fundamental Research Funds for the Central Universities for generous financial support.

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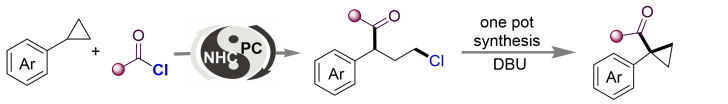
1,3-chloroacylation of cyclopropanes employing bifunctional benzoyl chloride



47 examples, up to 95%

18 examples, up to 91%

- Unprecedented 1,3-chloroacylation of chemical feedstocks
- Novel acylation source (bifunctional reagent) in radical NHC catalysis
- Modularized platform for γ–carbonyl substituted primary alkyl chlorides & acylcyclopropane
- Complement with the well-established FC-type acylation and ATRA strategy
- Dual organo-catalysis
- Oxidativie quenching