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Visible light-mediated organocatalyzed 1,3-aminoacylation of cyclopropane employing N-benzoyl saccharin as bifunctional reagent

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The carboamination of unsaturated molecules using bifunctional reagents is considered an attractive approach for the synthesis of nitrogen-containing compounds. However, bifunctional C–N reagents have never been employed in the carboamination of cyclopropane. In this study, we use an *N*-heterocyclic carbene (NHC), *N*-benzoyl saccharin, as a bifunctional reagent and a photoredox catalyst for a dual-catalyzed 1,3-aminoacylation of cyclopropane. NHCs play multiple roles, functioning as Lewis base catalysts to activate C–N bonds, promoting the oxidative quenching process of PC*, and acting as efficient acyl radical transfer catalysts for the formation of C–C bonds. The oxidative quenching process between the excited-state PC* and acyl NHC adduct is the key to the photooxidation generality of aryl cyclopropanes.

Nitrogen-containing compounds have broad applications and are commonly found in biologically active molecules, natural products, and drug compounds. Therefore, the development of nitrogen-containing compounds through C–N bond formation have garnered increasing attention in the organic synthesis community. The carboamination[1–3] of unsaturated molecules offers an efficient strategy for introducing amine and carbon functional groups into substrates in a single step, facilitating the synthesis of complex nitrogen-containing compounds. In this carboamination method, the use of bifunctional reagents[3–8] for C–N bond cleavage[9,10] is regarded as an attractive high-atom, step-economic approach to increase molecular complexity and diversity. The polar[11,12] or radical[13] [3 + 2] cycloaddition of strained aziridines with unsaturated molecules is a fundamental and important transformation for the synthesis of *N*-containing heterocycles. However, the employment of unstrained bifunctional C–N reagents is still an emerging area. In 2014, the Nakao[14] and Douglas[15,16] research groups independently made contributions to this field by activating *N*–CN bonds and enabling the vicinal additions across intramolecular carbon-carbon double bonds (Fig. 1a, Left). Huang and coworkers provided further progress and developed intermolecular carboamination reagents, namely, aminals and *N*- and *O*-acetals. They achieved Pd-catalyzed C–N activation using bifunctional reagents and intermolecular addition to unsaturated carbon–carbon bonds[17–24], such as allenes[18], conjugated dienes[19–21], and 1,3-enynes[22–24] via aminomethyl cyclopalladated complexes (Huang complexes)[17] (Fig. 1a, Middle). Despite their importance, these protocols are restricted primarily to unsaturated carbon–carbon bonds. Cyclopropane, which has double-bond character[25,26], is not suitable for these types of transformations. The design of bifunctional carboamination reagents with a different reaction model might provide a solution for C–N bond addition to cyclopropane.

Visible-light-mediated photocatalysis (PC) has been successfully employed as a powerful tool that enables controllable radical reactions[27–30]. Light-mediated protocols can activate the C–C bonds of aryl cyclopropane[28–43] under mild conditions, employing radical cations[31–43] as the key intermediate. Feng[35–40], Studer[41,42], and others[43]

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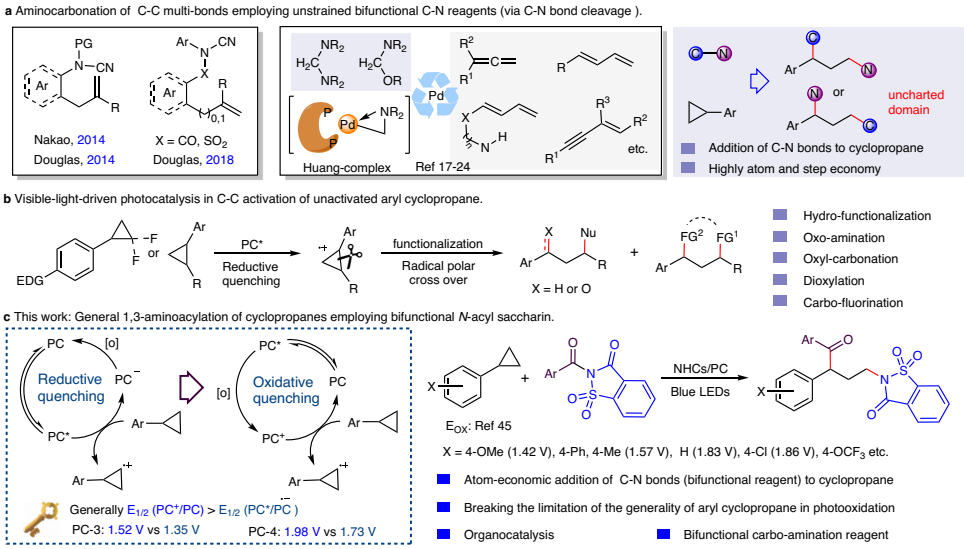
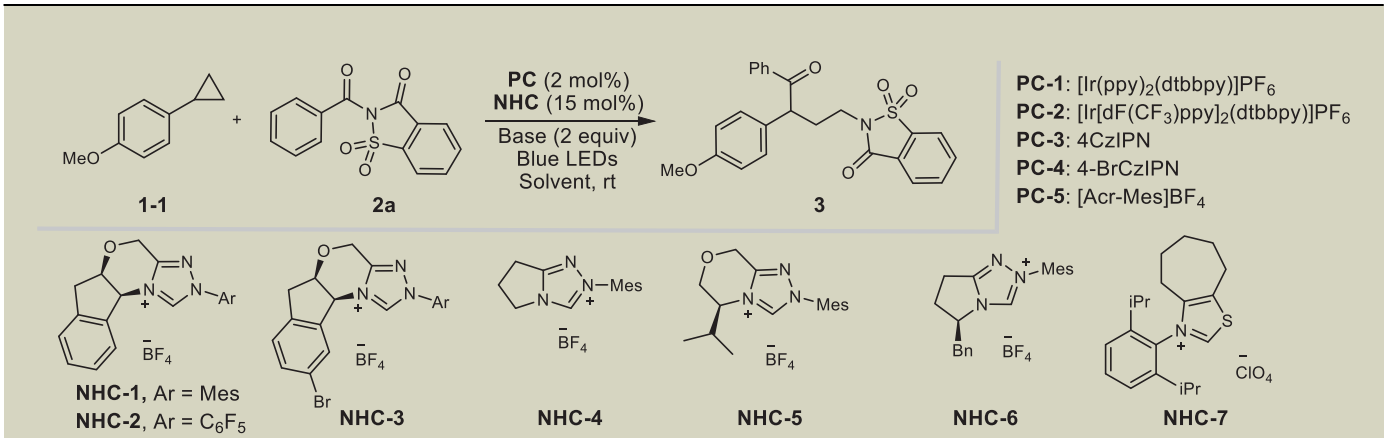


Fig. 1 | Motivation for NHCs/PC dual-catalyzed addition of amide (C-N bonds) to cyclopropane. a Aminocarbonation of C-C multi-bonds employing unstrained bifunctional C-N reagents (via C-N bond cleavage). **b** Visible-light-driven photocatalysis in C-C activation of unactivated aryl cyclopropane. **c** General 1, 3-aminoacylation of cyclopropanes employing bifunctional *N*-acyl saccharin.

Table 1 | Condition Optimizations[a]



Entry	PC (mol%)	NHCs (15 mol%)	Solvent (2 mL)	Yields
1	PC-1 (2)	NHC-1	DCM	41%
2	PC-2 (2)	NHC-1	DCM	73%
3	PC-3 (2)	NHC-1	DCM	94%
4	PC-4 (2)	NHC-1	DCM	96%
5	PC-5 (2)	NHC-1	DCM	trace
6	PC-3 (1)	NHC-1	DCM	67%
7	PC-3 (2)	NHC-2	DCM	trace
8	PC-3 (2)	NHC-3	DCM	87%
9	PC-3 (2)	NHC-4	DCM	36%
10	PC-3 (2)	NHC-5	DCM	94%
11	PC-3 (2)	NHC-6	DCM	85%
12	PC-3 (2)	NHC-7	DCM	17%
13	PC-3 (2)	NHC-1	$PhCF_3$	65%
14	PC-3 (2)	NHC-1	DCE	82%
15	PC-3 (2)	NHC-1	CH_3CN	12%
16	PC-3 (2)	NHC-1	THF	37%
17[b]	PC-3 (2)	NHC-1	DCM	95%

[a]Unless otherwise noted, all the reactions were carried out with **1** (0.1 mmol), **2** (0.2 mmol), NHCs (0.015 mmol), Cs_2CO_3 (0.2 mmol), and PC (0.002 mmol) in solvent (2 mL), with 40 W blue LEDs at 30 °C for 12 h. isolated yields. [b]Racemic NHC-1 was employed.

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have developed visible light-mediated reductive quenching-driven C–C activation of cyclopropanes, realizing hydrofunctionalization[35] or 1,3-difunctionalizations[36–43], including oxoamination[36,43], oxylcarbonation[39–42], dioxylation[38], and carbofluorination[37] (Fig. 1b). Notably, the photoredox cycle relies on a reductive quenching mechanism and is restricted by the high oxidation potential of aryl cyclopropane[34,44,45], and the oxidation ability of PC*, strong-electron-donating aryl cyclopropane or multisubstituted aryl cyclopropane, is needed. In most cases, the reduction potential of $E_{1/2}$ (PC^+/PC) is significantly greater than that of $E_{1/2}$ ($PC^*/PC^{\bullet-}$)[27]; thus, we recognized that and switched the photoredox cycle to an oxidative quenching scenario, potentially providing a solution for the reaction generality of aryl cyclopropanes (Fig. 1c, Left). *N*-heterocyclic carbenes (NHCs) exhibit unique reactivity in activating carbonyl groups[46,47] and can serve as versatile acyl radical transfer catalysts in radical–radical cross couplings[48–66]. Inspired by NHC-catalyzed C–N activation[54,67] and our continued interest in NHC catalysis[66,68,69], we now disclose general and practical visible light-mediated organocatalysed 1,3-aminoacylation[64,65] of cyclopropane[45] employing *N*-benzoyl saccharin as a bifunctional[3–8] carboamination reagent (Fig. 1c, Right). To the best of our knowledge, this protocol represents a new approach for the catalytic addition of C–N bonds to cyclopropane using bifunctional reagents.

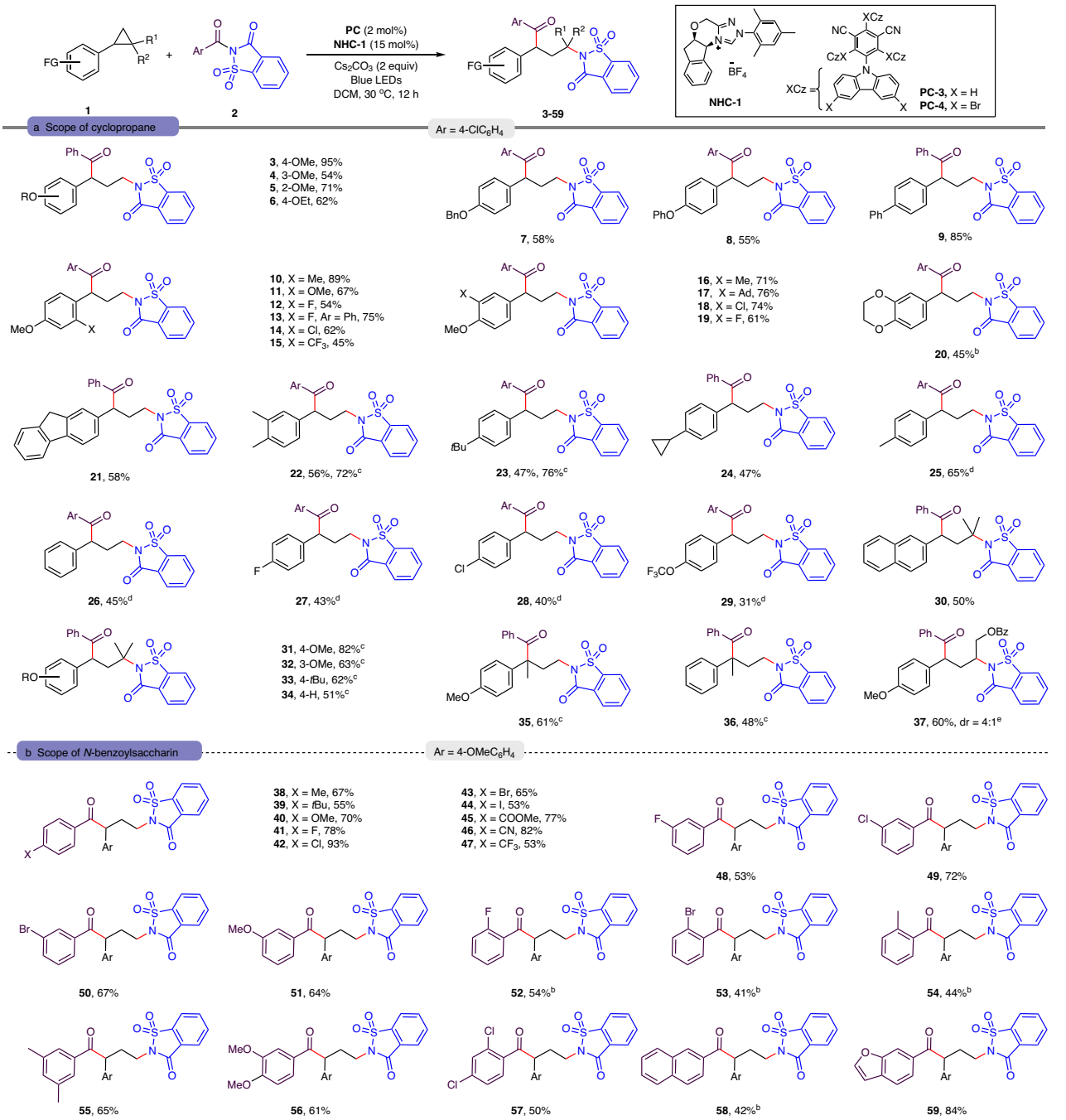

Fig. 2 | Scope of the substrate[a]. **a** scope of cyclopropane. **b** scope of *N*-benzoylsaccharin. [a]Conditions A: Unless otherwise noted, all the reactions were carried out with **1** (0.1 mmol), **2** (0.2 mmol), NHCs (0.015 mmol), Cs_2CO_3 (0.2 mmol), and PC (0.002 mmol) in DCM (2 mL), with blue LEDs at 30 °C for 12 h. [b]Conditions B: Using **2** (4.0 equiv) for 72 h. [c]Conditions C: **PC-4** instead of **PC-3**, 24 h. [d]Conditions D: **PC-4** instead of **PC-3**, NHCs (0.02 mmol), with blue LEDs at 50 °C for 72 h. [e]Conditions E: **PC-4** instead of **PC-3**, using **2** (3.0 equiv) for 24 h.

Results

Reaction optimization

Our initial experiments involved utilizing the triazolium salt **NHC-1** and $[Ir(ppy)_2(dtbbpy)]PF_6$ as a catalyst in DCM under blue LED irradiation to realize C–N addition of *N*-benzoyl saccharin **2a** to cyclopropane **1**–**1**, a condition that had shown outstanding reactivity in our previous investigations[66]. Interestingly, the yield of the designed 1, 3-aminoacylation products **3** was 41%. We conducted a photocatalyst screening (Table 1, entries 2–5) and found that the easily accessible organophotocatalyst 2, 4, 5, 6-tetra(9*H*-carbazol-9-yl)isophthalonitrile (4CzIPN, **PC-3**) and its derivative **PC-4** exhibited significantly high efficiency, yielding 94% and 96% of the desired product **3**, respectively. However, the acridine-based photocatalyst PC-5 was not suitable for this aminoacylation system. Reducing PC loading slowed the reaction, as shown in entry 6. Our exploration of different NHC precursors revealed that the triazolium salt **NHC-1** was the optimal choice (entries 7–12), as even the cycloheptane-fused thiazolium salt **NHC-7** yielded only 17% of the product (entry 12). An investigation into various solvents also produced relatively poor results (entries 13–16). Despite the use of a chiral NHC catalyst (Table 1, entries 3, 8, and 10–11), ineffective chiral induction (<10% ee) was observed in all cases. Therefore, racemic NHC-1 (entry 17) was chosen as the optimal NHC catalyst for further evaluation.

Substrate scope

With optimal conditions established, we explored the scope of aryl cyclopropane substrates amenable to aminoacylation (Fig. 2a). The introduction of an electron-donating OMe group on the phenyl ring at the para-, meta-, and ortho-positions facilitated this transformation, resulting in the production of **3**–**5** in yields ranging from 54% to 94%. Other strong electron-donating groups, such as ethoxy, benzyloxy, and phenoxy groups as well as a phenyl group at the para position of the aryl ring, were also compatible, yielding **6**–**9** in moderate to high amounts. Electron-donating (alkyl and alkoxy), halogen, and electron-withdrawing groups at the ortho- (**10**–**15**) or meta-position (**16**–**19**) of the 4-methoxyphenyl ring were well tolerated, indicating the system's tolerance to various functional groups and steric hindrance. In this transformation, 2, 3-dihydrobenzo[b][1,4]dioxine and 9*H*-fluorine-substituted cyclopropanes proved effective, yielding desired products **20** and **21** in yields of 45% and 58%, respectively. Furthermore, we demonstrated the generality and robustness of the aminoacylation system by testing a range of challenging aryl cyclopropanes featuring moderate electron-donating (3, 4-dimethyl **22**, tertiary butyl **23**, cyclopropyl **24**, methyl **25**, hydrogen **26**, halogen (fluorine **27**, chlorine **28**), and strong electron-withdrawing (trifluoromethoxy, **29**) groups at the para position of the aryl ring. We employed **PC-4** as the photocatalyst, obtaining the corresponding γ-amino ketones in yields ranging from 31% to 76%. Notably, the use of strongly oxidizing **PC-4**, rather than **PC-3**, significantly increased the reactivity, as exemplified by **22** (56% to 72%) and **23** (47% to 76%). This marks the first instance of PC-catalyzed radical difunctionalization of a general aryl cyclopropane, overcoming the limitations of previous reports that focused primarily on strong electron-donating substrates. Additionally, 1,1,2-trisubstituted cyclopropanes were confirmed as valuable substrates, producing **30**–**34** in yields ranging from 50% to 82%. Electron-rich substrates exhibited increased reactivity. Furthermore, 1,1-disubstituted cyclopropanes were compatible with the aminoacylation system and produced **35** and **36** in yields of 61% and 48%, respectively. For the 1,2-disubstituted cyclopropane bearing a hydroxyl (OH) group, the 1,3-aminoacylation/OH-acylation product **37** was produced with a 60% yield and 4:1 dr.

Next, we explored the effectiveness of *N*-benzoyl saccharin in this redox–neutral, metal-free catalytic system (Fig. 2b). A wide array of electron-donating, halogen, and electron-withdrawing (ester carbonyl, cyano, and trifluoromethyl) functional groups at the para position of the aromatic ring of *N*-benzoyl saccharin were well tolerated, producing the corresponding γ-amino ketones **38**–**47** in yields ranging from 53% to 94%. Notably, the tolerance of halogen groups, specifically iodine, provides potential for further cross-coupling transformations. *Meta*-substituted *N*-aroyl saccharins were also amenable, yielding **48**–**51** in acceptable amounts. However, *ortho*-substituted *N*-aroyl saccharins exhibited relatively lower reactivity, resulting in the formation of **52**–**54** with yields of only 41%–54%, even with extended reaction times. In contrast, disubstituted *N*-aroyl saccharins were compatible, producing desired products **55**–**57** in moderate yields. Finally, naphthalene and heterocyclic rings were tolerated, yielding 42% and 84% of **58** and **59**, respectively. However, C–N reagents derived from aliphatic acyl chlorides were not suitable for this aminoacylation cascade. Interestingly, this 1,3-aminoacylation of cyclopropane could be extended to three-component coupling employing benzoyl fluoride as an acylation reagent source (Fig. 3). Saccharin, diphenylsulfonamide, and *N*-(p-tosyl)carbamic acid ester were proven to be suitable substrates and produced the desired products **3** and **61**–**67** in moderate to high yields.

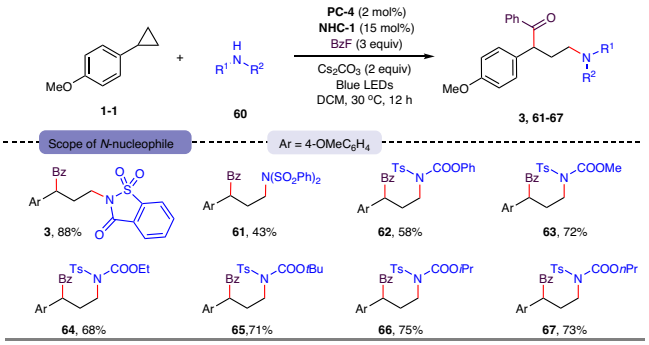

Fig. 3 | Three-Component 1,3-Aminoacylation of Cyclopropane. [a] Conditions E: Unless otherwise noted, all the reactions were carried out with **1** (0.1 mmol), **60** (0.2 mmol), benzoyl fluoride (0.3 mmol), NHCs (0.015 mmol), Cs_2CO_3 (0.2 mmol), and PC (0.002 mmol) in DCM (2 mL), with blue LEDs at 30 °C for 12 h.

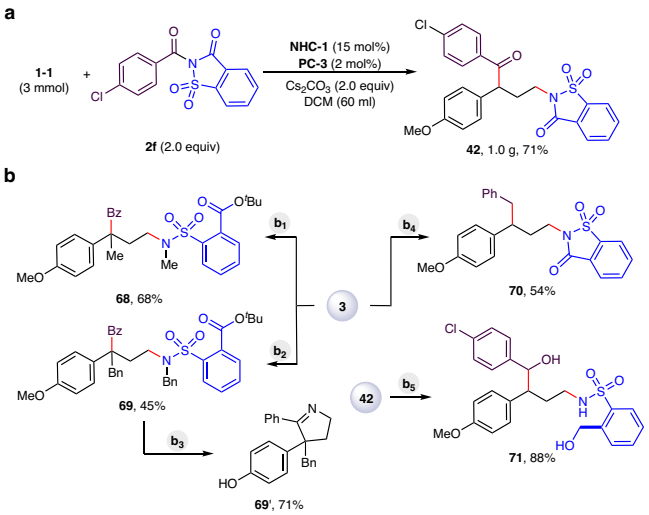

Fig. 4 | Synthetic applicability. a Large-scale synthesis. **b** Follow-up transformations. Reaction conditions: $\mathbf{b_1}$, **3** (0.1 mmol), KO*t*Bu (4.0 equiv), 18-crown-6 (1.0 mol %), CH_3I (4.0 equiv), THF (2.0 mL), rt. 1 h. $\mathbf{b_2}$, **3** (0.1 mmol), KO*t*Bu (4.0 equiv), 18-crown-6 (1.0 mol%), $PhCH_2Br$ (4.0 equiv), THF (2.0 mL), rt. 1 h. $\mathbf{b_3}$, **69** (0.1 mmol), PhOH (3.0 equiv), HBr (48%, 0.6 mL), 95 °C, 18 h. $\mathbf{b_4}$, **3** (0.1 mmol), Et_3SiH (2.5 equiv), TFA (1.0 ml), rt, 24 h. $\mathbf{b_5}$, **42** (0.1 mmol), $NaBH_4$ (2.0 equiv), MeOH (1.0 mL), 0 °C, 1 h.

large-scale synthesis and follow-up transformations

To underscore the synthesis value of this aminoacylation system, we conducted large-scale synthesis and follow-up transformations. We

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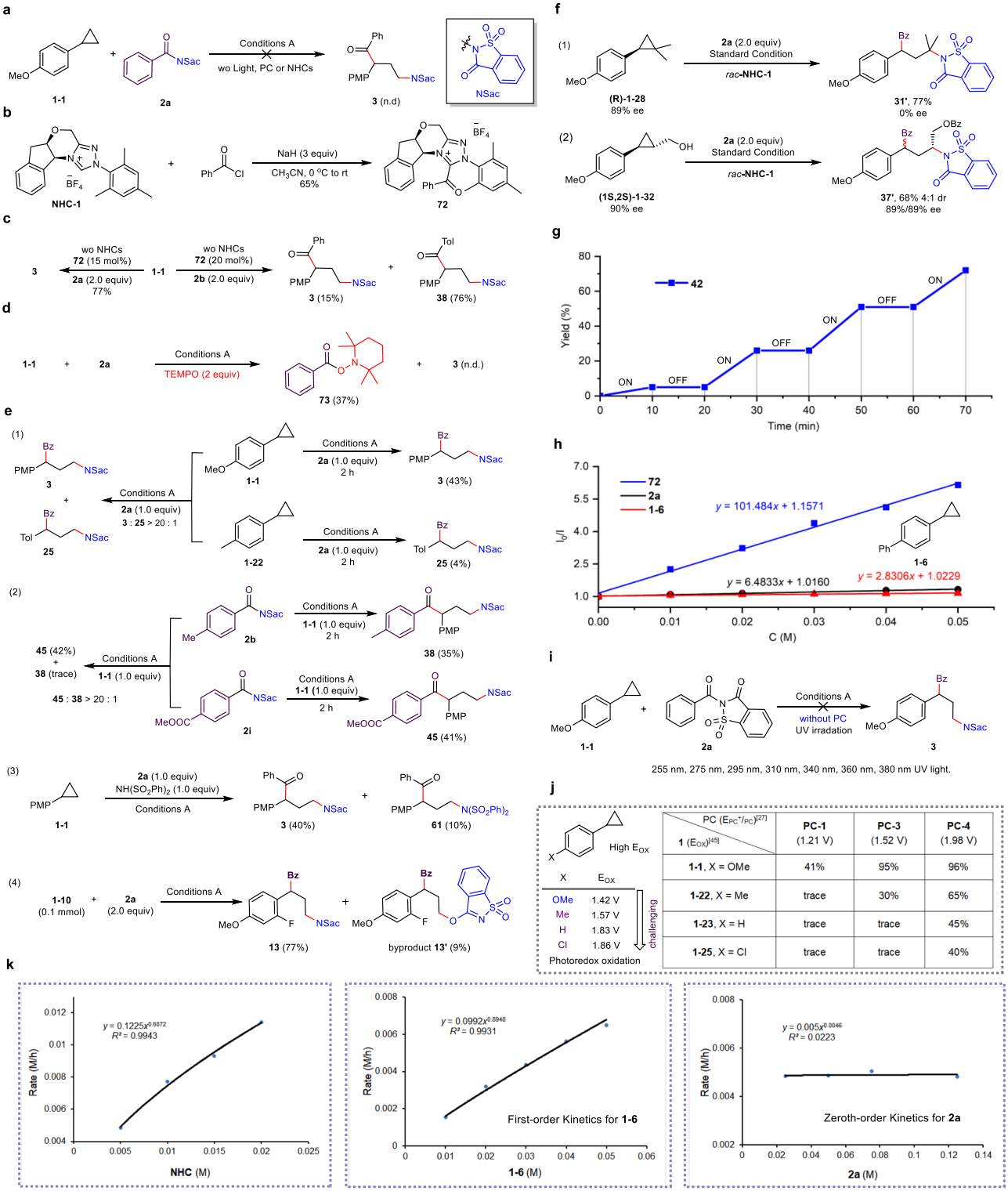

1 (E_{OX})[45] \ PC ($E_{PC^+/PC}$)[27]	PC-1 (1.21 V)	PC-3 (1.52 V)	PC-4 (1.98 V)
1-1, X = OMe	41%	95%	96%
1-22, X = Me	trace	30%	65%
1-23, X = H	trace	trace	45%
1-25, X = Cl	trace	trace	40%

X	E_{OX}
OMe	1.42 V
Me	1.57 V
H	1.83 V
Cl	1.86 V

Fig. 5 | Mechanistic investigations. a Control experiment. **b** Preparation of NHC-adduct. **c** Catalistic acitivity of NHC-adduct. **d** Radical capture experiment. **e** Competing experiment. **f** Ring-opening of enantiomerically enriched **1-28, 1-32**. **g** Light on/off experiments. **h** Stern-Volmer quenching studies. **i** Excitation experiments with UV light. **j** The effect of PC ($E_{PC+/PC}$) and cyclopropane (E_{OX}) on reactivity. **k** Reaction progress kinetic analysis.

successfully achieved gram-scale synthesis, obtaining a 71% yield of **42** (Fig. 4a). **3** underwent carbonyl α C–H alkylation and esterification ring opening of the saccharin motif (FigS. 4b$_1$ & 4b$_2$), producing 68% and 45% yields of **68** and **69**, respectively. Furthermore, deprotection of the phenolic hydroxyl and amino groups occurred, generating cyclized 3,4-dihydro-2*H*-pyrrole **69'** in a 71% yield (Fig. 4b$_3$). The carbonyl group was reduced to methylene using Et_3SiH in TFA, resulting in a 54% yield of **70** (Fig. 4b$_4$). Additionally, when $NaBH_4$ was employed as a reductant, **42** underwent reduction, and ring opening resulted in an 88% yield of **71** (Fig. 4b$_5$).

Mechanistic investigations

To further elucidate the mechanism involved, we conducted a series of investigations (Fig. 5). Control experiments confirmed that light

irradiation, photoredox catalysts, and NHC catalysts were essential for cascade aminoacylation (Fig. 5a). NHC-adduct **72** was initially prepared following Martin's methods[70] (Fig. 5b). The catalytic activity of **72** was confirmed through the ring-opening 1,3-aminaiton/acylation cascade of cyclopropane in the absence of NHCs (Fig. 5c, Left). When **2b** was utilized as a bifunctional reagent, **3** (originating from **72**) and **38** (originating from **2b**) were produced with yields of 15% and 76%, respectively (Fig. 5c, Right), indicating the intermediate and catalytic activity of **72**. The addition of the radical inhibitor 2, 2, 6, 6-tetramethylpiperidine 1-oxyl (TEMPO) inhibited the transformations, and the acyl radical-trapped byproduct **73** was produced with a 37% yield, indicating the involvement of a radical pathway (Fig. 5d). We conducted several competing experiments, as shown in Fig. 5e. The electron density of cyclopropane appeared to play a crucial role in the reaction rate, with strong electron-donating aryl cyclopropanes reacting faster than moderate ones under competitive and parallel conditions (Fig. 5e_1). Interestingly, under competing conditions, electron-deficient *N*-aroyl saccharins reacted much faster than electron-rich saccharins did (Fig. 5E_2, Left), while similar reaction rates were observed under parallel conditions (Fig. 5e_2, Right). Furthermore, the yields of **45** under competitive and parallel conditions were similar, supporting the idea that the C–N cleavage step might be included in the product-determining step but not the rate-determining step. Competitive experiments with additional nucleophilic reagents, such as $NH(SO_2Ph)_2$, revealed that **3** (40%) and **61** (10%) were competitive compounds (Fig. 5e_3). Furthermore, for cyclopropane **1**–**10**, 1, 3-oxoacylation product **13'** and normal *γ*-amino ketone **13** were found to be competitive compounds, and they were produced with 9% and 77% yields, respectively. These results indicate that the ring-opening process of cyclopropane may occur via nucleophilic attack by amide anions. The ring opening of enantio-enriched **1**–**28** and **1**–**32** demonstrates the stereospecificity of the aminative nucleophilic ring opening process of cyclopropane, whereas the acylation process results in a non-stereospecific configuration (Fig. 5f). To delve deeper into the mechanism of the photoredox cycle, we conducted photochemical experiments. The transformation occurred only under light irradiation, contradicting the radical chain mechanism (Fig. 5g). Emission quenching experiments (Fig. 5h) revealed that excited PC* was more likely to be quenched by acyl NHC-adduct **72** (K_{SV} = 101.5 L/mol) than by cyclopropane **1-6** (K_{SV} = 2.8 L/mol) and *N*-benzoyl saccharin **2a** (K_{SV} = 6.5 L/mol). In the absence of a photocatalyst, directly irradiating the reaction with different wavelengths of UV light was unable to produce the desired targets (Fig. 5i). Control experiments revealed that the degree of reactivity matched the oxidation potential of cyclopropane[45] and the reduction potential of $E_{1/2}(PC^+/PC)$[27] (Fig. 5j). These findings, combined with those of the emission quenching experiments, suggest a preference for the oxidative quenching process[65,66] rather than the energy transfer pathway[6–8,71,72]. Finally, we conducted kinetic experiments, which indicated a first-order dependence on the concentration of cyclopropane (Fig. 5k, Middle), whereas *N*-aroyl saccharin exhibited a zeroth-order dependence (Fig. 5k, Right). An increase in the concentration of NHCs had a promotive effect on the reaction rate (Fig. 5k, Left).

On the basis of previous reports and our experimental results, we proposed possible catalytic cycles (Fig. 6). NHCs act as Lewis base catalysts, promoting the cleavage of C–N bonds and generating NHC-adduct **I** and the saccharin anion. Under blue LED irradiation, excited 4-CzIPN* ($E_{1/2}$ ($4CzIPN^+$/4CzIPN*) = −1.04 V vs. SCE) underwent an oxidative quenching process with NHC-adduct **I** (− 0.78 V vs. SCE, Figure S15), generating persistent NHC-attached acyl radical **II** and oxidized PC^+. Single-electron transfer occurred between PC^+ [for 4CzIPN, $E_{1/2}(PC^+/PC)$ = 1.52 V] and cyclopropane, regenerating ground-state PC and forming cyclopropane radical cation **III**, thus closing the photoredox cycle. The employment of highly oxidized PC^+ [for PC-4, $E_{1/2}(PC^+/PC)$ = 1.98 V] improved substrate applicability. Moreover, nucleophilic attack by the saccharin anion on radical cation **III** activated C–C bonds

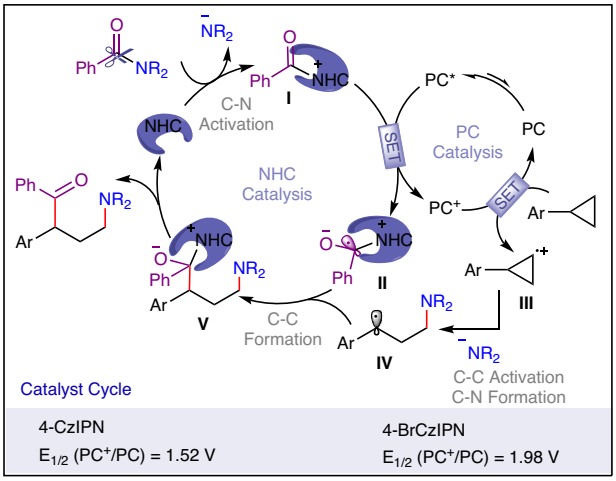

Fig. 6 | Proposed catalytic cycle. Oxidative quenching driven NHC/PC dual catalysis.

and formed C–N bonds, generating benzyl radical **IV**. Moreover, radical–radical cross-coupling[73] between **IV** and **II** produced **V**, and the dissociation of NHCs led to the formation of the final product.

In summary, we demonstrated the use of visible-light-mediated NHCs for a photoredox dual-catalyzed aminoacylation of cyclopropanes, employing readily available and bench-stable *N*-benzoyl saccharin as a bifunctional carboamination reagent. The direct addition of the C–N bonds of N-containing compounds to cyclopropanes under metal-free and mild conditions is an important advancement in this research area. This protocol overcomes the generality limitation of aryl cyclopropane in photooxidation. Mechanistic investigations revealed that the oxidative quenching process between the excited-state PC* and acyl NHC adduct achieved successful photooxidation of cyclopropanes. NHCs play multiple roles, including functioning as Lewis base catalysts to activate C–N bonds, promoting the oxidative quenching process of PC*, and acting as efficient acyl radical transfer catalysts for the formation of C–C (acyl) bonds. Ongoing research in our lab is exploring the application of this NHC/PC dual-catalyzed oxidative quenching system for other challenging transformations.

Methods

General procedure for the aminoacylation of cyclopropanes with *N*-benzoyl saccharin as bifunctional reagent

Into a nitrogen-filled glove box, a vial (10.0 mL) equipped with a magnetic stir bar was charged with **NHC-1** (6.2 mg, 0.015 mmol), 4CzIPN (1.6 mg, 0.002 mmol), Cs_2CO_3 (65.1 mg, 0.2 mmol), **2** (0.2 mmol) and DCM (2.0 mL). Then **1** (0.1 mmol) were added. The vial was removed from the glovebox, and then the reaction mixture was irradiated with Blue LED at room temperature for 12 h. After the reaction finished that monitored by TLC, the reaction mixture was quenched by water. The mixture was extracted with DCM (3 × 5.0 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and the solvent was evaporated under vacuum. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate = 3:1) to give the corresponding product. (See SI for more details on experimentation.)

Data availability

Data supporting the findings of this study are available within the article and Supplementary Information files. The source data underlying Fig. 5g, Fig. 5h, Fig. 5k, Supplementary Figs. S2–S15 are provided as a Source Data file. Source data are available and provided with this paper. All other data are available in the main text or the Supplementary Information. All data are available from the corresponding author upon request. Source data are provided with this paper.

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G.Z. & J.S. conceived and designed the experiments. M.L., Y.W., and X.S. performed the experiments and analyzed the data. G.Z., J.S. and Q.Z. co-wrote the manuscript. Z.Z. and Q.Z. provided constructive advice. Z.Z. polishing the manuscript. All authors contributed to the discussions.

Competing interests

The authors declare no competing interests.

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