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ARTICLE

Photocatalytic Construction of N-Acyl-N,O-Acetal-Linked Pyridines via Aminocyclopropane Ring Opening

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Pyridine and quinoline linkers are privileged motifs in medicinal chemistry, yet their site-selective installation into complex scaffolds remains challenging. Here we report that aminocyclopropanes serve as precursors to N-acyl-N,O-acetal linkers installed onto pyridines via visible-light-driven ring opening under oxidant-free conditions. Ring-opened radical is captured by *N*-aminopyridinium salts to forge C(sp³)–C(aryl) bonds at the C4-selective site of the pyridine core, while the concomitantly released *N*-centered radical oxidizes the reduced photocatalyst, enabling efficient turnover. Subsequent nucleophile trapping furnishes N-acyl-N,O-acetals bearing pyridine or quinoline units with broad scope across both heteroarenes and aminocyclopropanes, including late-stage diversification of complex molecules. Substituting methanol with $TMSN_3$ provides azido-aminals, further expanding accessible architectures. The resulting N-acyl-N,O-acetal moieties function as versatile linchpins that engage diverse downstream manifolds, thereby enabling modular assembly and late-stage diversification of pyridine-containing targets.

Introduction

Pyridine and quinoline are among the most ubiquitous heteroarenes in pharmaceuticals, agrochemicals, ligands, and functional materials, reflecting their exceptional versatility and frequent occurrence in clinical candidates and approved drugs (Fig. 1a).[1] Their tunable basicity, metabolic stability, and well-defined hydrogen-bond-accepting characteristics make them particularly attractive for pharmaceutical design, where pyridine incorporation enables the introduction of solubilizing groups, photoaffinity tags, and heterobifunctional tethers with tailored functional properties.[2]

In parallel, N-acyl-N,O-acetals (and their hemiaminal congeners), frequently encountered as key motifs in bioactive and pharmaceutical molecules,[3] represent bench-stable and readily diversifiable scaffolds that are attracting increasing attention.[4] Nucleophile-induced substitution at the acetal carbon, acetal exchange, and controlled hydrolysis, oxidation, or reductive amination provide rapid entry to families of medicinally relevant building blocks. Owing to their facile activation under both Brønsted-acidic and metal-catalyzed conditions, these motifs function as reliable linchpins for fragment coupling, rearrangement, and heterofunctionalization.[5] However, general and site-selective strategies that enable the direct installation of N,O-acetal linkers—particularly at the C4 position of pyridines and the corresponding site in quinolines—under mild conditions remain scarce. The C4 position offers an orthogonal exit vector from the pyridyl core, enabling bond formation in a distinct spatial direction and providing a well-defined platform for constructing bifunctional linkers, photoaffinity tags, and PROTAC-type heterobifunctional tethers.

Cyclopropanes have emerged as C3 synthons that combine operational stability with latent reactivity unmasked by ring opening.[6] While Lewis-acid and transition-metal activation of suitably polarized cyclopropanes is well established,[7] substrates lacking strong electronic bias—such as mono-donor/acceptor and arylcyclopropanes—often remain recalcitrant. Recently, photochemistry-driven single-electron transfer (SET) has emerged as a powerful strategy to achieve these demanding conversions.[8] It has proven particularly effective in delivering ring-opening functionalizations under mild conditions.[9] Among these, aminocyclopropanes are particularly attractive: SET oxidation generates an amidyl radical that undergoes β-scission to give a distonic iminium radical primed for further functionalization.[10] Despite advances in radical chemistry of aminocyclopropanes, direct, C4-selective heteroarylation that simultaneously forges pyridyl- and quinolyl-linked N,O-acetal (or hemiaminal) frameworks has remained underexplored. The integration of C4-selective heteroaryl functionalization with concurrent N,O-acetal (or hemiaminal) formation would thus provide a powerful and modular platform for the synthesis of functional molecules and for late-stage diversification.

N-Aminopyridinium salts have recently emerged as versatile pyridine electrophiles that undergo radical coupling under mild, site-selective conditions.[11] A key advantage is that N–N bond fragmentation releases a sulfonamidyl fragment that can act as an internal terminal oxidant, obviating external oxidants and enabling closed catalytic cycles.[12] We reasoned that these attributes would permit efficient capture of ring-opened γ-radicals derived from aminocyclopropanes, forging C(sp³)–C(aryl) bonds with intrinsic preference for addition at the pyridyl C4 site (and the corresponding quinoline position), thereby appending a functionalized linker in a single step. Here we report a visible-light-driven coupling of aminocyclopropanes with *N*-aminopyridinium salts that directly installs N-acyl-N,O-acetal (hemiaminal) scaffolds into the pyridine or quinoline under neutral, oxidant-free conditions (Fig. 1b). The transformation displays broad functional-group tolerance across both heteroarenes and aminocyclopropanes, is operationally simple, and

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delivers excellent C4 regioselectivity via a SET-initiated β-scission/addition/rearomatization sequence.[11d,f] Crucially, the resulting N-acyl-N,O-acetals serve as versatile synthetic linchpins that engage diverse functionalization manifolds. The intact scaffold undergoes diverse nucleophilic substitution reactions at the acetal carbon with organometallic reagents, indoles, thiols, cyanide, and phosphines, as well as Mukaiyama and Petasis-type reactions, underscoring its versatility for further functionalization. This strategy opens access to structurally diverse pyridine-containing motifs that were previously difficult to obtain, broadening the accessible chemical space for pyridyl derivatives. It provides a modular late-stage route to 4-pyridyl-linked architectures, transforming aminocyclopropanes into general precursors that enable both structural remodeling and functional diversification.

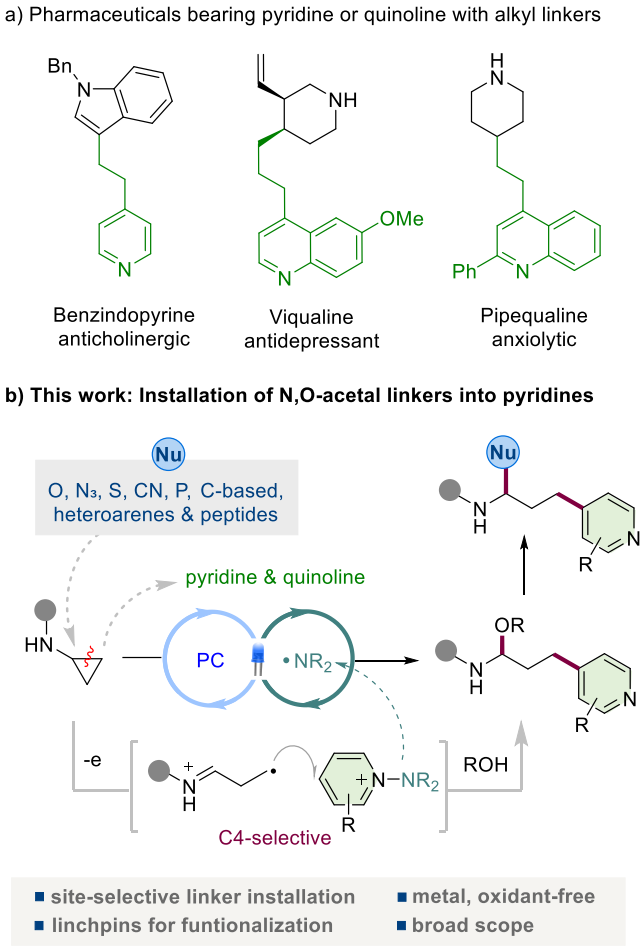
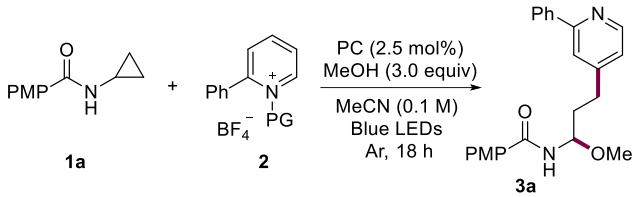


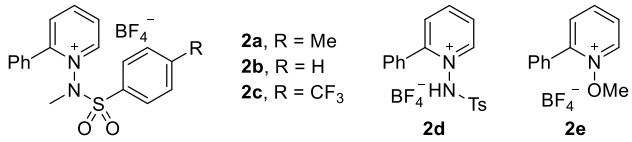
Fig. 1 Photocatalytic construction of pyridyl-linked N-acyl-N,O-acetals via aminocyclopropane ring opening promoted by PC/amidyl radicals

Results and discussion

To evaluate the feasibility of our design, we examined the model coupling between *N*-cyclopropyl-4-methoxybenzamide (**1a**) and *N*-aminopyridinium salt **2** in MeCN using the 3,6-di-*tert*-butyl-9-mesityl-10-phenylacridinium tetrafluoroborate as photocatalyst (PC) and MeOH under blue-LED irradiation (Table 1). The initial reaction afforded the ring-opened γ-pyridyl *N,O*-acetal **3a** in 65% yield with exclusive C4-selectivity (entry 1). Systematic variation of reaction parameters identified temperature control as the key factor influencing performance; implementation of precise thermal regulation significantly improved consistency. Further thermal profiling revealed that mild cooling enhanced the yield, whereas heating led to diminished efficiency (entries 2 and 3). At –20 °C, the reaction rate decreased, yet prolonged irradiation afforded **3a** in 81% yield (entries 4 and 5). Screening of photocatalysts confirmed that the original acridinium photocatalyst was optimal (entries 6–9, each E_{red} = +2.08 V, 1.21 V, 0.66 V, 1.35 V vs SCE respectively),[13] consistent with the need for a strong photooxidant to engage **1a**. Examination of the aryl substituent on the pyridinium electrophile showed that both unsubstituted and CF_3-substituted aryl groups maintained high C4-selectivity, with only a modest reduction in reactivity in the latter case (entries 10 and 11). In contrast, protonated or N–O-substituted salts (**2d** and **2e**) exhibited reduced efficiency and diminished selectivity due to formation of the C2-substituted product, consistent with prior reports [11j] (entries 12 and 13).

Table 1 Optimization for the reaction conditions





Entry	PC	Salt	Temp	Yield
1	[^{t}Bu$_2$-Mes-Ph-Acr]BF$_4$	**2a**	25 °C	65%
2	[^{t}Bu$_2$-Mes-Ph-Acr]BF$_4$	**2a**	40 °C	58%
3	[^{t}Bu$_2$-Mes-Ph-Acr]BF$_4$	**2a**	10 °C	68%
4	[^{t}Bu$_2$-Mes-Ph-Acr]BF$_4$	**2a**	–20 °C	34%
5	[^{t}Bu$_2$-Mes-Ph-Acr]BF$_4$	**2a**	–20 °C	81%[a] (80%)
6	[Mes-Acr]BF$_4$	**2a**	–20 °C	69%[a]
7	[Ir{dF(CF$_3$)ppy}$_2$dtbbpy]PF$_6$	**2a**	–20 °C	48%[a,b]
8	[Ir(ppy)$_2$dtbbpy]PF$_6$	**2a**	–20 °C	11%[a,b]
9	4CzIPN	**2a**	–20 °C	30%[a]
10	[^{t}Bu$_2$-Mes-Ph-Acr]BF$_4$	**2b**	–20 °C	78%[a]
11	[^{t}Bu$_2$-Mes-Ph-Acr]BF$_4$	**2c**	–20 °C	68%[a]
12	[^{t}Bu$_2$-Mes-Ph-Acr]BF$_4$	**2d**	–20 °C	41%[a](1:1)
13	[^{t}Bu$_2$-Mes-Ph-Acr]BF$_4$	**2e**	–20 °C	31%[a](1.4:1)

Reaction conditions: **1a** (0.05 mmol), **2** (1.5 equiv), PC (2.5 mol%), MeOH (3.0 equiv) in MeCN (0.5 mL) under irradiation with 440 nm LEDs (10 W) at 25 ℃ for 18 h under argon. Yields determined by ^{1}H NMR spectroscopy using caffeine as an internal standard. Isolated yield and regioisomeric ratio (C4 vs C2) in parentheses. PMP = p-methoxy phenyl. [a]Reaction time: 40 h. [b]1 mol% of PC used.

With the optimized conditions in hand, we investigated the scope to underscore generality and late-stage utility (Tables 2 and 3). Substitution at C2 of the pyridinium electrophile was broadly tolerated

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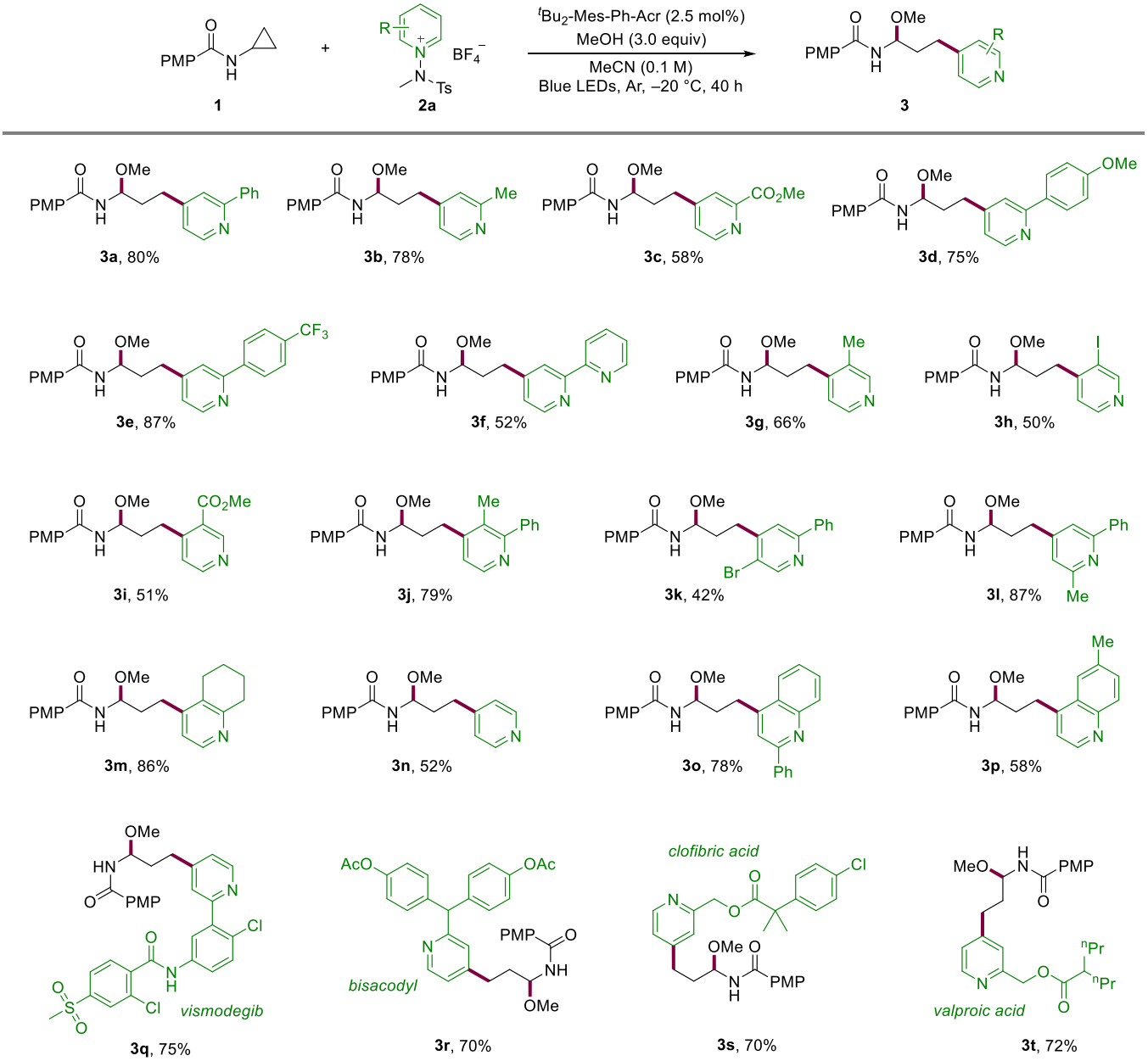
across electronic regimes, furnishing good yields for both electron-donating and electron-withdrawing groups (**3a–3c**). Phenyl-ring substitution proved productive—methoxy and trifluoromethyl delivered high yields (**3d**, **3e**)—and a bipyridyl unit remained competent (**3f**). C3-substituted salts, including halide and ester variants, reacted smoothly (**3g–3i**). Likewise, disubstituted pyridines underwent the transformation with comparable efficiency (**3j–3l**). Notably, fused-ring substrates afforded the desired product **3m** in excellent yield, while unsubstituted pyridine underwent smooth conversion (**3n**). The platform extended to quinolines bearing C2 or C6 substitution (**3o**, **3p**), indicating translatability across azine scaffolds. For late-stage derivatization, derivatives of vismodegib, bisacodyl, clofibric acid, and valproic acid were functionalized in good efficiency while preserving C4 selectivity throughout (**3q–3t**).

Turning to the aminocyclopropane partner (Table 3, top), an aryl-substituted cyclopropane delivered product **4a**. Para-substituted arenes bearing electron-donating or electron-withdrawing groups were compatible (**4b**, **4c–4f**), and meta/ortho substitution patterns were likewise tolerated with comparable efficiencies (**4g–4j**). Extended aromatics such as naphthalene and benzothiophene performed well (**4k**, **4l**). Ring-size increase from cyclopropyl to cyclobutyl remained viable (**4m**). Aliphatic and benzylic variants were accommodated (**4n–4p**), as were ether-containing substrates (**4q**); common N-protecting groups (Cbz and Troc) were retained (**4r**, **4s**).

Table 2 Scope of pyridyl rings



Reaction conditions: **1a** (0.1 mmol), **2** (0.15 mmol), ^{t}Bu$_2$-Mes-Ph-Acr (2.5 mol%), MeOH (0.3 mmol) in MeCN (1.0 mL) under irradiation with 440 nm LEDs (10 W) at –20 ℃ for 40 h under argon.

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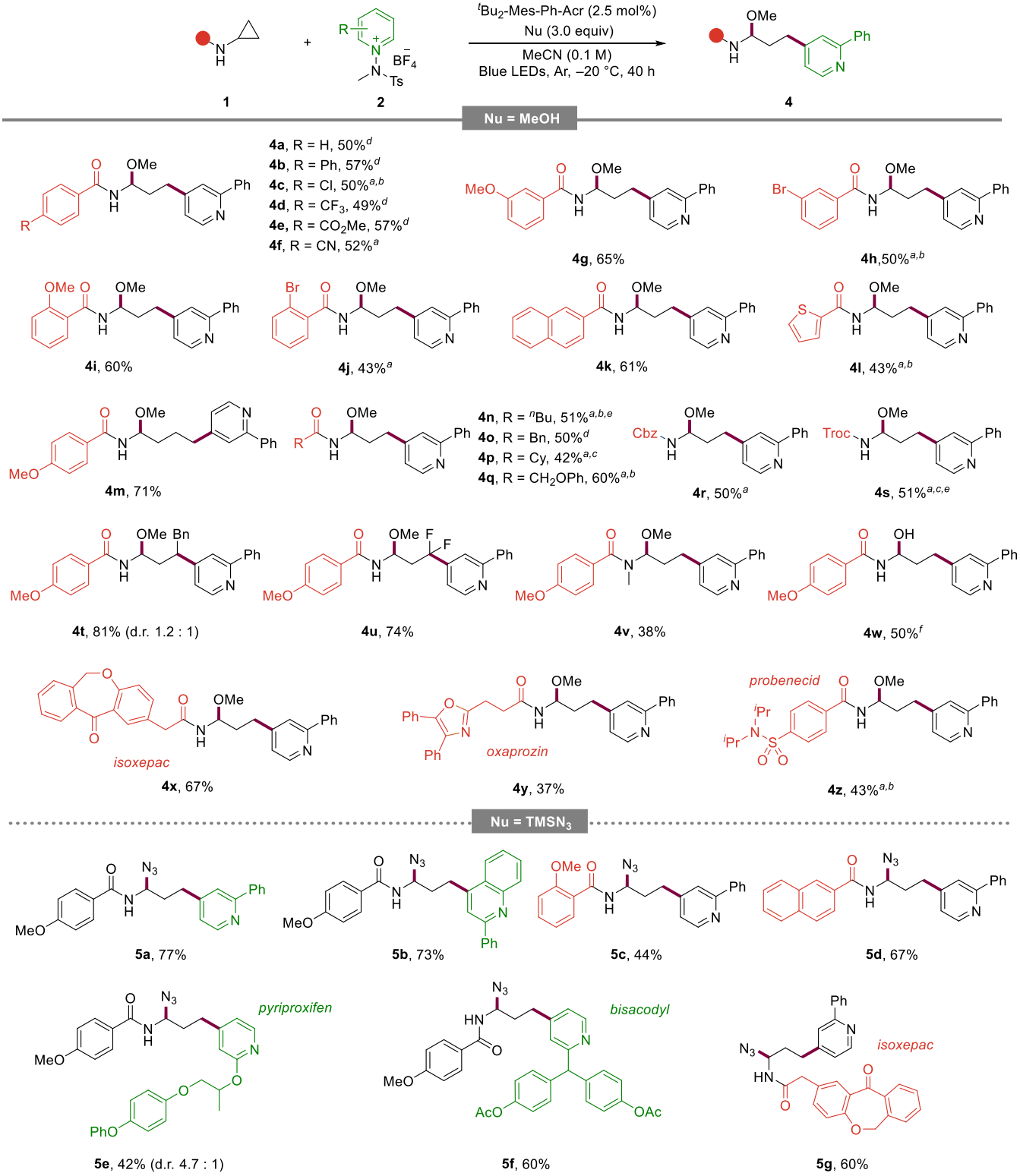
Table 3 Aminocyclopropane scope and extension to azide nucleophile.



Reaction conditions: **1** (0.1 mmol), **2a** (0.15 mmol), ^{t}Bu$_2$-Mes-Ph-Acr (2.5 mol%), MeOH (0.3 mmol) in MeCN (1.0 mL) under irradiation with 440 nm LEDs (10 W) at –20 ℃ for 40 h under argon atmosphere. Azidation: $TMSN_3$ (0.3 mmol) used instead of MeOH. [a]Reaction under room temperature. [b]24 h for reaction time. [c]72 h for reaction time. [d]Reaction under room temperature, 24 h for reaction time, 5 mol% of PC used. [e]5 equiv of MeOH and **2b** used. [f]Yield of Inseparable diastereomer mixtures. [g]H_2O instead of MeOH. Diastereomeric ratios determined by 1H NMR analysis of the crude mixtures.

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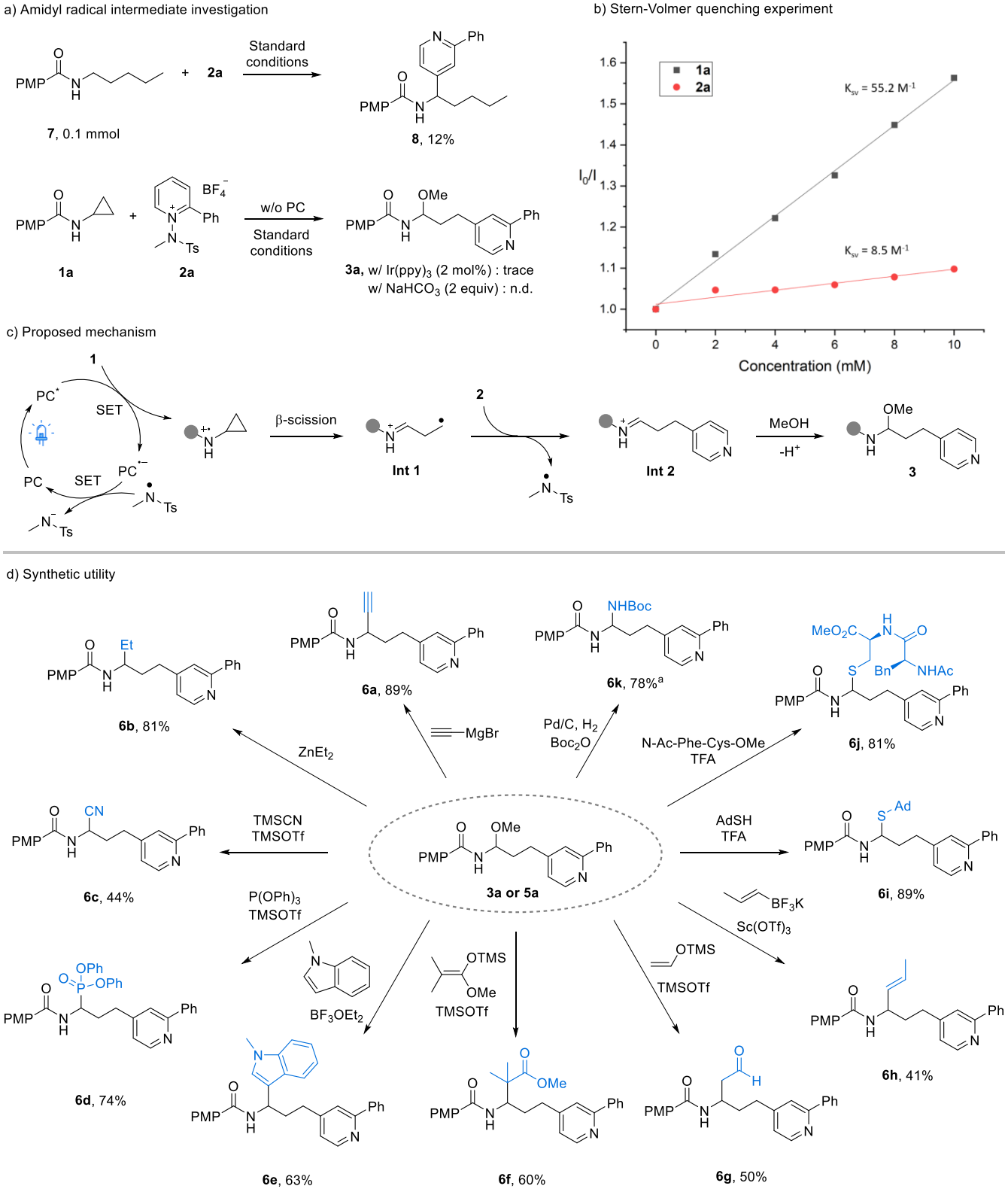

Fig. 2 Mechanistic studies and synthetic utility. [a]From **5a**.

To expand the versatility of the reaction, we tried changing the substituents, the reaction was also successfully carried out in the case of 1,2-disubstituted and difluorine substituted aminocyclopropane (**4t, 4u**). Notably, the desired products were secured even from the tertiary amide substrate (**4v**), previously reported to be unreactive or susceptible to decomposition owing to product instability.[10b-d,10f] Also,

substituting water for methanol as the nucleophile furnished the corresponding product under standard conditions (**4w**). Finally, late-stage diversification of pharmaceutically relevant scaffolds (isoxepac, oxaprozin, probenecid) proceeded in synthetically useful yields (**4x–4z**). Collectively, the scope highlights broad compatibility across electronic properties, substitution patterns, and molecular complexity, enabling late‑stage diversification while preserving C4 selectivity.

To expand the nucleophile scope, we explored $TMSN_3$ as an azide source (Table 3, bottom). Under the optimized photoredox conditions, a variety of pyridinium salts and aminocyclopropanes were smoothly converted into the corresponding azido aminals. Within the pyridinium series, both a C2-substituted pyridine (**5a**) and a C2-substituted quinoline (**5b**) furnished the desired products in high yields. Electron-rich and extended aromatic aminocyclopropanes were also competent partners: the *o*-methoxy benzamide derivative (**5c**) and the naphthamide analogue (**5d**) delivered the products efficiently. Furthermore, late-stage azidation of drug-derived substrates such as pyriproxyfen (**5e**), bisacodyl (**5f**), and the bioactive scaffold isoxepac (**5g**) proceeded in synthetically useful yields.

To elucidate the reaction pathway, we performed a series of control and trapping experiments. Excluding either the photocatalyst or light completely suppressed product formation, and the reaction proved sensitive to air (Table S6 in the SI), ruling out a two-electron mechanism. Radical inhibition by TEMPO halted the reaction, while butylated hydroxytoluene and 1,1-diphenylethylene significantly reduced conversion; the TEMPO adduct was detected by LC-MS, confirming radical intermediacy (Table S7 in the SI) . Evidence for an *N*-centered radical was obtained using linear pentyl benzamide: under standard conditions, **7** underwent H-atom transfer to give **8**, consistent with amidyl generation (Fig. 2a, Top).[14] And the formation of product **4v** from a tertiary amide lacking an N–H bond demonstrates that the reaction proceeds without N–H abstraction by the N-methyl-tosyl radical, thereby supporting a SET-based pathway. In addition, employing $Ir(ppy)_3$, which is insufficiently oxidizing to activate the aminocyclopropane. led to only trace product formation. Likewise, the use of a base to promote an electron–donor–acceptor complex resulted in no reaction (Fig. 2a, bottom). Taken together, these data indicate that H-abstraction from the amide by the N-methyl-tosyl radical is unlikely to be a productive pathway. Finally, the low quantum yield ($\Phi = 0.145$) further supports that any chain-propagation pathway is minimal (see SI). Stern–Volmer quenching confirmed that **1a** efficiently quenches the excited photocatalyst, supporting initial SET oxidation of the aminocyclopropane (Fig. 2b). On the basis of these results and precedent, we propose the mechanism shown in Fig. 2c. Photoexcited acridinium (E_{red} = +2.15 V vs SCE)[13] oxidizes the aminocyclopropane (E_p = +1.68 V vs SCE);[10c] subsequent β-scission yields a distonic iminium radical cation (**Int-1**). Coupling with the *N*-aminopyridinium electrophile forms the pyridylated iminium ion (**Int-2**) with concurrent *N–N* bond cleavage to release an *N*-methyl-tosyl radical ($E_{red,cal}$ = +0.47 V vs SCE in MeCN)[12b], which closes the catalytic cycle via oxidation of the reduced photocatalyst (E_{ox} = -0.52 V vs SCE)[13]. Trapping of the iminium by the nucleophile (MeOH or $TMSN_3$) affords the observed *N,O*-acetal or azido aminal products.

To demonstrate scalability and practicality, gram-scale reactions (5 mmol *N,O*-acetal, 3 mmol azido aminal) delivered products in 61% and 65% yield, respectively (Table S8 in the SI). The resulting scaffolds underwent diverse downstream transformations (Fig. 2d): Grignard and organozinc additions furnished alkynylated and alkylated derivatives (**6a**, **6b**); Lewis-acid activation enabled cyanation, phosphorylation, and indole C3-alkylation (**6c–6e**). Mukaiyama and Petasis-type reactions with silyl enol ethers or tetrafluoroborate salts provided ester, aldehyde, and alkene motifs (**6f–6h**). TFA-mediated thiol additions generated stable *N,S*-acetals (**6i**) and allowed peptide-based thiols to be incorporated (**6j**), demonstrating compatibility with biomolecular substrates. Finally, reduction of azido aminal product **5a** yielded the corresponding amine, which were readily protected as Boc derivative **6k**. Overall, these mechanistic and synthetic studies underscore both the radical nature and the broad synthetic versatility of this transformation, establishing a robust platform for late-stage diversification of pyridine-linked scaffolds.

Conclusions

This work establishes a broadly applicable platform for the installation of N-acyl-N,O-acetal moieties onto pyridine and quinoline via visible-light activation of aminocyclopropanes. By converting strain release into selective $C(sp^3)$–C(aryl) bond formation, this method enables the mild, oxidant-free installation of N-acyl-N,O-acetals linkers into pyridines, delivering excellent C4-regioselectivity and broad substrate scope. The transformation integrates radical reactivity with programmable functionalization, offering a general approach for late-stage diversification and modular assembly of heteroaromatic frameworks. Beyond providing a practical tool for medicinal chemistry, this strategy redefines aminocyclopropanes as versatile precursors for N-acyl-N,O-acetals installation and diverse nucleophile incorporation, enabling modular access to heteroaryl frameworks bearing tunable functionalities.

Author contributions

D. K. and S. H. conceived the idea of the project. D. K., E. Y. and Y. C. performed the experiments, and analyzed the data. All authors wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

Detailed synthetic procedures, supporting experimental results, and complete characterization data for all new compounds can be found in the ESI.

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Data availability

Detailed synthetic procedures, supporting experimental results, and complete characterization data for all new compounds can be found in the ESI.