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Photoinduced Site-Selective C-H Functionalization by Pyridine N-oxide Based HAT Catalysts

Received 00th January 20xx,
Accepted 00th January 20xx

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Introduction and concept design

Pyridine *N*-oxide derivatives, readily accessible and versatile reagents, have long been recognized as electro-pair donors, mild oxidants, and ligands in metal complexes.[1] Thereafter, widespread applications of pyridine *N*-oxides based on the classic and well-established two-electron transfer chemistry have been found in synthesis and catalysis.[2] In addition, the capability of pyridine *N*-oxides to participate in the single-electron transfer process has been documented as well.[3] For example, early electrochemical studies of pyridine *N*-oxides revealed that they could undergo single-electron oxidation to generate N-oxide cation radical,[3a,3b] however, the utility of this intriguing species in radical chemistry and synthesis has long been ignored until recently. By applying photoredox catalysts, a strategy for vinyl radical generation through photoinduced single-election oxidation of pyridine *N*-oxides and alkynes was presented by our group and Wu respectively.[4] Accordingly, an *ortho*-alkylation of pyridine *N*-oxide and photocatalyzed cyclopropanation of ene-ynamide were disclosed.[4] With our group's continuous effort in the study of single-electron transfer chemistry of pyridine *N*-oxides in organic synthesis and catalysis, here, we report the development of pyridine *N*-oxide derivatives as effective photoinduced hydrogen atom transfer (HAT) catalysts for site-selective C-H functionalization.

In recent years, the strategy of synergistically combining photoredox and HAT catalysis has offered a highly attractive avenue for accessing direct C-H functionalization.[5] In general, photoredox-induced generation of heteroatom-centered (N, O, S, and halide) radical from HAT reagent promotes the HAT process for inert C-H bond and subsequent functionalization. A variety of photoinduced HAT catalysts (e.g. quinuclidine derivatives,[6] halides,[7] benzoates,[8] and *N*-hydroxy compounds[9]) have been reported for diverse C–H functionalization. Many of the stated examples dealt with activated C–H bonds or C(sp^3)–H bonds that are equivalent. In the past few years, a few photoredox/HAT systems for selective functionalization of unactivated C(sp^3)–H bonds have emerged, while challenges still persist. For instance, the utility of benzoate salts as photoinduced HAT catalyst was reported by Glorius, while it has been limited to trifluoromethylation.[8a] Most recently, Matsumoto and Maruoka reported photoinduced C–H alkylation by cationic DABCO-based HAT catalyst, which shown good to high site-selectivity for tertiary C–H bonds for limiting scope.[10] Site-selective tertiary C–H azidation, thiolation, and alkylation were achieved respectively by applying phosphate salt,[11] tetrafluoropyridinyl disulfide,[12] and CH_2Br_2[7n] as photoinduced HAT reagents in stoichiometric amounts. Despite the impressive progress, it is still desired to develop new photoredox/HAT catalytic platforms that 1) can encompass the catalytic manners of both photosensitizer and HAT reagent, and 2) are based on readily accessible scaffolds allowing facile structural/activity tuning to enable selective HAT of unactivated C(sp^3)–H bonds. In this regard, we describe here, in conjunction with an acridinium photoredox catalyst, readily available and tunable pyridine *N*-oxides could serve as effective hydrogen atom transfer (HAT) catalysts for site-selective C-H functionalization of a broad-range of substrates, including unactivated hydrocarbons. Notably, this research demonstrates that variation of pyridine *N*-oxide substituents significantly affects their activity/selectivity towards photoinduced C-H bond functionalization, including stronger C–H bonds (1° and 2°). The effective activity and facile electronic/steric tunability of pyridine *N*-oxides make it promising platform and new chemical access for catalyst-controlled selective C–H functionalization.

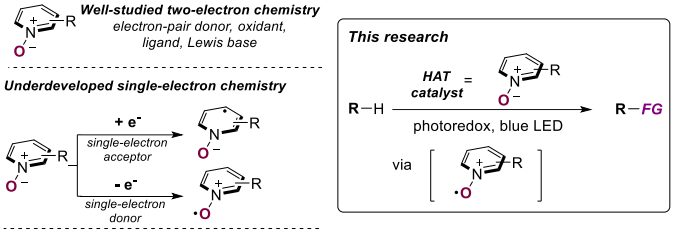

Figure 1. Photoinduced pyridine *N*-oxide based HAT catalyst for C-H functionalization.

Our group recently developed a photocatalytic strategy for β-oxypyridinium vinyl radical generation through photoredox catalyzed single-electron oxidation of a pyridine *N*-oxide/alkyne system (Figure 2a).[4a,4c] In a possible mechanistic pathway, acridinium photoredox catalyzed single-electron oxidation of pyridine *N*-oxides leads to the generation of *N-oxide* cation radicals, which react with alkynes giving β-oxypyridinium vinyl radical intermediates. Inspired by these results, we propose that the highly electrophilic pyridine *N-oxide* cation radicals, which could be produced by photoredox catalyzed single-electron oxidation of pyridine *N*-oxides, may

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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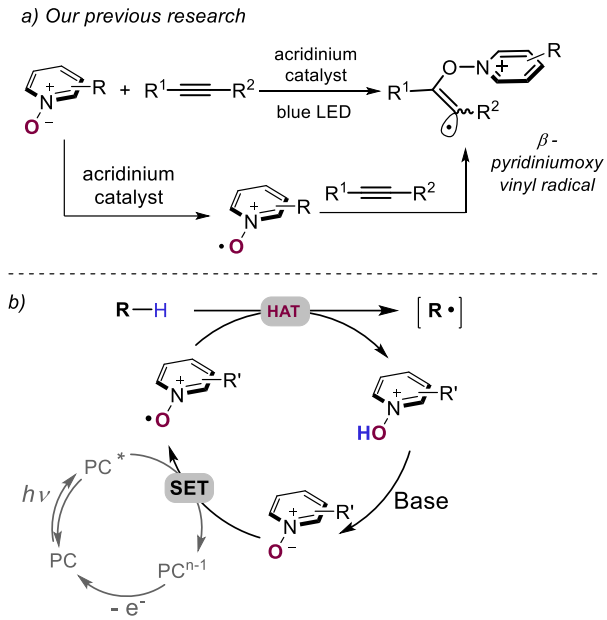


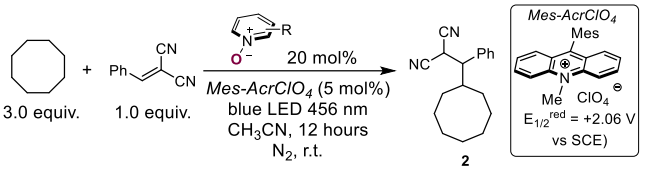
Figure 2. a) Our previous research. b) Proposed photoinduced pyridine *N*-oxide based HAT catalyst for carbon radical generation.

act as a HAT mediator to abstract H atom from a C-H bond for carbon radical generation and subsequent functionalization (Figure 2b). Moreover, the resultant protonated pyridine *N*-oxides with mild acidity (pka = -1.7-2 in water, 5.6-12.2 in acetonitrile)[89] would allow feasible deprotonation for *N-oxide* regeneration, thus achieving HAT process in a catalytic fashion.

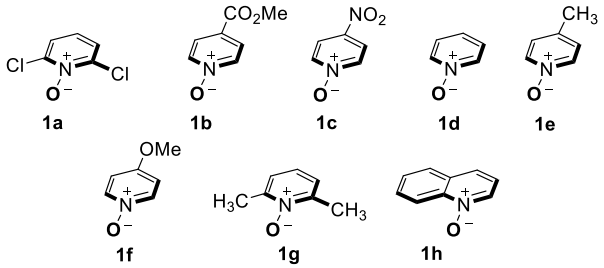
Results and discussion

To test the principle, our study was commenced by the evaluation of a series of commercial pyridine *N*-oxide derivatives as HAT catalysts in the photoinduced catalyzed C−H alkylation of cyclooctane with benzalmalononitrile (Table 1). Based on the oxidation potentials of pyridine *N*-oxides and previous studies,[3a,3b,4] we predicted that 9-mesityl acridinium photocatalysts, which possess high excited-state oxidizing power (Mes-Acr-Me+ $E_{1/2}^{red*}$ = +2.06 V vs SCE) and have been applied in a number of photocatalytic transformations,[14] could conveniently promote single-electron oxidation of pyridine N-oxides. To guide our investigation, DFT calculations for O-H bond dissociation energies (BDEs) of various protonated pyridine *N*-oxides were performed as well. As shown in Table 1, in the presence of 9-mesityl-10-methylacridinium perchlorate (Mes-Acr-MeClO$_4$) under irradiation blue LEDs (λ_{max} = 456 nm) at room temperature, 2,6-dichloropyridine *N*-oxide (**1a**, 20 mol%) was identified as the most effective HAT catalyst (entry 1, **2**, 96% yield). Both the **1a** and photocatalyst were necessary for productive reactivity. When 10 mol% of **1a** was applied, a lower reaction yield (entry 2, 81%) was obtained, which may be attributable to the small-degree (9%) deoxygenation of 2,6-dichloropyridine *N*-oxide. Methyl isonicotinate *N*-oxide (**1b**, 20

Table 1. Screening of pyridine *N*-oxides. [a]



Entry	*N*-oxide	BDE (O-H, kcal/mol)[b]	$E_{½}^{ox}$ (V vs SCE)[c]	**2** (%)d
1	**1a**	111.1	2.06	96
2	**1a**[e]			81
3	**1b**	106.7	1.98	82
4	**1c**	108.6	2.14	<5
5	**1d**	105.2	1.75	66
6	**1e**	102.9	1.61	8
7	**1f**	98.4	1.36	<5
8	**1g**	103.2	1.70	20
9	**1h**	97.7	1.55	6
10	**1a**[f]	111.1	2.06	73



[a] Reaction conditions: cyclooctane (1.2 mmol, 3.0 equiv.), benzalmalononitrile (0.4 mmol, 1.0 equiv.), 20 mol% of *N*-oxide, and 5mol% of photocatalyst were dissolved in dry CH_3CN (4.0 ml) under blue LED lamps (λ_{max} = 456 nm, 34 W, more information at Kessil.com) for 12 h. [b] BDEs of O-H in protonated *N*-oxides is computed at the M06-2X Level in acetonitrile. [c] see SI. [d] Yields were determined by analysis of the ^{1}H NMR spectra of reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. [e] 10 mol% of 2,6-dichloropyridine *N*-oxide. [f] 0.4 mmol (1.0 equiv.) of cyclooctane.

mol%) exhibited moderate catalytic activity (entry 3, 83%). Based on reaction monitoring by ^{1}H NMR spectroscopy (Figure S1), we found that deoxygenation of **1b** (42%) occurred to a substantially higher degree than **1a** (9%), which may explain the diminished catalytic efficiency. The effective HAT reactivity of 2,6-dichloropyridine *N*-oxide for unactivated C(sp^3)–H bond (BDEs ≥ 100 kcal/mol) is consistent with our calculation that protonated **1a** has the highest O-H BDE value (111.1 kcal/mol) in the analogous evaluated. Although with relatively high BDE (O-H, 108.6 kcal/mol), 4-nitropyridine *N*-oxide **1c** is not an effective HAT catalyst (entry 4). It may be due to its high oxidation potential (+2.13 V vs SCE), which could not be oxidized by photocatalyst to generate *N*-oxide cation radical. Pyridine *N*-oxide, the ones with electro-donating substituents, and quinoline *N*-oxide, possessing lower BDE exhibited low or non-catalytic activities (entries 5-9). Besides the consideration of BDE, we rationalize that the lower acidity of electron-donating substituted pyridine *N*-oxides may be partially account on their inert activity. Because the regeneration of *N*-oxide catalyst relies on the deprotonation step after HAT, less acidic pyridine *N*-oxides with electron-donating substituents would slow down this process. Mes-Acr-PhBF$_4$ (88%) and Mes-(^{t}Bu)$_2$Acr-PhBF$_4$

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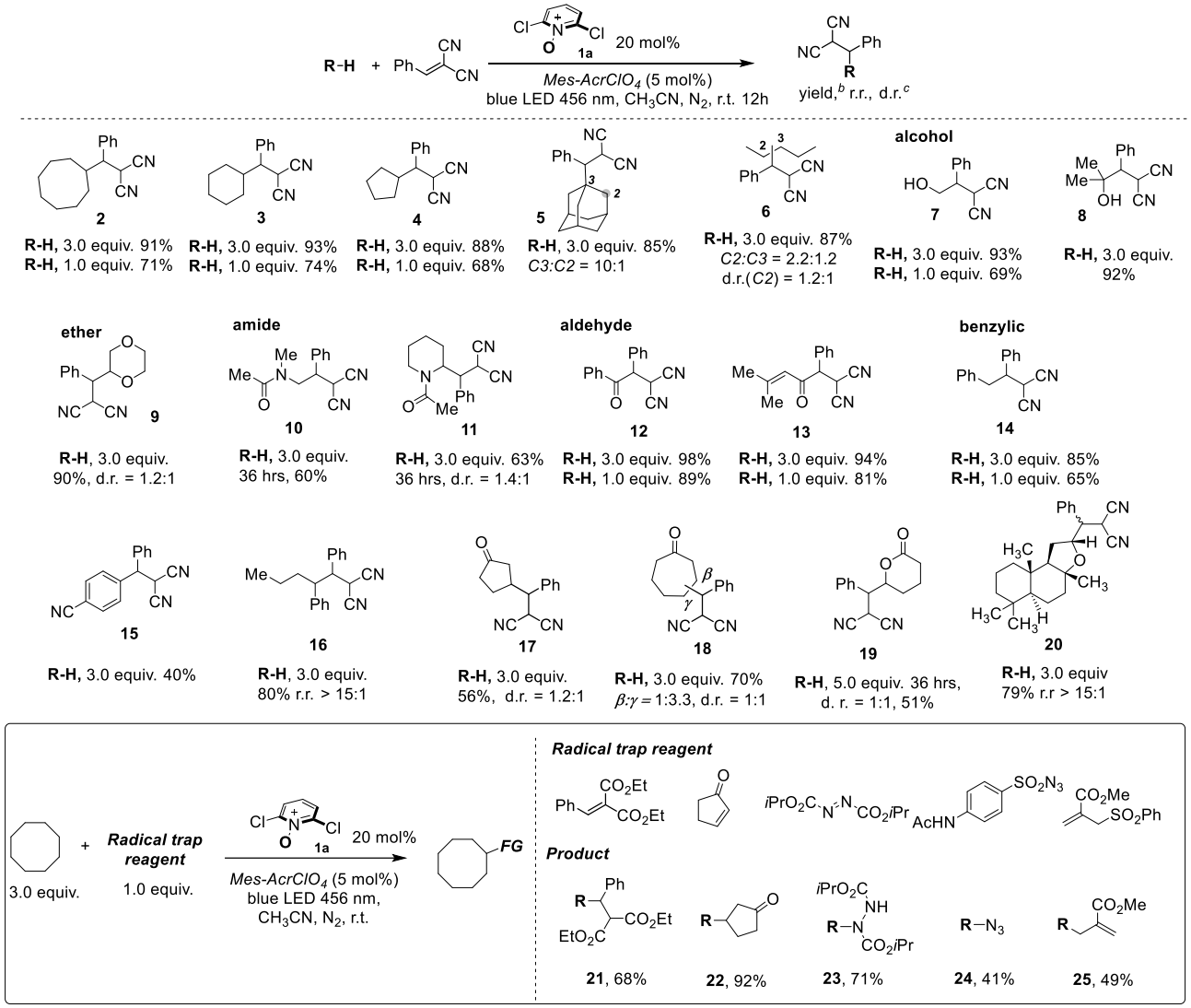
(92%) are comparable to Mes-Acr-$MeClO_4$ by merging with **1a** giving the desired product (Table S1). Moderate reaction efficiency (68%) was received when 2,4,6-triphenylpypylium tetrafluoroborate was applied as photocatalyst (Table S1). Neither iridium ($Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$),nor ruthenium ($[Ru(bpy)_3][PF_6]_2$) photocatalysts were effective catalysts for this reaction. Noteworthy, satisfactory yield of product (entry 10, 73%) was received when cyclooctane was used in 1.0 equivalent. Although relative high loading (**1a**, 20 mol%) is required, the economic and synthetic feasibility of pyridine N-oxides make them attractive and practical catalysts for C-H functionalization.

With the viable catalyst system and condition (Table 1, entry 1) in hand, we investigated the generality of C-H substrates (1.0 or 3.0 equiv.) catalyzed by 2,6-dichloropyridine *N*-oxide/Mes-Acr-$MeClO_4$ (Table 2). Both cyclic and acyclic hydrocarbons provided alkylation products in good to excellent yields, while the reaction of acyclic substrate gave mixtures of regioisomers and diastereoisomers (**2** to **6**). Noteworthy, 2,6-dichloropyridine *N*-oxide shown good selectivity for adamantane for the tertiary C–H bonds (**5**, 85%, r.r. = 10:1). Besides unactivated C(sp^3)-H bonds, a variety of C-H bonds adjacent to a heteroatom and benzylic C-H bonds (**7** to **16**), including alcohols, ether, aldehydes, amides, and toluene derivatives, could also be alkylated smoothly in moderate to excellent yields. The electrophilic nature of pyridine *N*-oxide cation radical was further illustrated by the selective alkylation of cyclic ketones and δ-valerolactone proceeded at more hydridic C-H bonds (**17**-**19**). Additionally, regioselective alkylation on the α-oxy C-H bond of ambroxide (**20**) demonstrated the synthetic value of this protocol in the late-stage functionalization of complex molecular. Different electron-deficient olefins, such as diethyl benzylidenemalonate

Table 2. Scope of 2,6-dichloropyridine *N*-oxide/Mes-Acr-$MeClO_4$ catalyzed C-H functionalization.



[a] Reactions were performed with 0.5 mmol of radical trap reagent (0.1 M). [b] Combined isolated yields of isomers. [c] Diastereoselectivity (d.r.) and regioselectivity (r.r.), where relevant, were determined by analysis of the ^{1}HNMR of the crude product.

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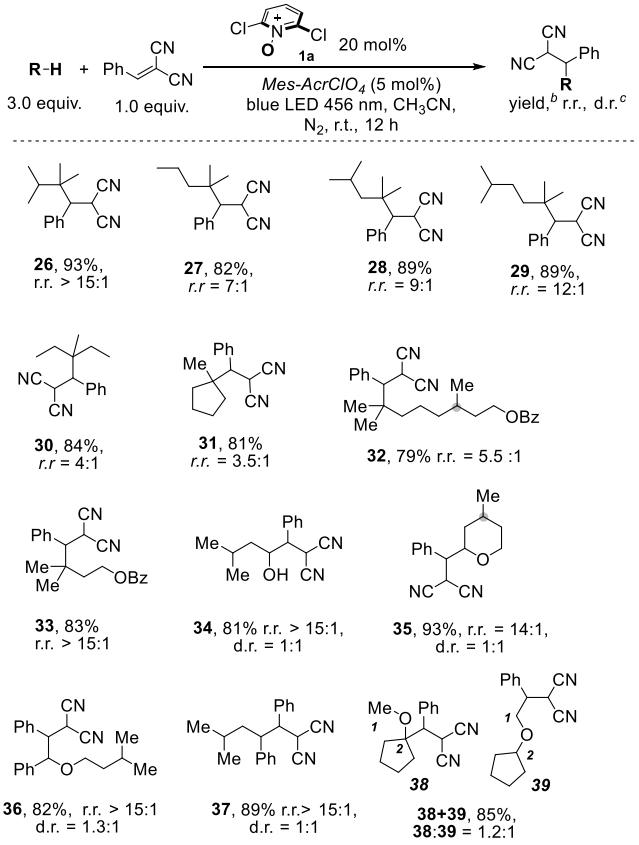
and cyclopentenone, were proved to be competent alkylation reagents for cyclooctane under the 2,6-dichloropyridine *N*-oxide photocatalytic system (**21** and **22**). We could also extend the utilization of this strategy to C-H amination, azidation, and allylation by simply changing the radical trapping reagent (**23**-**25**). Although the unoptimized condition produced the diverse C–H functionalization products in moderate yields, a proof of principle for the modularity of our approach is demonstrated.

Table 3. Site-selective 2,6-dichloropyridine *N*-oxide/Mes-Acr-$MeClO_4$ catalyzed C-H alkylation.[a]



[a] Reactions were performed with 1.5 mmol C-H substrate and 0.5 mmol of benzalmalononitrile (0.1 M). [b] Combined isolated yields of isomers. [c] Diastereoselectivity (d.r.) and regioselectivity (r.r.) were determined by analysis of the ^{1}HNMR of the crude product.

We next sought to evaluate the site-selectivity of the catalytic system on C-H substrates with multiple reactive sites. As shown in Table 3, regarding a wide range of unactivated alkanes, the alkylation reactions afforded the corresponding products in high yields and preferentially proceeded at tertiary C–H bonds with moderate to high site-selectivities (**26-31**). Benzoate ester of dihydrocitronellol bearing two tertiary C–H sites was examined, and alkylation was favored at the most remote tertiary C-H site with 5.5:1 site-selectivity (**32**). High site-selectivity and reactivity for tertiary C–H bond of isoamyl benzoate (**33**) were observed. In contrast, alkylation of isoamyl alcohol exclusively occurred at the α-oxy C-H site (**34**). We found that our protocol is highly selective for the most hydridic C–H bond in 4-methyltetrahydropyran (**35**). When reactions of substrates bearing both benzylic and tertiary C–H bonds were performed, full selectivity for the benzylic site was attained (**36** and **37**). However, using **1a** as the HAT catalyst, a non-selective alkylation of methoxycyclopentane possessing a tertiary C–H bond and a primary C–H bond adjacent to an oxygen atom was received (**38** and **39**). The obtained site-selectivity achieved by 2,6-dichloropyridine *N*-oxide/Mes-Acr-$MeClO_4$ is comparable to the reported HAT/photoredox systems with CH_2Br_2 and phosphate salt as HAT reagent,[7n,11] providing a complementary and catalytic HAT system for selective C-H functionalization.

Seeing the documented importance and significant effect of HAT reagents' structural characteristics in determining the reactivity and selectivity of HAT processes,[6-9,10,15] we predict that the reaction outcome of C-H functionalization could be altered by fine-tuning the structure of the pyridine *N*-oxide based HAT catalysts. Specifically, the use of *N*-oxides with steric demanding substituents at *ortho*-position may derive the C-H functionalization towards the less sterically hindered sites. In this regard, starting from commercial 6-chloropicolinic acid, HAT catalysts **1i**, **1j**, and **1k** bearing ester and amides substituents were synthesized in two steps by oxidation and coupling with methanol, isopropanol, or *L*-alanine methyl ester. As shown in Figure 3, more sterically bulkier **1i**, **1j**, and **1k** catalyzed reactions generally provide a higher level of functionalizations at less sterically hindered C-H sites compared to 2,6-dichloropyridine *N*-oxide, however, general lower HAT reactivities were observed. In the case of methoxycyclopentane with non-site-selective alkylation by **1a**, when **1i**, **1j**, and **1k** were applied, HAT preferentially proceeds at primary C–H bond adjacent to the oxygen atom (**1j**, **38**:**39** = 1:3.3, eq 1). In methylcyclopentane, a decreased relative ratio of site selectivity was obtained under **1i**, **1j**, and **1k** catalyzed conditions (eq 2). As for the reactions of branched alkanes (eq 3 and 4), 2,6-dichloropyridine *N*-oxide was found to be a highly selective HAT catalyst for tertiary C-H bonds. Switching the HAT catalyst to 2-chloro-6-(alkoxycarbonyl)pyridine *N*-oxide **1i** or **1j** led to a substantial increase in the amount of primary and secondary functionalization products. In contrast, catalyst **1k** was not an effective HAT catalyst for unactivated C(sp^3)–H bonds under the same condition, probably due to the extra stability of **1k** gained from the intramolecular hydrogen bond formation (N-O--H-N).[16] Further investigations and design of new pyridine *N*-oxide based HAT catalyst that could be able to target specific stronger C-H bonds, such as 1° or 2°, are ongoing in our laboratory.

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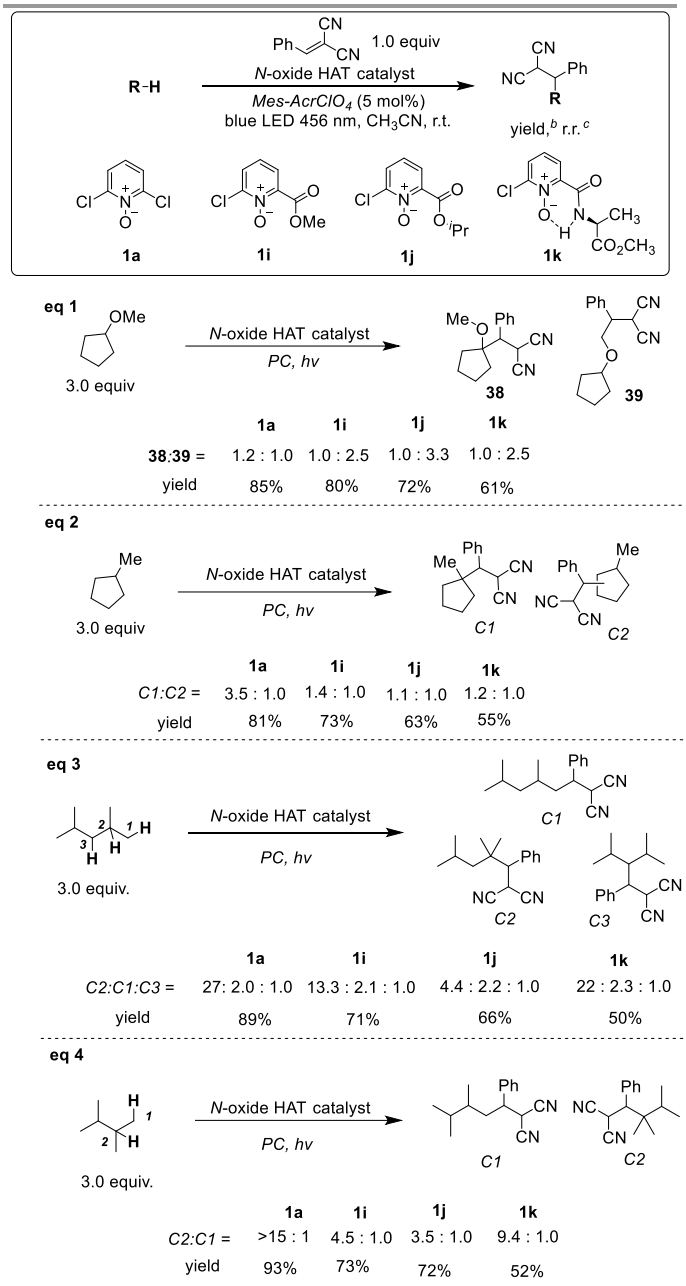

Figure 3. Site selectivity evaluation. Reactions conditions: C-H substrate (1.2 mmol), benzalmalononitrile (0.4 mmol), *N*-oxide (30 mol%), 36 h. See SI for experimental details. Combined isolated yields of isomers. Regioselectivity were determined by analysis of the ^{1}HNMR of the crude product. photoinduced condition. Taken together with the synthetical feasibility of pyridine *N*-oxide derivatives, the results shown above indicate that the pyridine *N*-oxide based HAT catalytic approach may become a valuable and practical strategy for selective C-H functionalization.

To lend further insight into the mechanism, investigations including fluorescence quenching experiments, electrochemical studies, and radical inhibition experiments, were performed. First, the Stern–Volmer fluorescence quenching analysis determined that the light-excited photocatalyst Mes-Acr$^+$* was quenched by 2,6-dichloropyridine *N*-oxide (K_{sv} = 53.19) rather than cyclooctane or benzalmalononitrile. It is consistent with our electrochemical studies that the strong oxidizing ability of Mes-Acr$^+$ allows it to oxidize 2,6-dichloropyridine *N*-oxide ($E_{1/2}^{ox}$ = + 2.06 V versus SCE) via single-electron oxidation. Moreover, besides the expected suppression of the photoinduced C-H alkylation with the addition of radical scavenger 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO), the formation of **40** from 2,6-dichloropyridine *N*-oxide cation radical **I** and TEMPO was detected by ESI-MS analysis (Figure 4). Herein, in accord with our experimental and computational evidence and our previous work,[4] a plausible mechanism featuring a HAT/photoredox dual-catalytic cycle is proposed in Scheme 4. Excited photocatalyst (Mes-Acr$^+$*) oxidizes 2,6-dichloropyridine *N*-oxide to the electrophilic *N*-oxide cation radial **I**, which abstracts a hydrogen atom from the C(sp^3)-H substrate producing alkyl radical **III** and protonated *N*-oxide **II**. Nucleophilic addition of radical **III** to benzylidenemalononitrile furnishes the radical intermediate **IV**, which is capable of oxidizing the reduced form of the acridinium catalyst to reset the photocatalytic cycle.[7a,7n,10] In the HAT catalytic cycle, the resultant carbanion intermediate **V** will function as a base to neutralize the protonated *N*-oxide regenerating HAT catalyst and giving the product.

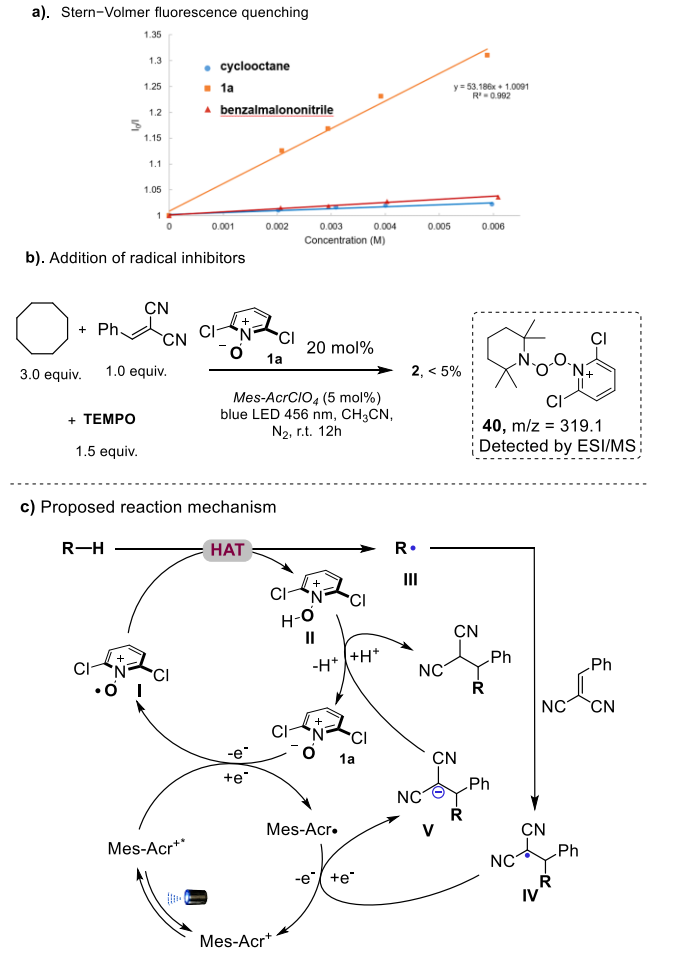

Figure 4. Mechanistic studies and proposed mechanism.

Conclusions

In summary, readily accessible and tunable pyridine *N*-oxide derivatives have been developed as effective photoinduced HAT catalysts for site-selective C-H functionalization. By the

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synergistic effects of acridinium photocatalyst and commercial 2,6-dichloropyridine *N*-oxide, site-selective alkylation of a variety of C-H substrates, including unactivated alkanes, has been achieved. The versatility of the approach is further highlighted by a diverse array of C-H functionalization reactions. Importantly, our research demonstrates that the reactivity/selectivity of pyridine *N*-oxide based HAT catalysts could be facilely tuned by operationally simple structural modification. The present catalytic strategy, benefiting from the synthetical feasibility of pyridine *N*-oxides, is believed to become a new and practical platform allowing the development of a modular system to access selective C-H functionalization through catalyst-control.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Support for this research from Indiana University–Purdue University Indianapolis is gratefully acknowledged. We thank Dr. Nicewicz for the discussion of the research results. We acknowledge the help from Prof. Rajesh Sardar for the cyclic voltammetry study.

Dedicated to Professor Michael P. Doyle on the occasion of his 80th birthday

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