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Visible-light-mediated photoredox decarbonylative Minisci-type alkylation with aldehydes under ambient air conditions†

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Visible-light-induced photoredox decarbonylative C–C bond formation with aldehydes is described for the first time. Minisci-type alkylation reactions of N-heteroarenes proceed smoothly at ambient temperature with air as the sole oxidant. The present sustainable protocol uses readily available organofluorescein as a photocatalyst, cheap and green oxidant and a sustainable power source, thus featuring potential for applications in late-stage modification of valuable molecules.

In recent years, visible light-induced photocatalysis has emerged as a powerful technique for molecule synthesis, which thereby greatly facilitates the discovery of novel reactivities.[1] From a green chemistry perspective, aerobic oxidation in combination with a mild photoredox mode and sustainable visible light as the power source is believed to be user- and environmentally friendly and thus of great significance in method development.[2] Consequently, great progress has been made in aerobic photocatalysis that enables oxidative functionalizations using dioxygen as the sole oxidant under ambient conditions.[3] Although numerous unique reactivities have been disclosed by the incorporation of aerobic oxidation and photoredox, this powerful strategy also provides opportunities for the benign modification of traditional oxidative processes requiring otherwise excessive amounts of environmentally unfavorable oxidants.[4]

N-Heteroarenes are privileged skeletons in a large number of valuable molecules including dyes, pesticides, drugs, and functional materials, among others. Thus, the synthesis of N-heteroarenes has been intensively studied. Minisci and coworkers pioneered a radical addition reaction that was well known as the Minisci reaction and provided a viable strategy to construct functionalized N-heteroarenes.[5] Thereafter, although the Minisci reaction has been widely studied[6] in the past few years including several mild photoredox systems,[7] many of them are dependent on the use of strong stoichiometric amounts of oxidants or elevated temperatures to produce the desired carbon radicals. For example, excessive amounts of strong oxidants (*e.g.*, iodobenzene acetate, potassium persulfate, peroxide, *etc.*) are generally required in the case of aldehydes as the radical precursors (Fig. 1a–c),[8] which thereby decompose to acyl radicals[9] or alkyl radicals upon further decarbonylation.[10] Recently, Lei's group described a mild visible-light-induced acylation of N-heteroarenes by the initiation assistance of *t*-butylhydroperoxide.[8b] Yang and coworkers reported decarbonylative alkylation using di-*tert*-butylperoxide at high temperature.[11] To the best of our knowledge, to date there is no example reported on the photoredox decarbonylative C–C couplings of aldehydes under visible light.[12] As part of our research interest in sustainable aerobic oxidation,[13] a photocatalytic aerobic decarbonylative alkylation of N-heteroarenes with aldehydes has been reported herein for the first time (Fig. 1d).

To commence our study, 4-methylquinoline (**1a**) and 2-ethylhexanal (**2a**) were selected as the model substrates for the aerobic decarbonylative alkylation under photocatalysis with visible light. To our delight, the reaction afforded the decarbonylative alkylation product **3a** in 40% yield, when

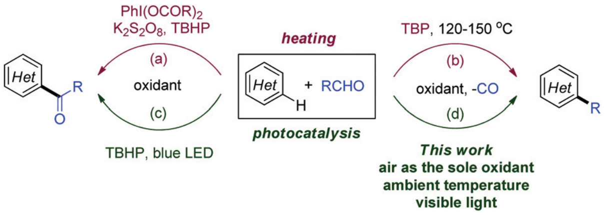

Fig. 1 The Minisci reaction with aldehydes.

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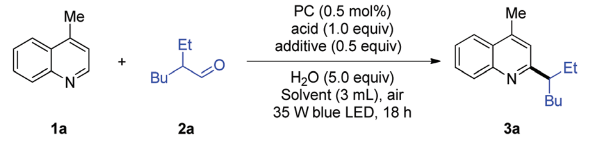
0.5 mol% Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 was used as the photocatalyst, 1.1 equiv. of CF_3SO_3H as the acid, 0.5 equiv. of LiBr as the additive, acetone/H_2O as the reaction media, and 35 W blue light-emitting diodes (LED) under an air atmosphere (Table 1, entry 1). In this system, the major by-product (2-(2-ethylhexyl)-4-methylquinoline) was produced by reductive alkylation (non-decarbonylation). The screening of acid additives revealed that CH_3SO_3H, $(PhO)_2PO_2H$, and TsOH·H_2O slightly enhanced the generation of **3a** (entries 2–4). With TsOH·H_2O as the optimal acid, the effect of solvent was tested (entries 5–8) and the results showed that 1,2-dichloroethane (DCE) was superior to other solvents screened to afford **3a** in 67% yield (entry 6). Then, we explored a series of halide additives and found that only bromides worked for this decarbonylative alkylation transformation (entries 9–14). Iodides and chlorides completely prohibited the desired reaction. Among other bromides, NaBr featured the same reactivity for the generation of **3a** (entry 9). In comparison, however, the systems with NaBr were cleaner after the reaction compared to those with LiBr or those without NaBr, in which the by-product of reductive alkylation was observed only in trace amounts. Hence, NaBr has probably enhanced the oxidizing capability of the aerobic systems. With respect to the photocatalysts, readily accessible 4CzIPN was found to be the best photosensitizer (70% yield, entry 18), while others with diminished oxidizing capacity (*e.g.*, Eosin Y, Rose Bengal, and Ru(bpy)$_3PF_6$) showed dramatically lower catalytic reactivities. The increase in the catalyst loading to 1 mol% led to a conspicuous enhancement in the yield (85% yield, entry 19). Control experiments indicated that both light stimulation and air atmosphere were essential for the present decarbonylative alkylation (entry 20).

Table 1 Optimization of the reaction conditions[a]



Entry	PC	Acid	Additive	Solvent	Yield[b] (%)
1	[Ir]PF_6	CF_3SO_3H	LiBr	Acetone	40
2	[Ir]PF_6	CH_3SO_3H	LiBr	Acetone	45
3	[Ir]PF_6	$(PhO)_2PO_2H$	LiBr	Acetone	50
4	[Ir]PF_6	TsOH·H_2O	LiBr	Acetone	56
5	[Ir]PF_6	TsOH·H_2O	LiBr	CH_3CN	45
6	[Ir]PF_6	TsOH·H_2O	LiBr	DCE	67
7	[Ir]PF_6	TsOH·H_2O	LiBr	DCM	52
8	[Ir]PF_6	TsOH·H_2O	LiBr	PhCl	41
9	[Ir]PF_6	TsOH·H_2O	NaBr	DCE	66
10	[Ir]PF_6	TsOH·H_2O	—	DCE	30
11	[Ir]PF_6	TsOH·H_2O	NaI	DCE	ND
12	[Ir]PF_6	TsOH·H_2O	LiCl	DCE	Trace
13	[Ir]PF_6	TsOH·H_2O	NH_4I	DCE	ND
14	[Ir]PF_6	TsOH·H_2O	KI	DCE	ND
15	Eosin Y	TsOH·H_2O	NaBr	DCE	33
16	RB	TsOH·H_2O	NaBr	DCE	18
17	[Ru]	TsOH·H_2O	NaBr	DCE	Trace
18	4CzIPN	TsOH·H_2O	NaBr	DCE	70
19[c]	4CzIPN	TsOH·H_2O	NaBr	DCE	85 (78)
20[d]	4CzIPN	TsOH·H_2O	NaBr	DCE	Trace

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (0.5 mol%), additive (0.1 mmol), acid (1.0 equiv.), solvent (3.0 mL), H_2O (1.0 mmol, 5.0 equiv., 18 μL), at ambient temperature, under air, 18 h. [Ir]PF_6 = Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6, RB = Rose Bengal, [Ru] = Ru(bpy)$_3PF_6$. [b] Yields were determined by crude ^1H NMR with CH_2Br_2 as the internal standard and isolated yields are given in parentheses. [c] Using 4CzIPN (1.0 mol%). [d] In the dark or under a N_2 atmosphere.

With the optimized reaction conditions in hand, we next probed the substrate scope and generality of the photoredox decarbonylative alkylations of N-heteroarenes under ambient reaction conditions (Fig. 2–4). Unfortunately, decarbonylation of primary alkylaldehydes and aromatic aldehydes was not observed in all cases of our current photoredox systems, which can be attributed to the relatively high bond dissociation energies of the corresponding acyl radicals and poor stabilities of the resultant primary alkyl and aromatic radicals.[14] Instead, we observed the formation of a small amount of reductive alkylation products when primary alkyl aldehydes and aryl aldehydes were used.

The decarbonylative couplings proceeded well to give the desired products in excellent yields when α-branched aliphatic carbaldehydes were used (75–93% yield, **3a–3e**, Fig. 2). Cyclic carbaldehydes showed slightly diminished reactivities (31–69% yield, **3f–3h**). Notably, the Boc-protected pyrrole moiety was successfully attached to the quinoline skeleton (52% yield, **3h**). Two artificial species, cyclamen aldehyde and Lily aldehyde, showed good reactivities in the current decarbonylative couplings (62% and 80% yield, **3i** and **3j**, respectively). Then, tertiary alkylations were exemplified by the use of pivalaldehyde, which gave 2-*tert*-butylquinoline in excellent yield (90% yield, **3k**). The robust nature of our aerobic photoredox systems was further reflected in the effective gram-scalable reactions that generated **3c** and **3k** in excellent yields (76% and 82%, respectively).

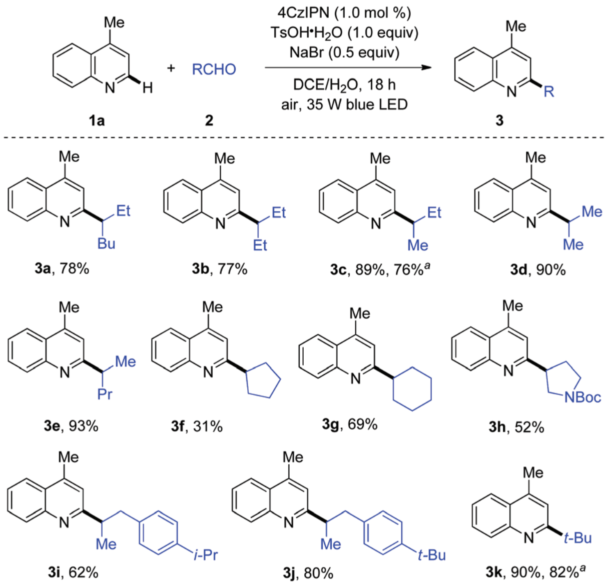


Fig. 2 Scope of secondary aldehydes for aerobic decarbonylative alkylations. [a] Yield on the 8 mmol scale.

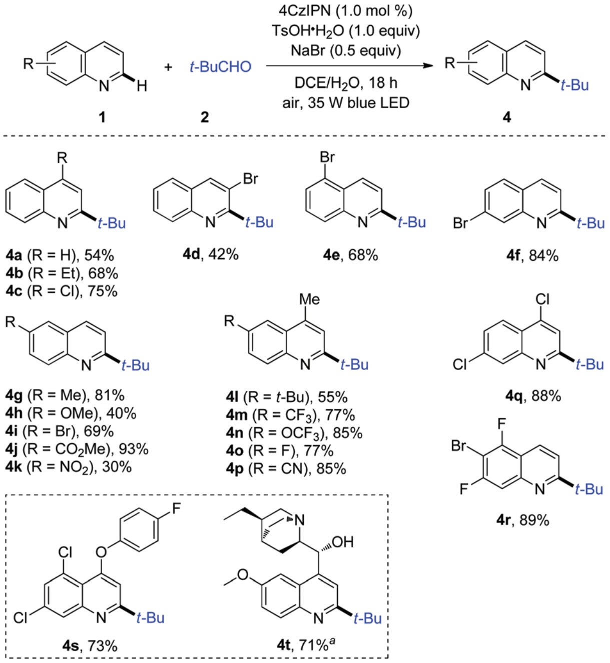


Fig. 3 Scope of quinolines for aerobic decarbonylative alkylations. ^{a} 1.6 equiv. of TsOH·H$_2$O were used.

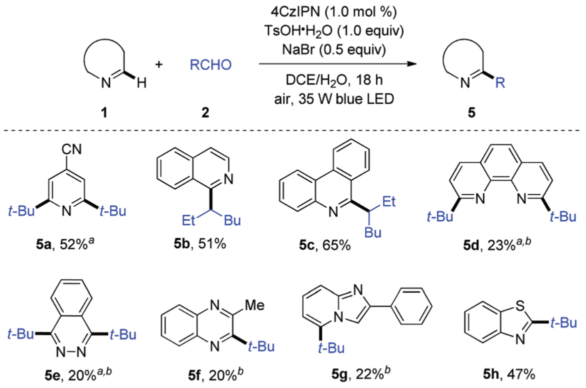


Fig. 4 Decarbonylative alkylations of N-heteroarenes with aliphatic aldehydes. ^{a} 4.0 equiv. of aldehyde were used. ^{b} 1.6 equiv. of TsOH·H$_2$O were used.

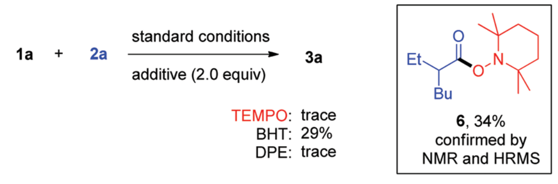
With respect to the N-heteroarene fragment (Fig. 3), undecorated quinolines mainly afforded C2 alkylated products in modest yields (54% yield, **4a**). Other 4-substituted quinolines with ethyl and chloride groups worked well to afford the corresponding products in good yields (**4b** and **4c**). Synthetically useful bromide attached at the C3, C5, C6, and C7 positions of quinoline was compatible with the photoredox system, leading to the expected products in moderate to excellent yields (42–84% yield, **4d–4f** and **4i**). Other functionalities including electron-donating methoxy (**4h**), and electron-withdrawing ester (**4j**), nitro (**4k**), trifluoromethyl (**4m**) and nitrile (**4p**) were all accommodated with yields ranging from 30% to 93%. Multi-halo-substituted quinolines worked well to afford **4q** and **4r** in excellent yields. To our delight, two biologically active molecules, quinoxyfen and hydroquinine, successfully transformed to their derivatives in the present systems (73% and 71% yield, **4s** and **4t**, respectively).

Besides quinolines, our viable aerobic photocatalytic systems proved to be applicable in the alkylations of other N-containing heteroarenes (Fig. 4). For example, isonicotinonitrile, a valuable pyridine motif, was compatible with two-fold alkylations (52% yield, **5a**). Isoquinoline and phenanthridine furnished the corresponding products **5b** and **5c** in 51% and 65% yields, respectively. Multi-nitrogen containing heterocycles such as 1,10-phenanthroline (**5d**), phthalazine (**5e**), quinoxaline (**5f**), and imidazo[1,2-*a*]pyridine (**5g**) were also obtained, albeit in low yields. Lastly, we were glad to find that benzothiazole performed with modest efficiency (47% yield, **5h**).

Given the established selective aerobic alkylations *via* aldehyde decarbonylation, we became motivated to construct a working model to illustrate mild decarbonylative photocatalysis. First, we found that the addition of a radical scavenger such as TEMPO, BHT, and 1,1′-diphenylethylene (DPE) could prevent the model reaction under standard reaction conditions (Fig. 5a), revealing that a radical pathway was probably involved in the reaction process. Furthermore, an acyl radical was trapped by TEMPO to form *O*-acylhydroxylamine **6**, whose structure was confirmed by NMR and HRMS. Then, we performed Stern–Volmer quenching experiments for the excited 4-CzIPN photocatalyst in the presence of both the reactant and O$_2$ (Fig. 5b). Interestingly, no obvious quenching of the charged 4-methylquinoline was observed. Also, 2-ethylhexanal (**2a**), which bears highly negative reduction potential,[15] is not a quencher, suggesting that a reductive quenching mechanism is unlikely. On the other hand, O$_2$ is a strong quencher ($K_{SV} > 300$), which suggests that oxidative quenching is more likely operative.

Based on the above experimental observations, a possible mechanism for aerobic photoredox decarbonylative alkylations was proposed (Fig. 6). Firstly, the 4CzIPN (PC) photocatalyst is excited with visible light and quenched with O$_2$ to form a

(a) radical trapping experiments



(b) Stern-Volmer fluorescence quenching of 4-CzIPN

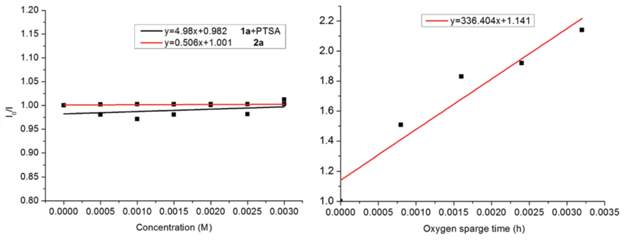


Fig. 5 Key findings of mechanistic studies.

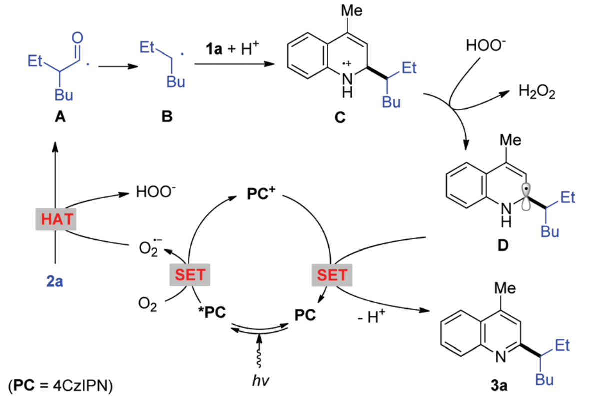


Fig. 6 Possible reaction mechanism.

superoxide radical anion ($O_2^{\bullet -}$), along with highly oxidized [4CzIPN]$^+$ [$E_{1/2}$(PC$^+$/PC) = +1.52 V *vs.* a saturated calomel electrode (SCE)].[16] The superoxide radical anion is capable of abstracting hydrogen atoms from aldehyde **2a** to generate an acyl radical (**A**), driven by the polar effect in the transition state.[17] Then **A** is decomposed into an alkylradical (**B**) by decarbonylation. Radical addition of **B** to the charged **1a** affords the radical cation **C**. Finally, the sequential deprotonation of **C** and single-electron oxidation by [4CzIPN]$^+$ occur to yield the final alkylated quinoline **3a**.

Conclusions

In summary, we have developed aerobic photoredox decarbonylative Minisci-type alkylations with aldehydes as the alkylating reagent. The present method was found to tolerate a range of N-heteroarenes bearing various functionalities. Hence, secondary and tertiary alkylated N-heteroarenes were afforded under ambient conditions. This protocol represents the first photoredox decarbonylative C–C coupling. Mechanistically, rather than the well-known ketyl radical mechanism of aldehydes under photocatalysis, acyl radical formation by a highly oxidizing photocatalyst is involved, which may inspire other cases of mild decarbonylative C–C coupling with green O_2 as an oxidant.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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