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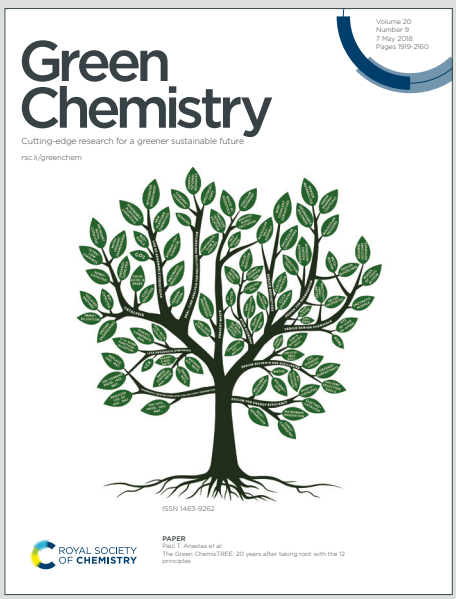

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LiBr-promoted photoredox neutral Minisci hydroxyalkylations of quinolines with aldehydes

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Photoredox-neutral hydroxyalkylations of quinolines with aldehydes, induced by sustainable visible light under mild conditions, is described. Non-toxic and inexpensive LiBr is found to be the key for the success of the atom-economic Minisci method. Combined with a highly oxidative photocatalyst and visible light irradiation, the bromide additive mediates the H abstraction/acyl radical formation directly from aldehydes. The present mild photoredox neutral protocol provides an important alternative especially for the challenging Minisci hydroalkylations, as well as a promising approach for atom-economic Minisci reactions with broader N-heterocycle spectra.

Nitrogen-containing heterocycles, such as quinoline and its analogs, are of prominence as key structural units of numerous bioactive natural compounds and pharmaceuticals. Many FDA approved drugs contain this privileged quinoline ring structure.[1] Of them, hydroxyalkylated quinoline derivatives display a unique ability to selectively disrupt biofilm formation,[2] which is growingly being recognized as a major component of bacterial pathogenesis.[3] Given the efficacy of initial lead compounds such as quinine (**I**), the scientific community synthesized and tested a vast array of quinoline derivatives possessing a β-amino alcohol motif.[4] Representatively, the 2-aryl quinoline compounds **II** and **III** (Fig. 1), for example, found to feature high antibacterial activities (EC50 = 11.1 and 9.6 μM, respectively).[5]

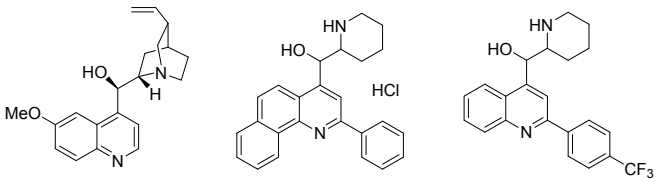

Fig. 1 Highly valuable hydroxyalkylated quinoline derivatives.

Because of the high pharmaceutical importance of quinoline derivatives, the synthetic chemistry of this structural motif has accordingly attracted considerable attention. While transition-metal-catalyzed cross couplings provide powerful approaches for functionalized heterocycles, to date the access to hydroxyalkylated quinoline derivatives mainly relies on stepwise Grignard chemistry,[6] where formally heteroaryl magnesium halides add to corresponding carbonyls. Minisci reaction refers generally to radical-type C-C couplings of aza-heteroaromatics that give broad and versatile opportunities for heterocycle functionalizations including alkylation, arylation, and acylation.[7] Among numerous viable Minisci reaction systems, however, few of them are suitable for hydroxyalkylations, probably because of the variability of hydroxyalkyl radicals and over-oxidation of the otherwise resultant hydroxyalkylated products under oxidative conditions.[8] In 2011, Li group demonstrated a $PdCl_2$/BINAP-based catalytic oxidative system that enables hydroxyalkylations of quinolines and analog aza-heteroaromatics with alcohols (Fig. 2a).[9] The potent photoredox catalysis[10] has proved in recent years to be an important alternative for Minisci reactions,[11] of which hydroxyalkylations was realized with methanol under mild conditions (Fig. 2b).[12] Instead of hydroxyalkyl radical formation,[13] recent results in photocatalysis reveal that acyl radicals attacking may lead to non-acylated products,[14] which poses a possible access to hydroxyalkylations. Very recently, Melchiorre and co-workers discovered the first photoredox neutral Minisci hydroxyalkylations through basically visible-light-induced acyl radical formation from 4-acyl-1,4-dihydropyridines (acyl-DHPs) (Fig. 2c).[15] With the insight obtained from our recent experimental results in the reductive Minisci alkylations with aldehydes wherein acyl radicals were directly generated through deprotonated electron transfer (DPET) with bromo radical,[16] we speculate that hydroxyalkylations of heteroaromatics would be selectively accomplished from

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readily available aldehyde feedstocks in a redox-neutral manner (Fig. 2d).

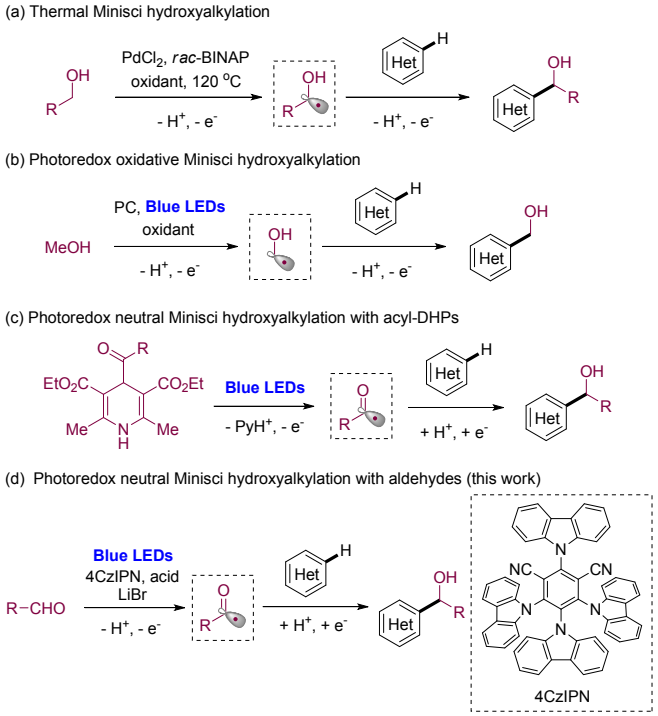
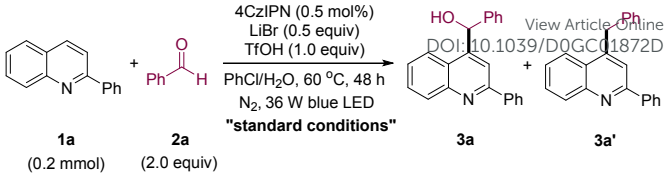


Fig. 2 Minisci hydroxyalkylations

To this end, we began our study with choosing 2-phenylquinoline (**1a**) and benzaldehyde (**2a**) as the model substrates and LiBr as the key moderator. As expected, the main challenge was to inhibit the over-reacted reductive benzylation reaction. Systematic screening of reaction parameters afforded the optimal result that the desired **3a** was obtained in good yield (77%) and satisfactory chemoselectivity (~13:1) (Table 1, entry 1). Similarly to our previous results, additional $(PhO)_2PO_2H$ (1.0 equiv) benefited the benzylation reaction (50%),[16b] together with the hydroxyalkylated quinoline product **3a** generated in a considerable yield (34%) (entry 2). 4CzIPN proved to be the best choice of photocatalysts (PCs), and among others only $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$, possessing similar photoredox potential, could be an option of PCs (entry 3). Moreover, LiBr was superior to other bromide or halide additives (entries 4-7). Notably, reducing the equivalents of **2a** (1.5 equiv) did not improve the selectivity, but instead both alkylation products were formed in diminished yields with the quinoline reactant **1a** incompletely consumed (entry 8). A similar result was observed when the reaction was carried out at room temperature (entry 9). Control experiments revealed that visible light irradiation, photocatalyst, bromide, and acid were all necessary (entry 10). The addition of water, which increased the solubilities of bromide additive and protonated quinolines, dramatically enhanced the efficiency of the target alkylation, while only 16% yield was obtained when removing the additional water (entry 11).

Table 1. Optimization of reaction conditions[a]



Entry	Deviation from standard conditions	Yield[b]	
		3a	**3a'**
1	None	77 (72)	6
2	With additional $(PhO)_2PO_2H$ (1.0 equiv)	34	50
3	$Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ instead of 4CzIPN	66	8
4	NaBr instead of LiBr	32	<5
5	Bu_4NBr instead of LiBr	52	24
6	LiCl instead of LiBr	22	11
7	NaI or KI instead of LiBr	n.d	n.d
8	Using 1.5 equiv of **2a**	50	5
9	At 25 °C, 50 °C	42, 62	<5
10	In dark or no PC or no LiBr or no acid	n.d	n.d
11	No water	16	<5

[a] Reaction condition: **1a** (0.2 mmol), **2a** (0.4 mmol), photocatalyst (PC, 0.5 mol%), halide additive (0.5 equiv), acid (1.0 equiv), water (50 equiv), PhCl (1 mL), N_2, 36 W blue LED, 48 h. $[Ir]PF_6$ = $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$. [b] Yields were determined by crude ^1H NMR with CH_2Br_2 as internal standard and isolated yield was given in parentheses.

With the optimized reaction conditions in hand, we next probed the substrate scope and generality of the LiBr-promoted photoredox neutral Minisci hydroxyalkylations. A broad range of substituted benzaldehydes were smoothly employed to react with 2-phenylquinoline **1a** (Fig. 3), generating the corresponding C4 functionalized quinoline derivatives in moderate to excellent yields (**3a**-**3p**, 49-93%). The present photocatalytic system found to well tolerate such ubiquitous functionalities as alkyl, alkoxy, and halogen (F, Cl, Br). Notably, in this protocol, both electronic and steric effects of the benzaldehyde substrates were elusive for the final productivity. In this regard, for example, the best efficiency was arisen from the coupling with 2-bromo-5-fluorobenzaldehyde (**3p**, 93%), while some other ortho-substituted benzaldehydes gave the desired products only in modest yields. Among heteroaromatic aldehydes tested, thiophene-2-carbaldehyde was productive, giving the hydroxyalkylated product bearing a thiophene moiety in good yield (**3q**, 73%). Other aromatic aldehydes including 2-naphthaldehyde worked, albeit in low yield (**3r**, 73%). Unfortunately, aliphatic aldehydes could not participate into this kind of Minisci reaction, in which major quinoline substrate was recovered. For example, only trace amount of product was detected by TLC and GC-MS when cyclopropanecarbaldehyde was used (**3s**), while no alkylation product by ring opening of cyclopropane was observed.

Subsequently, a number of quinoline derivatives were subjected to our LiBr-promoted photoredox system (Fig. 4). The experimental results revealed that the reaction efficiency is

highly dependent upon the substituent attached on the quinoline unit. Unexpectedly, 2-methylquinoline featured modest reactivity with poor chemoselectivity. By contrast, 2-arylquinolines worked smoothly to afford the target molecules in moderate to excellent yields (**4a**-**4h**, 51-89%), as well as that containing a thiophene moiety (**4i**). For a purpose of quinoline C2 functionalization, C4-occupied heterocycles were employed. In analogy to 2-methylquinoline, 4-methylquinoline gave also a poor selectivity in current system. To our delight, the 4-butyl and 4-chloro analogs were suitable substrates, delivering the expected hydroxyalkylation products **4k** and **4l** in 76% and 58% yields, respectively. Finally, while simple isoquinoline gave only trace amounts of target product, its bromo derivative at C6 can be incorporated into the present photocatalysis (**4n**, 47%). Other related N-heterocycles such as quinoxalinone, benzo[d]thiazole, and benzo[d]oxazole failed to work in the present systems.

Notably, benzylation products by reduction were detected as major side products by GC-MS in all cases of these reactions, albeit with generally low yields (<20%). Some benzylation products were formed in considerable yields that were then isolated and characterized (**3b'**, **3c'**, **3r'** and **4l'**, See ESI for details). Because of the same reason, the reaction yields did not enhanced when increasing the catalyst loading or performed within prolonged reaction time. Actually, in some cases, the use of more catalyst diminished the efficiency of the target transformation. We also tried to further screen the reaction conditions when aliphatic aldehydes were used. But we failed to obtain satisfactory results.

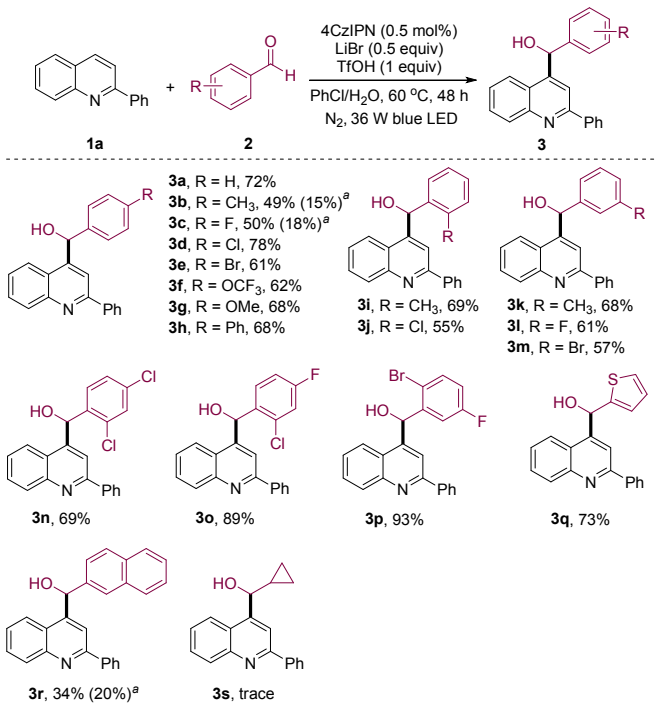


Fig. 3 Scope of aldehydes. [a] Yields of benzylation products were given in parentheses.

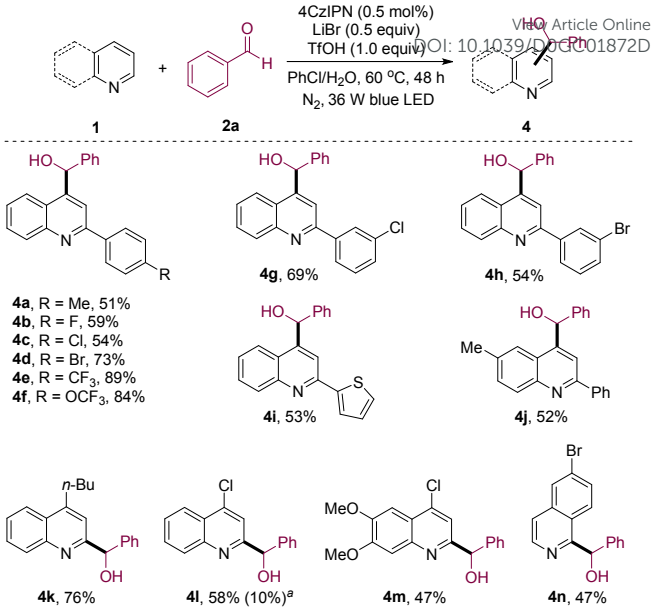


Fig. 4 Scope of quinolines. [a] Yields of benzylation products were given in parentheses.

To gain more mechanistic insight into the hydroalkylation reaction with aldehydes, we carried out some control experiments (Fig. 5). First, when we used deuterated benzaldehyde (**D-2a**) instead of **2a**, no D was incorporated into the final product **3a** (Fig. 5a), while the additional deuterium oxide led to 76% D incorporation (Fig. 5b). These results rule out the ketyl radical pathway and instead direct C-H scission of aldehyde would occur to form acyl radical. The radical trapping experiment further proved our speculation, in which benzoyl radical was captured by TEMPO and the generation of **3a** was completely prohibited (Fig. 5c). The Stern-Volmer quenching experiments of reactants and reagents to 4CzIPN were in line with those results to $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$.[16b] Hence, only the bromide featured obvious luminescence quenching effect to photocatalyst (Fig. 6), revealing the feasibility of the bromide oxidation in the initial step. Finally, we carried out a switched light-on/off experiment. The yield did not increase in dark, which therefore rule out a radical chain pathway.

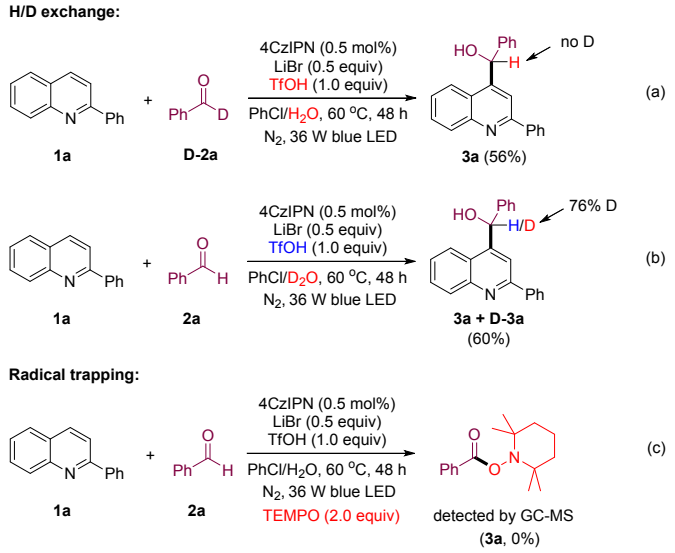


Fig. 5 Key findings of mechanistic studies.

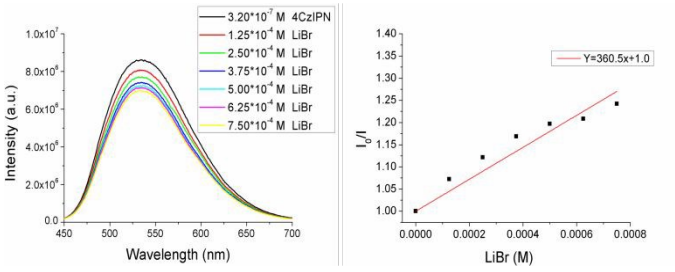


Fig. 6 Stern-Volmer quenching of LiBr to 4CzIPN.

Based on the experimental results and previous reports, a plausible reaction mechanism was proposed (Fig. 7). The photocatalyst 4CzIPN absorbs photons to form its exited state (*PC, $E_{1/2}$(*PC/PC$^-$) = +1.35 V vs SCE),[17] which undergoes a single electron transfer (SET) process with bromo anion ($E_{1/2}^{red}$ = +0.80 V vs SCE)[18] to generate bromo radical **A** and 4CzIPN anion (PC$^-$). The bromo radical would abstract H atom from aldehyde **2** via deprotonated electron transfer (DPET) (a comparable HBr Br–H bond dissociation energy = 87 kcal/mol,[19] benzaldehyde C(O)-H bond dissociation energy = 89 kcal/mol[20]) to access the acyl radical **B**, driven by the polar effect in the transition state.[21] Then, the radical addition of **B** to the charged N-heterocycle, deprotonation, and spin-centre shift (SCS) process[15] sequentially occur to generate the hydroalkyl radical **E**. Ultimately, the SET process from the reductive PC$^-$ ($E_{1/2}$(PC/PC$^-$) = −1.21 V vs SCE)[17] to the intermediate **E** furnishes the protonated product **F**, with late-stage workup to afford the final products. Our previous work revealed that the further photoreductive process of **F** by aldehyde led to the formation of **3a'**,[16b] although the exact mechanism is not clear in current stage.

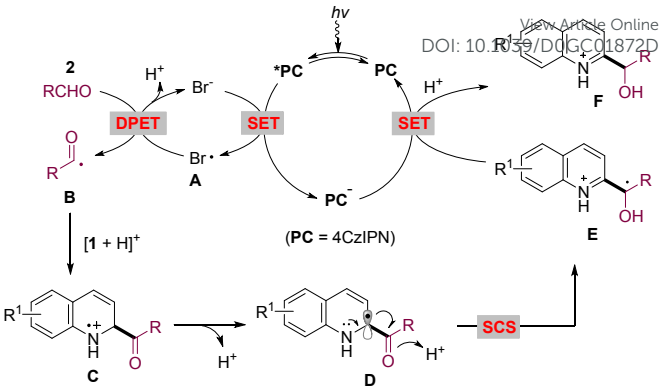


Fig. 7 Possible reaction mechanism.

The synthetic application of this protocol was further demonstrated by the versatile late-stage manipulation of the free hydroxyl group in the resultant products. Hence, dehydrogenative oxidation, bromination, and esterification were all readily realized via simple treatment under mild conditions, delivering a broader access to diversely functionalized quinolines (Fig. 8).

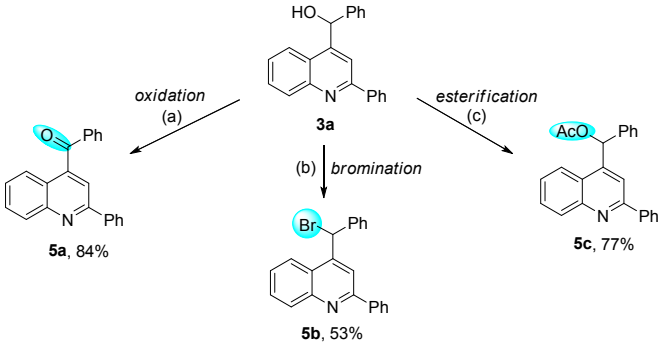


Fig. 8 Derivation of **3a**. Reaction conditions: (a) **3a** (0.2 mmol), Dess-Martin reagent (1.5 equiv), CH_2Cl_2 (0.2 M), 0 °C-rt, 4 h; (b) **3a** (0.2 mmol), PPh_3 (1.2 equiv), CBr_4 (1.5 equiv), CH_2Cl_2 (0.2 M), 0 °C-rt, 4 h; (c) **3a** (0.36 mmol), Ac_2O (2.0 equiv), DMAP (5 mol%), toluene (0.36 M), 0 °C-rt, 4 h.

Conclusions

In summary, we have developed a photoredox neutral Minisci hydroalkylation reaction of quinolines and related nitrogen-containing heterocycles. In this protocol, non-toxic and cheap LiBr plays an exceptional role as a moderator in the plausibly proposed SET/HAT cycle. Hence, acyl radicals were readily generated via directly endergonic C–H abstractions of aldehydes, which therefore commence the Minisci-type C-H functionalizations. Although there appear limitations with respect to substrate scope in this system, the major features regarding atom economy and mild photoredox neutral conditions make it an important and attractive alternative especially for the challenging Minisci hydroalkylations, as well as a promising approach for atom-economic Minisci reactions with broader N-heterocycle spectra.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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