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Photocatalytic Redox-Neutral Hydoxyalkylation of *N*-Heteroaromatics with Aldehydes

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Hiromu Fuse,[a] Hiroyasu Nakao,[a] Yutaka Saga,[b] Arisa Fukatsu,[c] Mio Kondo,[b] Shigeyuki Masaoka,[b] Harunobu Mitsunuma,*[a] and Motomu Kanai*[a]

A hydroxyalkylation of *N*-heteroaromatics with aldehydes was achieved using a binary hybrid catalyst system comprising an acridinium photoredox catalyst and a thiophosphoric acid organocatalyst. The reaction proceeded through the following sequence: 1) photoredox-catalyzed single-electron oxidation of a thiophosphoric acid catalyst to generate a thiyl radical, 2) cleavage of the formyl C–H bond of the aldehyde substrates by a thiyl radical acting as a hydrogen atom transfer catalyst to generate acyl radicals, 3) Minisci-type addition of the resulting acyl radicals to *N*-heteroaromatics, and 4) a spin-center shift, photoredox-catalyzed single-electron reduction, and protonation to produce secondary alcohol products. This metal-free hybrid catalysis proceeded under mild conditions for a wide range of substrates, including isoquinolines, quinolines, and pyridines as *N*-heteroaromatics, as well as both aromatic and aliphatic aldehydes, and tolerated various functional groups. The reaction was applicable to late-stage derivatization of drugs and their leads.

Introduction

The hydroxyalkylated *N*-heteroaromatics are ubiquitously present in bioactive compounds and are versatile intermediates in the synthesis of pharmaceuticals/agrochemicals. Although transition metal-catalyzed addition reactions of aromatic compounds to various electrophiles through C(sp^2)–H bond activation are reported,[1] the use of carbonyl groups as electrophiles has remained difficult due to the reversibility of the C–C bond-forming step.[1,2] Specifically, the catalyzed direct *N*-heteroarylation of aldehydes has been limited to a C3-selective dehydrogenative reaction in the presence of silanes, which proceeded at a high temperature (135 °C) and has a limited substrate scope.[3] Consequently, *N*-heteroarylation of aldehydes mainly relies on stoichiometric carbanion chemistry through the deprotonation of a C(sp^2)–H bond with pK_a greater than 40 using strong bases (Figure 1A (a)).[4] Regio- and chemoselective C–H metalation and functionalization reactions of *N*-heteroaromatics using less nucleophilic Brϕnsted bases are reported.[5] Several types of functional groups, however, are not compatible with those reaction conditions.

An alternative pathway to hydroxyalkylated *N*-heteroaromatics is an oxidative Minisci reaction (Figure 1A (b)).[6-8] Due to the inertness of an α-oxy C–H bond of alcohols, however, this process requires the strong oxidant and large excess of alcohols resulting low generality. On the other hand, Melchiorre recently reported the photochemical hydroxyalkylation of quinolines and isoquinolines by novel spin-center shift (SCS) process (Figure 1A (c)).[9,10] Although the reaction proceeded under mild conditions, the acyl radical sources, 4-acyl-1,4-dihydropyridines, were prepared from the corresponding ketoaldehydes by harsh conditions (i.e. heating neat at 120–130 °C). This limited substrate generality of hydroxyalkyl groups and made the overall process less atom economic. Herein, we report a new catalytic method for synthesizing hydroxyalkylated *N*-heteroaromatics through Minisci-type reaction between *N*-heteroaromatics and aldehydes, mediated by a hybrid catalyst system comprising an acridinium photoredox catalyst and a thiophosphoric acid (TPA) organo-hydrogen atom transfer (HAT) catalyst (Figure 1B).[11] Notably, this reaction proceeded under redox-neutral conditions with high atom economy. This is in contrast to previously-reported Minisci reactions between *N*-heteroaromatics and aldehydes, which required stoichiometric strong oxidants and produced acylated products.[12]

[a] Graduate School of Pharmaceutical Sciences, The University of Tokyo 7-3-1 Bunkyo-ku, Tokyo 113-0033, Japan. E-mail: h-mitsunuma@mol.f.u-tokyo.ac.jp; kanai@mol.f.u-tokyo.ac.jp
[b] Department of Applied Chemistry, Graduate School of Engineering, Osaka University, 2-1 Yamadaoka, Suita, Osaka 565-0871, Japan
[c] Department of Life and Coordination-Complex Molecular Science, Institute for Molecular Science (IMS), 5-1 Higashiyama, Myodaiji, Okazaki, Aichi 444-8787, Japan

† Footnotes relating to the title and/or authors should appear here.
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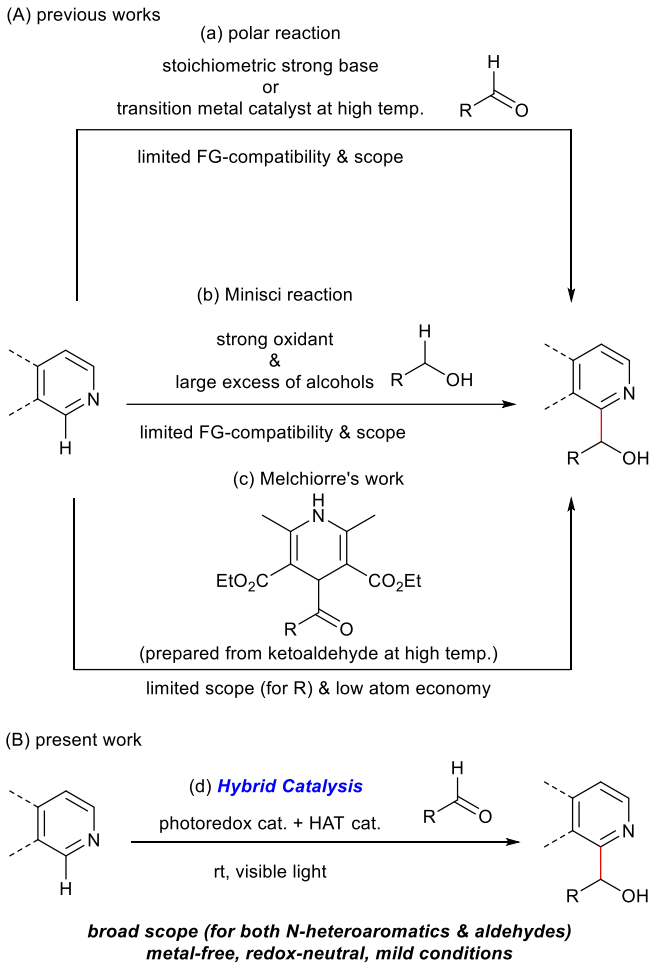

Figure 1. Overview of C–H hydroxyalkylation of *N*-heteroaromatics. (A) Previous works: (a) using a stoichiometric strong base or a transition metal catalyst. (b) oxidative Minisci reaction. (c) Melchiorre's work using 4-acyl-1,4-dihydropyridines. (B) Present work: (d) binary hybrid catalysis comprising a photoredox catalyst and an organo-HAT catalyst.

Results and discussion

Optimization of reaction conditions

Because the bond dissociation energy of a formyl C–H bond of aldehydes (88.7 kcal/mol)[13a] is much smaller than that of a C(sp^2)–H bond of *N*-heteroaromatics (105 kcal/mol),[13b] we planned to incorporate a SCS process in the overall catalytic cycle to produce alcohol products (see below). There are preceding examples in which the SCS process was combined with the photoredox-catalyzed Minisci-type reaction of *N*-heteroaromatics.[14] In those examples, formal alkylations of *N*-heteroaromatics were achieved using alcohols, ethers, or carbonyl compounds as an alkyl source. Especially, MacMillan[14a] and Huang[14c,d] achieved the incorporation of HAT and SCS processes. Despite the versatile roles of hydroxy groups in organic synthesis, however, they were eliminated in their reaction conditions. Moreover, their mechanistic studies implied hydroxyalkylated *N*-heteroaromatics were unstable in their reaction conditions.[14a,d]

Our working hypothesis for the catalytic cycle is shown in Figure 2. A photoredox catalyst Mes-Acr$^+$ in the excited state (*Mes-Acr$^+$) oxidizes an organocatalyst (RSH) to produce a radical (RS$^\bullet$) acting as a HAT catalyst. This radical cleaves the formyl C–H bond of aldehyde **2**. The resulting acyl radical **4** reacts with protonated *N*-heteroaromatics **5** through a Minisci reaction, giving radical cation **6**. Deprotonation of **6** affords benzylic carbon-centered radical **7**, which is converted to the α-oxy radical **8** via SCS. Finally, **8** is reduced by the reduced photoredox catalyst (Mes-Acr), and the subsequent protonation affords target compound **3**. On the basis of our previous findings, we envisioned that the combination of an acridinium photoredox catalyst (Mes-Acr$^+$) and TPA organocatalyst would realize the designed hybrid catalysis.[15,16]

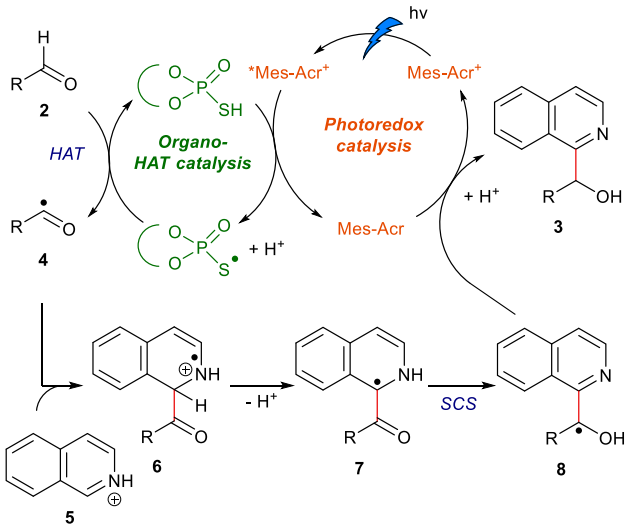

Figure 2. Proposed catalytic cycle.

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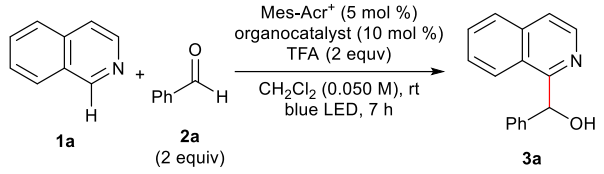
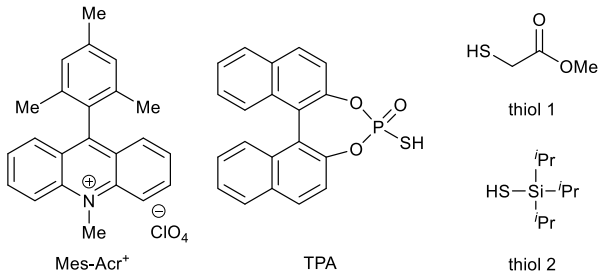
Table 1. Optimization of the Reaction Conditions.[a]



entry	organocatalyst	**3a** (%)[b]
1	TPA	94 (89)[c]
2	thiol 1	ND
3	thiol 2	ND
4	quinuclidine	3
5	benzoic acid	ND
6[d]	TPA	29
7	-	ND
8[e]	TPA	1
9[f]	TPA	ND
10[g]	TPA	ND



[a] General reaction conditions: **1a** (0.10 mmol), **2a** (0.20 mmol), Mes-Acr$^+$ (0.005 mmol), TPA (0.010 mmol), and TFA (0.20 mmol) were reacted in dichloromethane (DCM; 2.0 mL) at room temperature under blue LED irradiation for 7 h. [b] Yield was determined by ^{1}H NMR analysis of the crude mixture using 1,1,2,2-tetrachloroethane as an internal standard. [c] Isolated yield in parenthesis. [d] Without Mes-Acr$^+$. [e] Without TFA. [f] Without photoirradiation. [g] 1 equiv TEMPO was added.

We conducted optimization studies using isoquinoline (**1a**) and benzaldehyde (**2a**) (Table 1). Despite several possible side reactions such as reductive deoxygenation of **3a** and reduction of **2a**,[14] we identified the optimized reaction conditions comprising 5 mol % Mes-Acr$^+$ photoredox catalyst and 10 mol % TPA organocatalyst in the presence of 2 equiv TFA, affording **3a** in 94% yield (entry 1). Other organocatalysts for HAT, such as thiols,[14a,17a] quinuclidine,[17b] and benzoic acid[17c] did not afford the product (entries 2–5). Control experiments revealed that Mes-Acr$^+$, TPA, TFA, and visible light irradiation were indispensable for efficient reaction progress (entries 6–9). The addition of 1 equiv TEMPO inhibited the reaction (entry 10), indicating the presence of radical intermediates.

Substrate scope

Under the optimized conditions, we investigated the substrate scope (Figure 3). We first studied the aldehyde side (**3a**–**l**) using isoquinoline (**1a**) as an *N*-heteroaromatic substrate. Aromatic aldehydes containing various functional groups such as halogen (**3b**–**d**), ether (**3e**), trifluoromethyl (**3f**), and alkyl (**3g**) groups tolerated the reaction conditions. The electron density of the aromatic ring did not significantly affect the results. Moreover, steric hinderance at the *ortho*-position of the phenyl ring of aldehydes did not interfere with the reaction (**3g**). Aliphatic aldehydes, which are challenging substrates due to the presence of acidic α-C–H bonds and low electrophilicity,[3a] were a competent class of substrates in this reaction (**3h**–**l**). As a result, several hydroxy-alkylated isoquinolines containing ester (**3i**), phthalimide (**3j**), ketone (**3k**), and halogen (**3l**) were obtained in high yield. We then examined the scope of *N*-heteroaromatics. Various brominated isoquinolines exhibited good reactivity (**3m**–**p**). The reactions of isoquinolines containing amide (**3q**) and ester (**3r**) proceeded in good yield. This catalyst system was also applicable to the hydroxyalkylation of quinolines (**3s**–**z**). Quniolines containing ester (**3u**), halogen (**3v**–**x**), ether (**3y**), and phenyl (**3z**) groups were competent substrates. Moreover, pyridine derivatives were successfully converted to the corresponding products (**3aa**–**ad**). Ketone and ester functionalities were tolerated. Steric hinderance did not interrupt reaction progress and substituted pyridines were synthesized (**3ab**–**ac**).

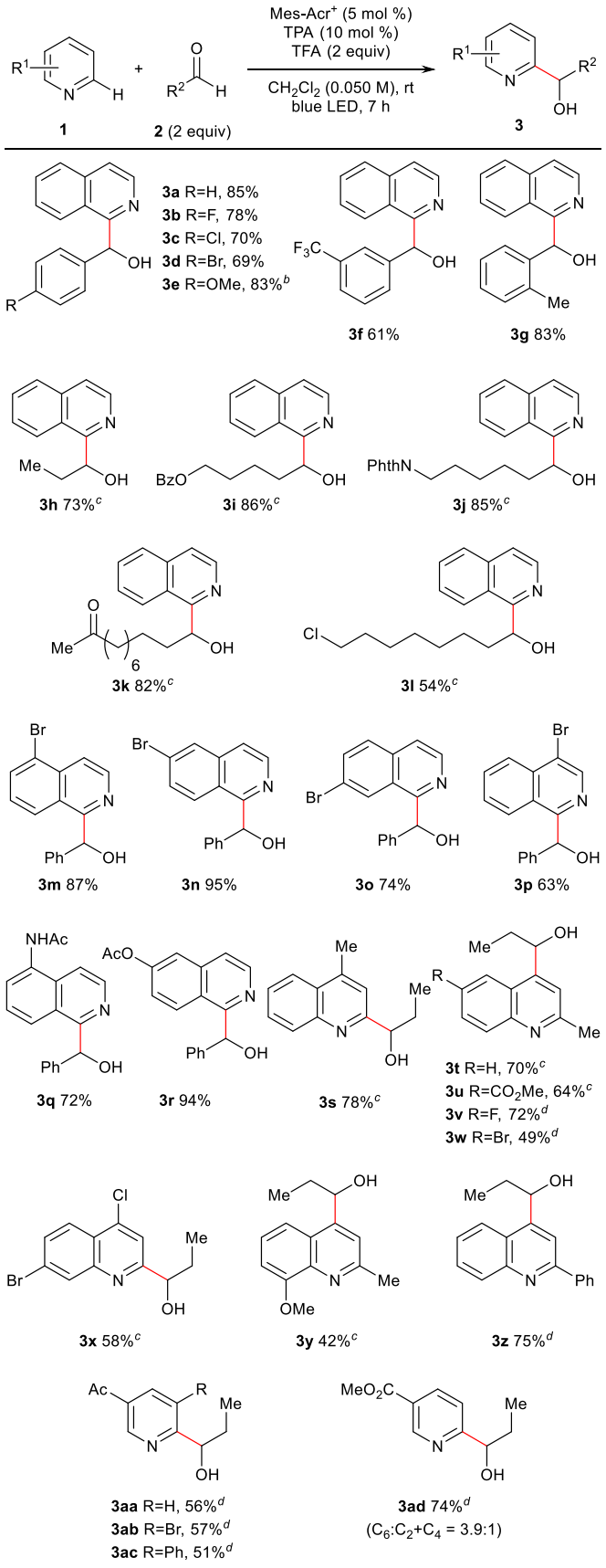


Figure 3. Substrate scope.[a]

[a] General reaction conditions: **1a** (0.10 mmol), **2a** (0.20 mmol), Mes-Acr$^+$ (0.005 mmol), TPA (0.010 mmol), and TFA (0.20 mmol) were reacted in dichloromethane (DCM; 2.0 mL) at room temperature under blue LED irradiation for 7 h. Yield is isolated yield unless otherwise noted. [b] 5 equiv of the aldehyde was used with the reaction time 13 h. [c] Reaction time was 3 h. [d] Reaction time was 5 h.

Furthermore, this reaction was applicable to late-stage modifications of complex molecules because of the mild conditions (Figure 4). Thus, camptothecin, which has anti-cancer activity, was transformed to the corresponding C7-hydroxyalkylated derivative (**3ae**). Introduction of functional groups to the C7-position of camptothecin could improve its pharmacologic properties.[18] A fasudil (ROCK2 inhibitor) derivative also reacted with propionaldehyde with excellent yield (**3af**). Functionalized hydroxyalkyl groups, which were difficult to use in the previous radical-mediated reactions, were also introduced to *N*-heterocycles under the present conditions (**3ag**–**3ak**). Thus, aldehydes derived from oxaprozin, loxoprofen, dehydrocholic acid, an amino acid derivative, and a sugar derivative afforded the corresponding *N*-heteroarylated products in good yields. It is noteworthy that substrates containing an oxazole ring which is susceptible to oxidative conditions (**3ag**)[19] or a relatively weak benzylic C-H bond (**3ah**) tolerated our reaction conditions.

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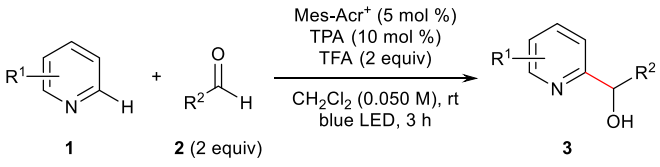
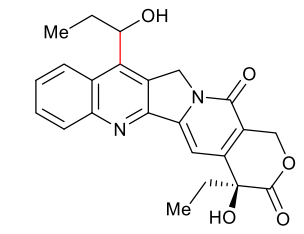
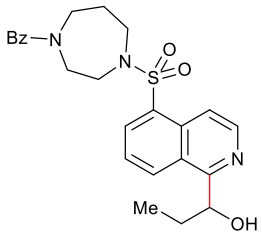


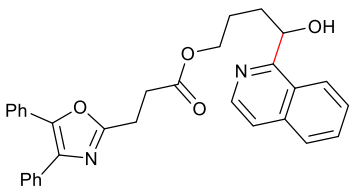
1 2 (2 equiv) 3



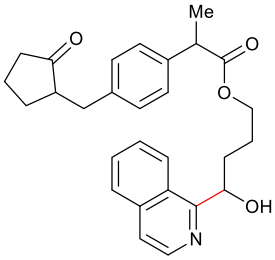
3ae 42%
(from camptothecin)



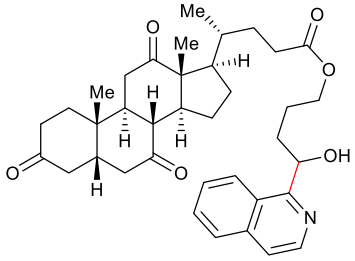
3af 99%
(fasudil derivative)



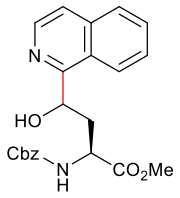
3ag 74%
(oxaprozin derivative)



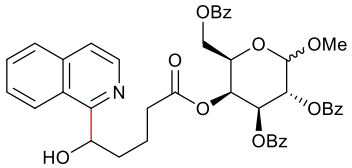
3ah 56%
(loxoprofen derivative)



3ai 67%
(dehydrocholic acid derivative)



3aj 51% (dr = 1.1/1)[b]
(homoserine derivative)



3ak 79% (dr = 1.1/1)[c]
(galactose derivative)

Figure 4. Late-stage modification of multifunctional substrates.[a]
[a] General reaction conditions: **1** (0.10 mmol), **2** (0.20 mmol), Mes-Acr+ (0.005 mmol), TPA (0.010 mmol), and TFA (0.20 mmol) were reacted in dichloromethane (DCM; 2.0 mL) at room temperature under blue LED irradiation for 3 h. Yield is isolated yield unless otherwise noted. [b] 1.2 equiv of the aldehyde was used. The target compound was isolated as the lactone. [c] Reaction was conducted at 0.035 mmol scale.

To gain preliminary insight into the mechanism, reactions were conducted using deuterated compounds (Figure 5). When benzaldehyde-*d* (**2a**-***d***) was exposed to the reaction conditions, target compound **3a** contained 85%-H at the α-position of the hydroxy group (Figure 5a). Thus, the formyl C–H bond of the aldehyde was cleaved in the overall catalytic cycle. When TFA-*d* was utilized as an acid additive, however, 62%-H was still incorporated at the α-position (Figure 5b). This result was contradictory to our hypothesis (Figure 2), and could be due to contamination by H_2O. Therefore, we assessed the H/D ratio incorporated in **3a** in mixed solvents containing variable amounts of D_2O. As a result, incorporation of D increased up to 95% according to the D_2O concentration (Figure 5b). This result indicates that the hydrogen atom at the α-position of the hydroxy group is introduced via protonation. These deuteration experiments support the feasibility of our mechanistic hypothesis shown in Figure 2. The quantum yield was determined to be 0.046, which supports that the reaction proceeded through a closed catalytic cycle, not a radical chain pathway (see SI for details).

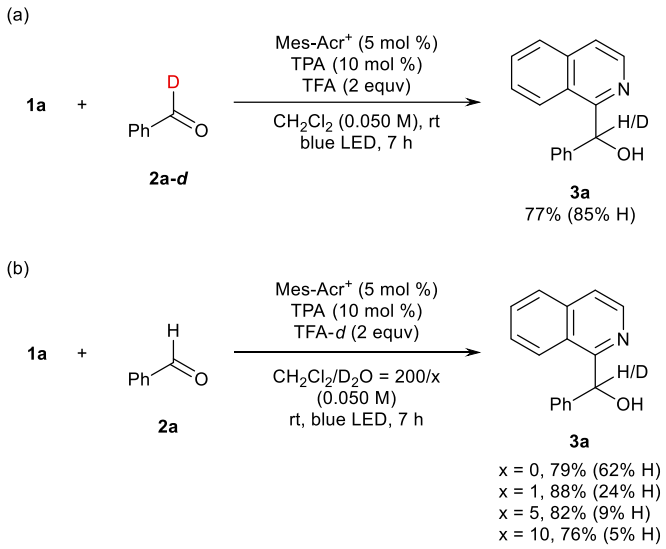


Figure 5. Mechanistic information for deuterium incorporation.[a]
[a] Yield was determined by ^{1}H NMR analysis of the crude mixture using 1,1,2,2-tetrachloroethane as an internal standard.

Conclusions

In conclusion, we developed a binary hybrid catalyst system to achieve a one-step, redox-neutral hydroxyalkylation of *N*-heteroaromatic compounds with aldehydes without using a metal species. The reaction proceeded under mild conditions and high atom economy, enabling a broad substrate scope and application to late-stage modifications of drug-related molecules. Keys to the success were the sequential HAT, Minisci, and SCS processes. Further mechanistic studies are ongoing in our laboratory.

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