Photocatalytic *N*-Heteroarylation of Aldehydes via Formyl C–H Activation

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Supporting Information Placeholder

ABSTRACT: A formal C–H addition of *N*-heteroaromatics to 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.

A one-step, redox neutral addition of organic molecules to carbonyl groups through catalytic activation of stable C–H bonds is an emerging-model chemical process for producing alcohols.[1] The addition of *N*-heteroaromatics to carbonyls (i.e., *N*-heteroarylation) is an especially attractive transformation because the produced 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).[4] Regio- and chemoselective C–H metalation and functionalization reactions using less nucleophilic Brφnsted bases are reported.[5] Several types of functional groups, however, are not compatible with those reaction conditions. Herein, we report a new catalytic method for synthesizing hydroxyalkylated *N*-heteroaromatics through the addition of *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).

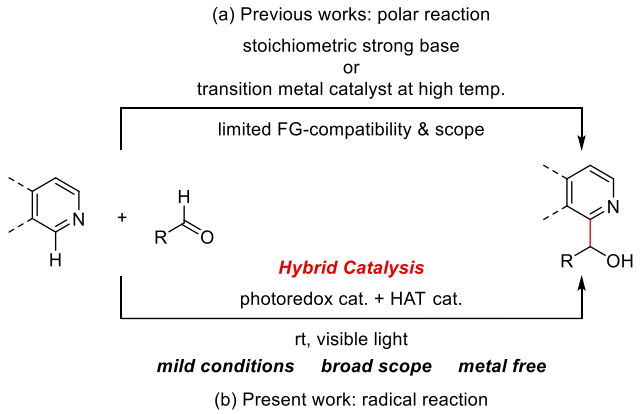


Figure 1. Overview of *N*-heteroarylation of aldehydes through C–H activation. (a) Previous works: using a stoichiometric strong base or a transition metal catalyst. (b) Present work: binary hybrid catalysis comprising a photoredox catalyst and an organo-HAT catalyst.

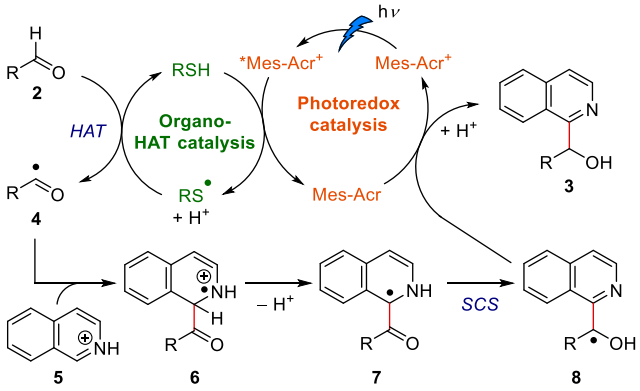


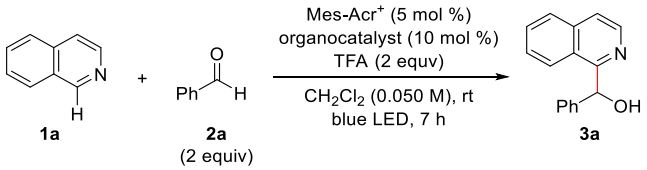
Figure 2. Proposed catalytic cycle.

Because the bond dissociation energy of a formyl C–H bond of aldehydes (88.7 kcal/mol)[6a] is much smaller than that of a C(sp^2)–H bond of *N*-heteroaromatics (105 kcal/mol),[6b] we planned to incorporate a spin-center shift (SCS) process[7] in the overall catalytic cycle to produce alcohol products (see below).

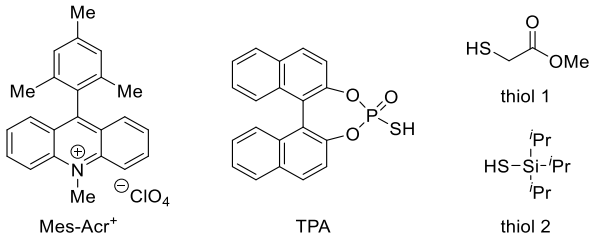
There are preceding examples in which the SCS process was combined with the photoredox-catalyzed Minisci-type reaction of *N*-heteroaromatics.[8-11] In those examples, formal alkylations of *N*-heteroaromatics were achieved using alcohols, ethers, or carbonyl compounds as an alkyl source.[8] Melchiorre recently reported the first photochemical hydroxyalkylation of quinolines and isoquinolines using 4-acyl-1,4-dihydropyridines as an acyl radical source.[12] In this precedent, the keto-radical intermediate (corresponding to **7** in Figure 2) generated by a Minisci reaction between *N*-heteroaromatics and the acyl radicals was converted to alcohol products **8** through the SCS process.

Our working hypothesis for the catalytic cycle is shown in Figure 2. A photoredox catalyst (Mes-Acr$^+$) in the excited state 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 followed by C-to-N single-electron transfer 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.[13]

Table 1. Optimization of the Reaction Conditions



entry	organocatalyst	**3a** (%)[a]
1	TPA	99 (85)[b]
2	thiol 1	ND
3	thiol 2	ND
4	quinuclidine	3
5	benzoic acid	ND
6[c]	TPA	29
7	-	ND
8[d]	TPA	1
9[e]	TPA	ND



[a]Yield was determined by ^{1}H NMR analysis of the crude mixture using 1,1,2,2-tetrachloroethane as an internal standard. [b]Isolated yield in parenthesis. [c]Without Mes-Acr$^+$. [d]Without TFA. [e]Without photoirradiation.

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**,[8] 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 almost quantitative yield (entry 1). Other organocatalysts for HAT, such as thiols,[8a,14a] quinuclidine,[14b] and benzoic acid[14c] 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).

Under the optimized conditions, we investigated the substrate scope (Figure 3). We first studied the aldehyde side (**3a**–**3l**) 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 hydroxyalkylated 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 functionalization of quinolines (**3s**–**u**). Moreover, pyridine derivatives were successfully converted to the corresponding products (**3v**–**w**). Ketone and ester functionalities were tolerated. Furthermore, this reaction was applicable to late-stage modifications of complex molecules because of the mild conditions (**3x**–**y**). Thus, camptothecin, which has anti-cancer activity, was transformed to the corresponding C7-hydroxyalkylated derivative (**3x**). Introduction of functional groups to the C7-position of camptothecin could improve its pharmacologic properties.[15] A fasudil (ROCK2 inhibitor) derivative also reacted with propionaldehyde with excellent yield (**3y**).

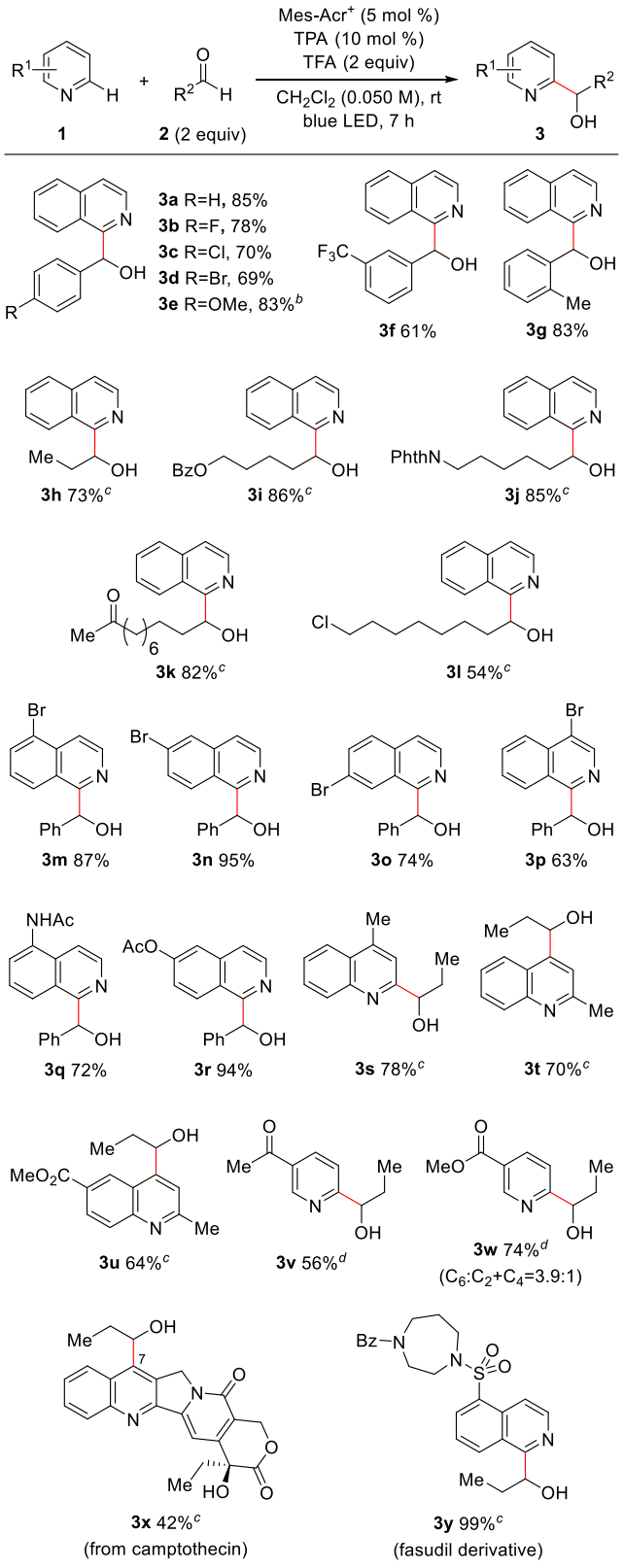


Figure 3. Substrate scope. [a]Yield is isolated yield unless otherwise noted. [b]5 equiv of the aldehyde was used with the reaction time 13 h. [c]Reaction time was 3 h. [d]Reaction time was 5 h.

To gain preliminary insight into the mechanism, reactions were conducted using deuterated compounds (Figure 4). 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 4a). 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 4b). 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 4b). 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.

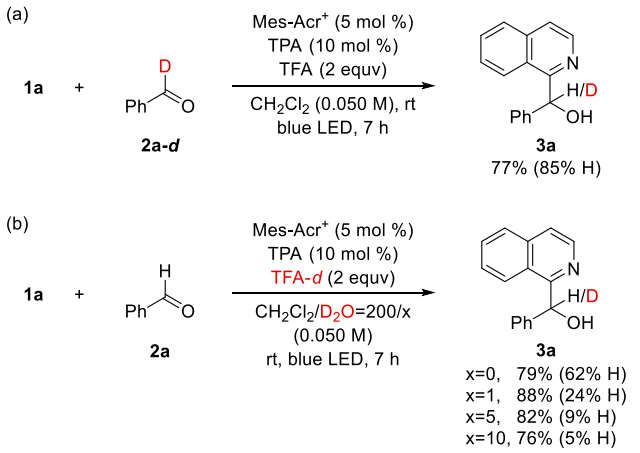


Figure 4. Mechanistic information for deuterium incorporation. Yield was determined by ^{1}H NMR analysis of the crude mixture using 1,1,2,2-tetrachloroethane as an internal standard.

In conclusion, we developed a binary hybrid catalyst system to achieve a one-step, redox-neutral *N*-heteroarylation of aldehydes through C–H bond activation without using a metal species. The reaction proceeded under mild conditions, 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.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interests.

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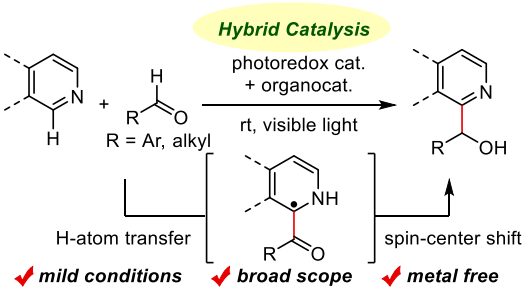
Hybrid Catalysis
photoredox cat.
+ organocat.
rt, visible light
R = Ar, alkyl
H-atom transfer
spin-center shift
mild conditions
broad scope
metal free