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Metal- and Acid-Free C−H Formylation of Nitrogen Heterocycles: Using Trioxane as an Aldehyde Equivalent Enabled by an Organic-Soluble Oxidant

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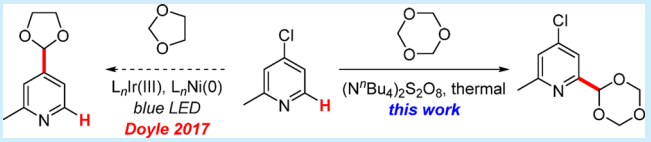
Supporting Information

ABSTRACT: A metal-free, innate, and practical C−H formylation of nitrogen heterocycles using trioxane as a formyl equivalent is reported. This reaction provides a mild and robust method for modifying medicinally relevant heterocycles with an aldehyde handle. The use of an organic soluble oxidant, tetrabutylammonium persulfate, is critical in promoting the desired coupling.



Nitrogen-containing heterocycles are critically important to drug discovery and are prevalent in many modern medicines.[1] Rapid and reliable access to functionalized heterocycles, therefore, greatly expedites the inventive process of medicinal chemistry. To this end, aldehydes are versatile and high-value functional handles that can be rapidly elaborated to compounds of biological interest. Aldehydes are most commonly synthesized through the reaction of organometallic reagents with *N*,*N*-dimethylformamide (DMF) under cryogenic conditions (i.e., Bouveault reaction, Figure 1a) and the palladium-catalyzed reductive formylation of aryl halides (Figure 1b).[2] The direct carbonylation of C−H bonds is perhaps the most atom economical way to construct aldehydes, but catalytic accounts are sparse.[3] In contrast, traditional methodologies such as the Vilsmeier−Haack and Duff reactions depend on the intrinsic nucleophilicity of the (hetero)arene undergoing formylation due to the electrophilic aromatic substitution mechanism at play. Inspired by early accounts of open-shell alkyl radical additions,[4] we identified an important gap in formylation reactions of electron-deficient heterocycles that leverages their innate reactivity.[5] We herein report a metal-free, innate, and practical C−H formylation of nitrogen heterocycles that uses trioxane as the formyl equivalent (Figure 1c). Notably, this reaction is mild and exhibits robust functional group tolerance.

The generation of free radicals α to a heteroatom (oxygen in particular) was originally described by Minisci in 1971.[4,6] These cross-dehydrogenative coupling (CDC) reactions have seen a resurgence in recent years[7] due to their potential positive impact on green and sustainable science. The observation that weak C−H bonds α to an O atom can undergo activation through a photoredox catalysis activation mode[8] culminated in a recent account of aldehyde synthesis by the Doyle[9a] group. Inspired by this, we envisioned a complementary approach that harnesses the direct activation of weak C−H bonds in acetals and couples these intermediates with a Minisci-type mechanism to achieve formylation of *N*-heterocycles (Figure 2).

We selected isoquinoline as a model substrate for initial examination utilizing MacMillan's conditions[8a] (Table 1). We opted to examine trioxane as a formyl equivalent based on Minisci's report,[4] which would simultaneously circumvent competing C−H cleavage at multiple sites.[9] In the presence of photocatalyst [Ir{dF(CF$_3$)ppy}$_2$(dtbpy)]PF$_6$ (2 mol %), trifluoroacetic acid (TFA, 1 equiv), and sodium persulfate ($Na_2S_2O_8$) under blue LED irradiation, we observed smooth coupling of isoquinoline (**1a**) and totrioxane (**2**) to liberate adduct **3a** in 73% conversion by LCMS (entry 1). The addition of phase transfer catalyst tetrabutylammonium chloride (N^{n}Bu$_4$Cl) improved the yields slightly (entry 2). To our surprise, when the reaction was conducted in the absence of the acid activator, comparable amounts of product could be obtained (entry 3). We replaced $Na_2S_2O_8$ with tetrabutylammonium persulfate ((N^{n}Bu$_4$)$_2$S$_2$O$_8$)[10] and observed an improved conversion to **3a** (entry 4), pointing to a critical rate enhancement effect due to the homogeneous

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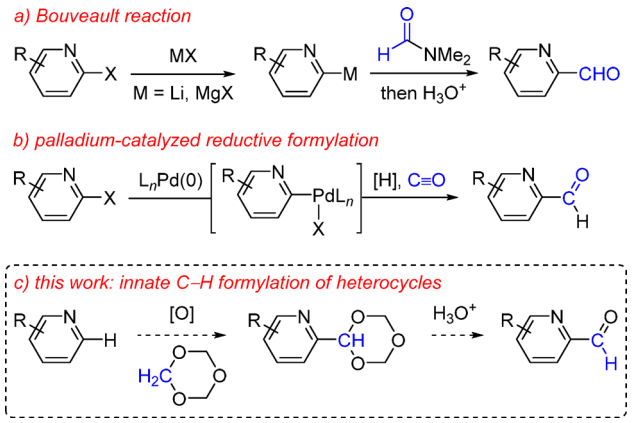


Figure 1. State-of-the-art methods in heterocycle formylation include (a) the Bouveault reaction and (b) the reductive carbonylation of aryl halides. We herein propose (c) an innate C−H formylation using trioxane under metal- and acid-free conditions.

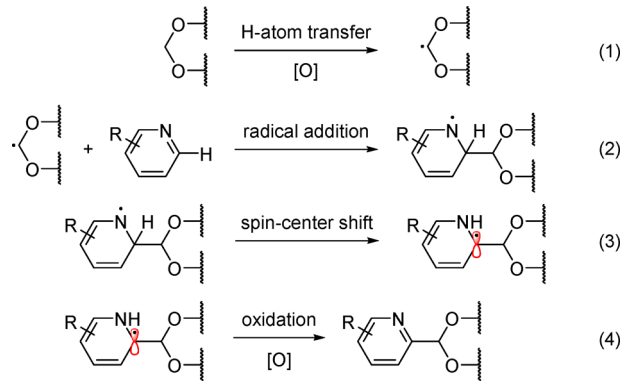


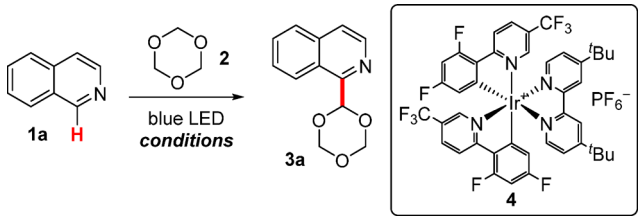
Figure 2. Reaction design: using acetal radicals for innate C−H formylation. The proposed mechanism involves H atom abstraction with an external oxidant (eq 1), addition of the resulting radical to the *N*-heterocycle (eq 2), spin-center shift of the adduct (eq 3), and reoxidation with an external oxidant to liberate the desired product (eq 4).

nature of the coupling conditions. Surprisingly, the control reaction in the absence of photocatalyst (but still with irradiation) afforded 68% of the desired product (entry 5).

These results led us to speculate whether the O−O bond of the persulfate anion alone was sufficient to promote coupling between isoquinoline and trioxane. Since persulfate activation is possible via transition metal redox chemistry, photochemical irradiation, and heat,[7g,h,11] and with an eye toward the practicality and general utility of this transformation, we elected to explore thermal activation. To our delight, we demonstrated that mild heating (50 °C) afforded the same results in our desired formylation reaction (entry 6). In contrast to Minisci's account, which requires iron salts, stoichiometric TFA, and refluxing conditions,[4] our protocol is practical, metal- and acid-free, and occurs with gentle heating. We expect that this important advance provides an avenue for using sensitive heterocycles and functional groups and will impact medicinal chemistry significantly.

Next, we evaluated the generality of our metal-free C−H formylation. A number of different isoquinolines undergo productive coupling at the C1 position (Figure 3). Importantly, in contrast to strategies involving organometallic catalysts,[9b] aryl chlorides and bromides are inert under these

Table 1. Reaction Optimization: Coupling Isoquinoline with Trioxane



entry	conditions	yield 1a[a] (%)	yield 3a[a] (%)
1	2 mol % **4**, TFA,[b] $Na_2S_2O_8$,[c] MeCN/H_2O	27	73
2	2 mol % **4**, TFA,[b] $Na_2S_2O_8$,[c] N^nBu_4Cl,[c] CH_2Cl_2/H_2O	4	79
3	2 mol % **4**, $Na_2S_2O_8$,[c] N^nBu_4Cl,[c] CH_2Cl_2/H_2O	24	67
4	2 mol % **4**, $(N^nBu_4)_2S_2O_8$,[c] CH_2Cl_2	<1	86
5	$(N^nBu_4)_2S_2O_8$,[c] CH_2Cl_2	17	68
6	$(N^nBu_4)_2S_2O_8$,[c] DCE, 50 °C, no light	<1	86

[a]Conversion as determined by LCMS. [b]1 equiv. [c]2.5 equiv. Conditions: isoquinoline (0.1 mmol), trioxane (1.5 mmol), solvent (0.2 M). All reactions (except entry 6) were conducted under Kessil lamp irradiation.

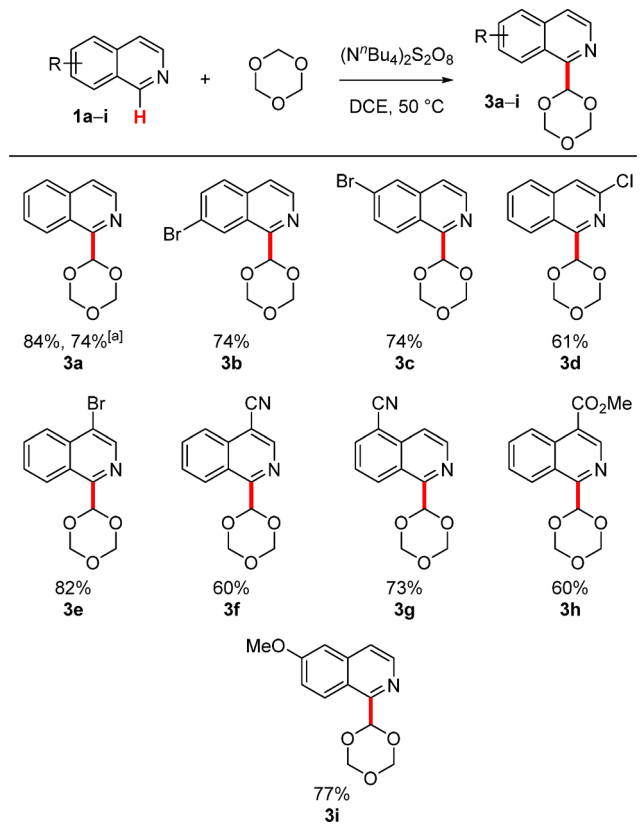


Figure 3. Reaction scope: coupling isoquinoline with trioxane. Conditions: isoquinoline (0.4 mmol), trioxane (6 mmol), N-$(^nBu_4)_2S_2O_8$ (1 mmol), DCE (0.2 M), 50 °C, 1−4 h. Isolated yields. [a] 5 mmol scale (~1 g).

reaction conditions (**3b**−**e**). Although radical-type S_NAr reactions have been reported,[12] we did not observe any substitution of the C−Cl bonds (**1d**). Varying the electronic character of the isoquinoline had minimal impact on reaction efficiency, and functional groups including nitriles and esters

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were tolerated (**3f–i**). We then turned our attention to other medicinally relevant *N*-heterocycles (Figure 4). To our delight, other bicyclic motifs undergo smooth coupling with trioxane, including quinolines (**3j–k**), quinoxalines (**3l**), quinazolines (**3m**), naphthyridines (**3n**), aza-indazoles (**3o**), and aza-indoles (**3p**). We were likewise pleased to observe facile C–H formylation of monocyclic structures, including pyridines (**3q**), pyrimidines (**3r**), and pyrazines (**3s**).[13] In each of these cases, no current methodologies provide rapid access to the direct formylation products in synthetically useful yields. Also, in contrast to methods involving transition metals, C–Cl and C–Br bonds are preserved in our formylations, thus highlighting an important complementarity to photoredox formylations (Figure 5).[9b]

In Minisci's original paper, aryl-trioxane adducts were converted to their corresponding aldehydes in refluxing aqueous sulfuric acid.[4] Importantly, unlike acetals or 1,3-dioxanes (i.e., cyclic acetals), accounts of aryl-trioxanes are extremely rare (<40 references) and these motifs are underutilized as aldehyde synthons, although they exhibit robust stability and hence are ideal for subsequent synthetic manipulations. Mindful of the sensitive functional groups of the various heterocycles examined above, we evaluated a number of Lewis acids for hydrolysis of the trioxane functional group. Rare earth salts were ineffective (e.g., $In(OTf)_3$), but a simple protocol involving treatment with BCl_3 for 10 min

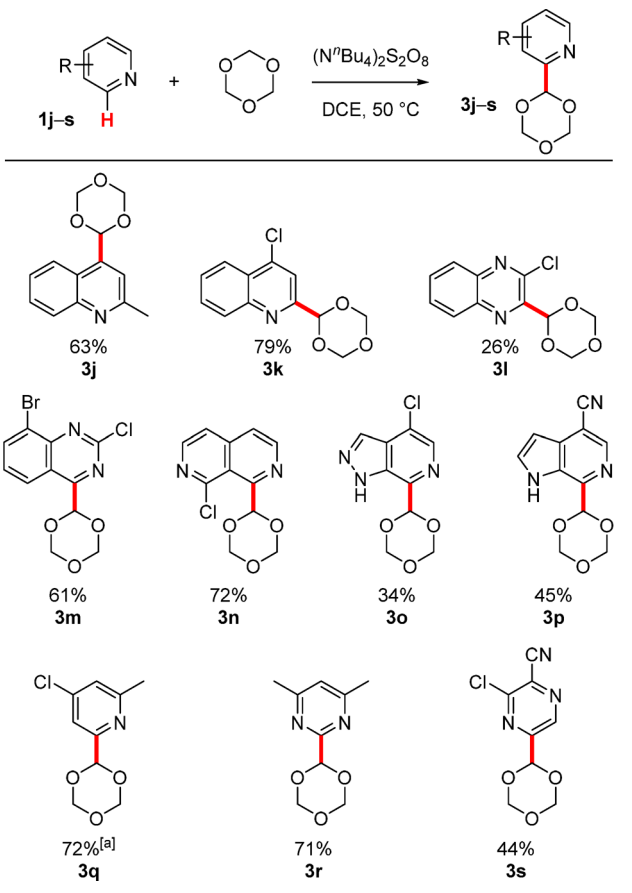

Figure 4. Reaction scope: coupling other heterocycles with trioxane. Conditions: heterocycle (0.4 mmol), trioxane (6 mmol), $(N^nBu_4)_2S_2O_8$ (1 mmol), DCE (0.2 M), 50 °C, 1–4 h. Isolated yields. [a] Conducted with TFA (0.8 mmol).

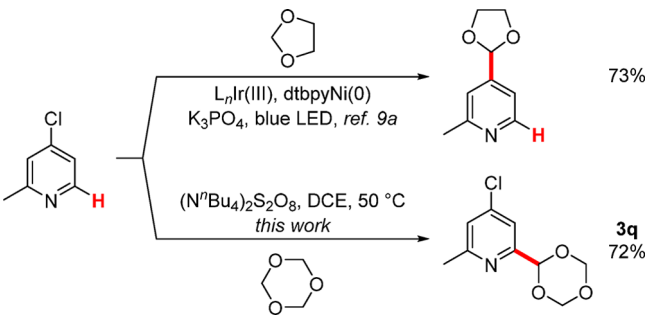

Figure 5. Divergent chemoselective formylation through a metallaphotoredox coupling (*top*)[9a] versus a metal-free radical addition (*bottom*).

provided the corresponding aldehydes in good yields (Figure 6), a hitherto unknown trioxane deprotection protocol.

To rationalize the site of observed C–H formylation of our *N*-heterocycle scope, we conducted a series of computational studies. Fukui indices are most commonly applied to predict the site of free radical additions.[14] Understanding the regioselectivity of functionalization, however, is complicated by the existence of multiple protonation states of *N*-heterocycles.[15] Of note, our method is independent of acidic additives such as TFA. In the proposed reaction mechanism (Figure 2), the putative trioxane radical undergoes addition to the substrate, leading to dearomatization as governed by orbital attractions. To our surprise, Fukui indices (f^+, f^-, and f^0)[16] only successfully predicted the site of coupling <50% of the time (see Supporting Information for details). Next, we conducted density-functional theory (DFT)[17] calculations to shed further light on the origin of the observed regioselectivity. Geometry optimizations and frequency calculations were performed at the B3LYP/6-31G**[18] level of theory, with single-point energies evaluated at the B3LYP/6-311++G** level. We opted to examine in greater detail the transition structure for the addition event of the trioxane radical to two model *N*-heterocycles, isoquinoline (**1a**) and 3-chloropyrazine-2-carbonitrile (**1s**).

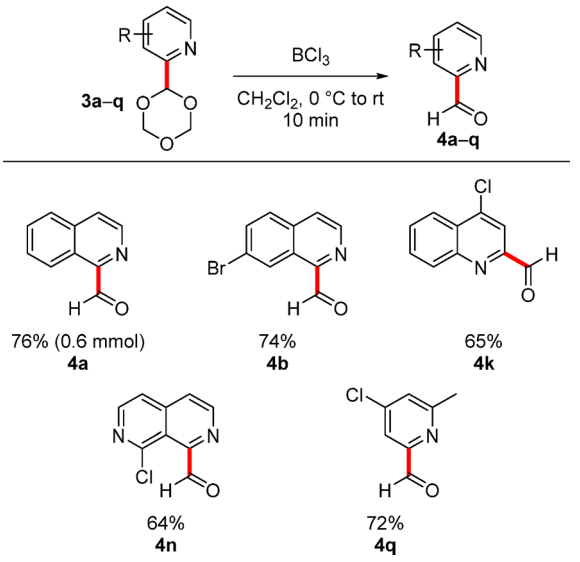

Figure 6. Conversion of aryl-trioxane adducts to aryl-aldehydes. Conditions: BCl_3 (2 equiv), CH_2Cl_2 (0.5 M), 0 °C to rt, 10 min. Isolated yields.

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Based on our calculations, we confirmed that both the sense and level of regioselectivities were well reproduced in accordance with the experimental data. Our transition structures show significant pyramidalization of the C undergoing radical addition. This step features an accessible activation barrier (Figure 7, $\Delta G^{\ddagger} \approx 17-20$ kcal mol^{-1}), and the regioisomeric transition states differ by at least 2.1 kcal mol^{-1}. For **1a**, the energy difference between the regioisomeric addition transition states (3.3 kcal mol^{-1}) is in line with the stability difference between the resulting radicals (3.1 kcal mol^{-1}). In this case, C1 addition liberates a radical with two benzenoid resonance structures, which is better stabilized compared to C4 addition, which produces a radical with only one resonance structure with an intact aromatic sextet. The intramolecular 1,2-hydrogen shift (Figure 2, eq 3) was predicted to have a high barrier ($\Delta G^{\ddagger} \approx 44$ kcal mol^{-1}) that is inaccessible at 50 °C, although a bimolecular mechanism for this shift cannot be ruled out as the shift is thermodynamically downhill. Investigations to fully elucidate and characterize the reaction mechanism are underway. Strategies to *de novo* predict regioselectivity in our trioxane couplings (and in general) are the subject of current studies, and will be reported in due course.

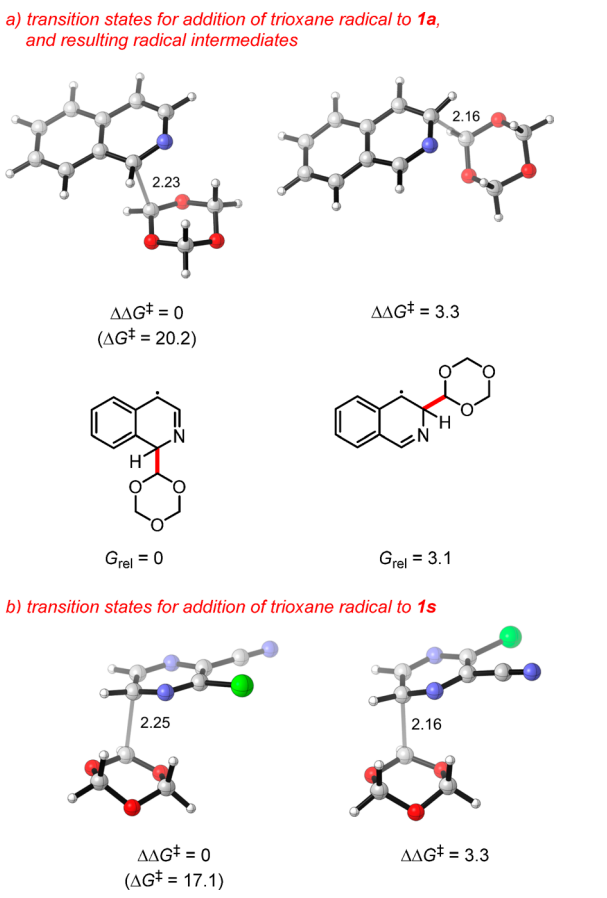

Figure 7. (a) Transition state for the addition of trioxane radical to selected sites of C−H bond functionalization of **1a**, and the structure of the resultant radicals. (Only resonance structures with an intact aromatic sextet are shown.) (b) Transition state for the addition of trioxane radical to selected sites of C−H bond functionalization of **1s**. All calculations performed at the B3LYP/6-311++G**//B3LYP/6-31G** level of theory. Activation Gibbs energies are reported in kcal mol^{-1}, and bond distances are reported in Å.

In conclusion, we have developed a robust protocol for the C−H formylation of *N*-heterocycles using trioxane as the aldehyde equivalent. Importantly, this reaction occurs under mild reaction conditions and is devoid of precious metals and stoichiometric acid additives. The use of $N(^{n}Bu_4)_2S_2O_8$ as a soluble source of oxidant proved to be critical for success. We anticipate that this method will continue to expand an ever-growing toolbox of synthetic tools for medicinal chemists.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02453.

Experimental procedures, spectral data, computational data (PDF)

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Notes

The authors declare no competing financial interest.

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