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Formyl-selective deuteration of aldehydes with D_2O via synergistic organic and photoredox catalysis†

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Formyl-selective deuteration of aldehydes is of high interest for labeling purposes and for optimizing properties of drug candidates. Herein, we report a mild general method for formyl-selective deuterium labeling of aldehydes with D_2O , an inexpensive deuterium source, via a synergistic combination of light-driven, polyoxometalate-facilitated hydrogen atom transfer and thiol catalysis. This highly efficient, scalable reaction showed excellent deuterium incorporation, a broad substrate scope, and excellent functional group tolerance and selectivity and is therefore a practical method for late-stage modification of synthetic intermediates in medicinal chemistry and for generating libraries of deuterated compounds.

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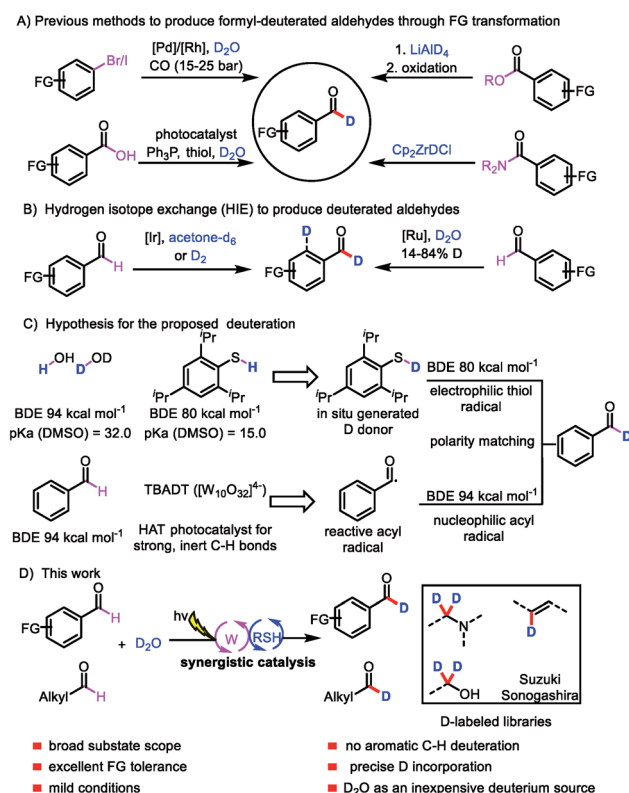
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Introduction

Deuterium labeling has a range of applications, including in the investigation of reaction mechanisms¹ and the analysis of drug absorption, distribution, metabolism, and excretion,² as well as in nuclear magnetic resonance spectroscopy³ and mass spectrometry.⁴ In recent years, interest in the incorporation of deuterium atoms into patented drugs and drug candidates to enhance their metabolism and pharmacokinetic properties has burgeoned.⁵ In 2017, the US Food and Drug Administration approved the first deuterated drug, deutetabenazine (Austedo),⁶ and the increasing demand for new deuterium-labeled drugs has motivated the development of efficient deuteration methods.⁷

Aromatic aldehydes are often used as building blocks for pharmaceutical synthesis owing to their versatile reactivity,⁸ indeed, they can be rapidly transformed to other compounds via C–C and C–X bond forming reactions. The development of an efficient protocol for constructing formyl-deuterated aromatic aldehydes can be expected to increase the availability of deuterated lead compounds. Aromatic aldehydes selectively labeled at the formyl position are traditionally produced from the corresponding esters by means of reduction with $LiAlD_4$ followed by oxidation,⁹ from the corresponding amides by reaction with deuterated Schwartz's reagent (obtained from $LiAlD_4$),¹⁰ from aryl halides via Pd/Rh-catalyzed reductive carbonylation,¹¹ or from carboxylic acids

via deoxygenative deuteration with synergistic photoredox and organic catalysis (Scheme 1A).¹² In terms of atom- and step-economy, the ideal protocol for preparing deuterated



Scheme 1 Strategies for synthesizing deuterated aldehydes; (A) previous methods to produce deuterated aldehydes through FG transformation; (B) hydrogen isotope exchange (HIE) to produce deuterated aldehydes; (C) hypothesis for the proposed deuteration; (D) our work.

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Table 1 Optimization of conditions for the catalytic formyl-selective deuteration reaction^a

Entry	Deviation from standard conditions	Deuteration ^b (%)
1	None	94
2	7b instead of 7a	63
3	7c instead of 7a	71
4	7d instead of 7a	78
5	NMP instead of DCM	13
6	MeCN instead of DCM	38
7	CHCl ₃ instead of DCM	62
8	2 mol% of TBADT	77
9	20 mol% of 7a	80
10	No TBADT	<5
11	No 7a	<5
12	No light	<5



^a Reaction conditions, unless otherwise noted: **1a** (0.3 mmol), TBADT (0.012 mmol), **7a** (0.12 mmol), and 1 : 1 (v/v) DCM/D₂O (3.0 mL) under an Ar atmosphere. ^b Deuterium incorporation was determined by integration of the residual formyl proton in the ¹H NMR spectrum. DCM = dichloromethane and NMP = *N*-methyl-2-pyrrolidinone.

after purification by column chromatography, indicating that decomposition and side-product formation were minimal. 6-Methoxy-2-naphthaldehyde was also a suitable substrate, giving **10b** in 90% yield with 92% deuterium incorporation. 1-Naphthaldehyde gave a product (**10c**) with lower deuterium incorporation (90%) than **10a**, presumably because the 1-position is more sterically hindered than the 2-position. We also tested benzaldehydes bearing substituents with various electronic and steric properties to obtain deuterated products **10d–10bb**. Specifically, benzaldehydes with electronically neutral functional groups, such as isopropyl, *t*-butyl, and phenyl, worked well under the optimal conditions, giving high yields with excellent deuterium incorporation (**10d–10f**, 93%). Halogenated molecules account for approximately 50% of the market-leading drugs because they are less susceptible to oxidation by cytochrome P450.²⁰ Furthermore, they offer a valuable platform for generating molecular complexity through cross-coupling reactions.²¹ Therefore, we were encouraged to find that benzaldehydes bearing fluoro, chloro, bromo, and iodo atoms gave the corresponding products (**10g–10k**) with high deuterium incorporation (90–96%). Trifluoromethyl and trifluoromethoxy groups, which have often been shown to improve the activity of pharmaceutical leads, were compatible with our protocol, showing good deuterium incorporation (**10l–10o**, 95–97%) regardless of their position on the benzene ring. Benzaldehydes with other electron-withdrawing groups (ester and cyano) were

smoothly transformed into the corresponding deuterated aldehydes (**10p** and **10q**). Moreover, electron-rich aldehydes were also reactive (**10r–10v**, 88–95% deuterium incorporation). Intriguingly, several relatively sensitive yet versatile functional groups—boronic esters (**10w** and **10x**), an alkyne (**10y**), and an alkene (**10z**)—tolerated the deuteration conditions well, which shows the potential utility of this protocol for synthetic and medicinal chemistry applications. Polysubstituted aldehydes were also suitable substrates (**10aa** and **10bb**). Being aware of the important role of heteroaromatic moieties in the scaffolds of pharmaceutical compounds, we were pleased to find that *N*- and *S*-heterocycles were also tolerated under our deuteration conditions (**10cc–10gg**). In addition, the reaction was amenable to scale up; when it was carried out on a 9 mmol scale, **10i** was isolated in 93% yield with no decrease in deuterium incorporation.

In addition to aromatic aldehydes, aliphatic aldehydes are also interesting because they constitute an even greater part of the –CHO family. However, few radical-based tools for convenient modification of aliphatic aldehydes have been developed. This is particularly true for branched aldehydes, which tend to undergo decarbonylation under radical conditions.²² However, when we subjected linear and branched aldehydes to our protocol, we found that all of them underwent formyl deuteration to afford the desired products (**10hh–10mm**, 90–98% deuterium incorporation), and no products of CO dissociation were observed. However, a limitation of this reaction was also uncovered. That is, deuteration also takes place at the α -positions of formyl.

This excellent functional group tolerance suggested that the protocol would be useful for the synthesis of structurally complex deuterated aldehydes, and indeed we were pleased to find that deuterated aldehydes derived from menthol, pregnenolone, ibuprofen, and fenbufen derivatives (**10nn–10qq**) could be accessed with uncompromised reactivities. In addition, the reaction of adapalene, an antiacne drug, afforded corresponding deuterated aldehyde **10rr** with high deuterium incorporation. These examples confirmed the potential utility of our protocol for practical late-stage modification of synthetic intermediates in medicinal chemistry applications (Table 2).

Because aldehydes are versatile functional groups that undergo a wide variety of organic transformations, the protocol reported herein can be used to access libraries of deuterated compounds (Scheme 3A). For example, deuterium-labeled aldehyde **10i** readily underwent reduction, reductive amination, and Horner–Wadsworth–Emmons olefination to deliver deuterated alcohol **11**, deuterated amine **12**,^{7a} and β -deuterated, α,β -unsaturated ester **13**. Importantly, **13** has not been accessed by direct labeling of the corresponding cinnamate ester.²³ Deuterium could also be incorporated into pharmaceutical molecules and advanced materials, as indicated by the successful Suzuki coupling reaction of **10i** to afford **14** and the Sonogashira coupling reaction of **10i** to provide **15**, which is difficult to obtain by currently available methods.

In a further demonstration of the utility of this catalytic formyl-deuteration method, we used it to synthesize silyl-



Table 2 Exploration of substrate scope^a

^a Reactions were performed on a 0.3 mmol scale, unless otherwise noted. ^b Some sites in compounds **10hh**, **10jj**, **10kk**, **10ll** and **10mm** (shown in their structures, with the deuteration percentage in square brackets) are deuterated. Isolated yields are given. See the ESI for experimental details. Deuterium incorporation was determined by integration of the residual formyl proton in the ¹H NMR spectra.

protected phenol **10tt**, which is an intermediate in the synthesis of enantiopure d₁-benzyl alcohols, in a single, high-yielding step and with a high deuterium incorporation from aldehyde **1tt** (Scheme 3B).²⁴ This method is superior to the existing route to

10tt, which employs stoichiometric quantities of reagents and requires five steps from aldehyde **1ss**.²⁴

Having explored the substrate scope and utility of the reaction, we conducted mechanistic studies to support the



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