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Visible-light-mediated deuteration of aldehydes with D_2O via polarity-matched reversible hydrogen atom transfer

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ABSTRACT

Hydrogen/deuterium exchange at the formyl groups of aldehydes is the most direct way to synthesize deuterated aldehydes, which are of interest for labeling studies and drug discovery. Herein, we report a mild, general protocol for visible-light-mediated metal-free deuteration of aldehydes in D_2O with synergistic photoredox and thiol catalysis. The protocol is highly efficient, has a broad substrate scope, and shows excellent functional group tolerance and selectivity, all of which make it suitable for generating libraries of deuterated compounds. The efficient deuteration was attributed to a photoredox-catalyzed polarity-matched reversible hydrogen atom transfer reaction between the aldehydes and the thiol.

1. Introduction

Deuterium-labeled compounds are of importance for drug discovery [1,2]; investigation of reaction mechanisms [3]; analysis of drug absorption, distribution, metabolism, and excretion [4–6]; nuclear magnetic resonance spectroscopy [7]; and mass spectrometry [8,9]. In addition, there has recently been a surge in applications for approval of deuterated pharmaceutical agents by the US Food and Drug Administration. The first deuterated drug, deutetrabenazine (Austedo), was approved by the FDA in 2017 [10], and many deuterated drug candidates are emerging [1,2]. Therefore, convenient, selective catalytic methods for generating deuterated building blocks are urgently needed [11–18].

Deuterated aldehydes are of particular interest because aldehydes can serve as building blocks for quick access to a wide array of biologically important molecules [19]. Traditionally, deuterated aldehydes are produced by reduction of the corresponding esters with $LiAlD_4$ and subsequent oxidation [20–22], by reactions of amides with deuterated Schwartz's reagent [23], by Pd/Rh-cocatalyzed reductive carbonylation reactions of aryl halides [24], and by deoxygenative deuteration of carboxylic acids (Scheme 1A) [25]. However, the ideal method for preparing deuterated aldehydes would be direct hydrogen isotope exchange (HIE), which would eliminate the need for functional group manipulation. In fact, the research groups of Tuttle and Newman independently reported Ir- and Ru-catalyzed HIE reactions of benzaldehydes (Scheme 1A) [26,27]. However, the chemoselectivity is difficult to control (deuteration of the aryl rings is observed), and the deuterium incorporation is unsatisfactory (14–84%). Recently, the groups of Wang and Yan developed catalytic HIE processes promoted by *N*-heterocyclic carbenes (Scheme 1A) [28,29]. Mechanistically, these HIE transformations proceed via ionic reaction pathways.

We envisioned that HIE could instead be accomplished by photoredox catalysis, which has recently emerged as a method for achieving organic transformations via radical processes [30–32]. In fact, we recently pioneered a general strategy for deuteration of aldehydes by D_2O with mediation by a synergistic combination of light-driven, tetra-*n*-butylammonium decatungstate–facilitated hydrogen atom transfer (HAT) and thiol catalysis (Scheme 1B)

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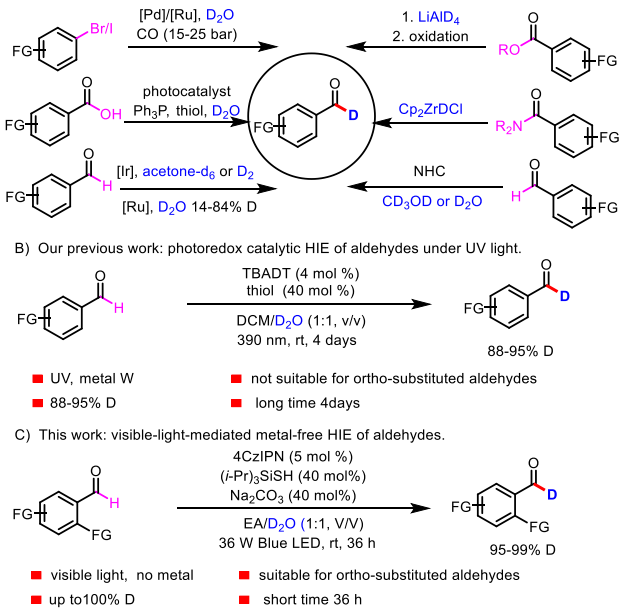


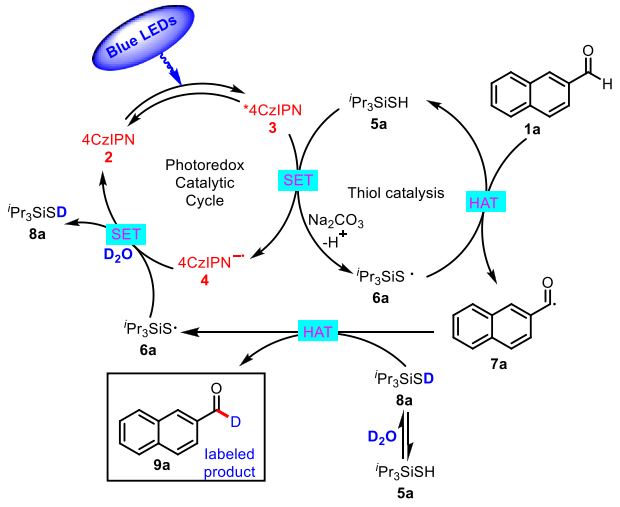
Scheme 1. Strategies for the synthesis of formyl-deuterated aldehydes.

[33]. In these previously reported reactions, the gap between the bond dissociation energies (BDEs) of the C(=O)H bonds of the aldehydes (94 kcal mol^{-1}) and the S–H bond of 2,4,6-triisopropylbenzenethiol (80 kcal mol^{-1}) drives HAT from the thiol catalyst to the nucleophilic acyl radical to form a deuterated aldehyde irreversibly. However, this strategy is unsuitable for the preparation of ortho-substituted deuterated aldehydes owing to the selectivity of the decatungstate for abstraction of sterically accessible C–H bonds. In addition, the reaction requires high-energy UVA (390 nm) irradiation, a toxic metal (tungsten), and a long reaction long time (4 days); and the deuterium incorporation is mainly 88–95%. Recently, two similar works were reported by Wang and Wu groups respectively [34,35].

Therefore, we set about developing a protocol for visible-light-mediated HIE reactions of aldehydes that affords 100% deuteration incorporation and does not require a metal or high-energy UV light. In addition, we wanted the new HIE protocol to be suitable for generating ortho-substituted deuterated aldehydes. To accomplish our aims, we would need to achieve visible-light-mediated reversible HAT between the aldehyde substrate and the thiol; in addition, we would have to overcome the challenge posed by the fact that the control of reversibility enables direct abstraction of the formyl hydrogen by a thiol radical, which produces an acyl radical that participates in a HAT reaction with the thiol catalyst [36,37]. We recognized that the choice of a suitable thiol catalyst, that is, one with a BDE close to that of the C(=O)H bonds, would be key to the success of our strategy. Moreover, we expected that the polarity matching effect and the greater strength of the C–D bond relative to the C–H bond (the BDEs are 341.4 and 338 kJ/mol, respectively) would facilitate C–D bond formation [38]. With these considerations in mind, we have developed a protocol for visible-light-mediated metal-free HIE reactions of aldehydes with D_2O with synergistic thiol and photoredox catalysis (Scheme 1C).

2. Results and discussion

We hypothesized that visible-light-mediated deuteration of aldehydes might proceed via the mechanism shown in Scheme 2 for 2-naphthaldehyde (**1a**). In this mechanism, initial photoexcitation

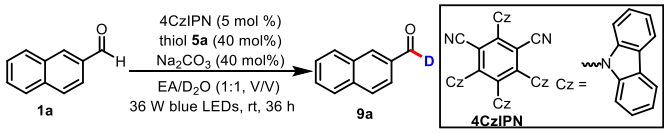


Scheme 2. Plausible mechanism.

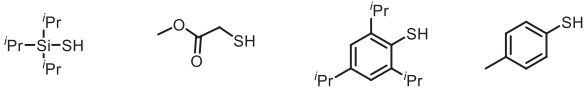
of 4CzIPN (**2**) generates excited-state species **3** ($E_{1/2}$ (*4CzIPN/$4CzIPN^{-\cdot}$) = +1.35 V vs. SCE in MeCN) [39], which is reductively quenched by triisopropylsilanethiol (**5a**, $E^{ox}_{1/2}$ = +0.28 V vs. SCE in MeCN) via single electron transfer to give reduced species **4** and thiyl radical **6a** after deprotonation by Na_2CO_3 [40]. The presence of a catalytic amount of base presumably facilitates deprotonation to generate thiyl radical **6a**. Radical **6a**, which is electrophilic, then undergoes a polarity-matched HAT reaction involving abstraction of the formyl hydrogen atom of 2-naphthaldehyde (**1a**), generating reactive nucleophilic formyl radical **7a**. At the same time, thiol catalyst **5a** undergoes an exchange reaction with the excess D_2O to give deuterated thiol **8a**, which serves as the deuterium source. Radical **7a** abstracts a deuterium atom from **8a** to generate deuterated aldehyde **9a** and thiyl radical **6a**. The similarity of the BDEs of the C(=O)H bond of the aldehyde (94 kcal mol^{-1}) and the S–H bond of **5a** (88 kcal mol^{-1}) make the HAT reaction between the aldehyde and the thiol reversible (**1a** to **7a** to **9a**) [34–36]. Moreover, the strength of the C–D bond can be expected to facilitate C–D bond formation. Single electron reduction of thiyl radical **6a** ($E^{red}_{1/2}$ = −0.82 V vs. SCE in MeCN) by reduced species **4** ($E^{1/2}$(4CzIPN/$4CzIPN^{-\cdot}$) = −1.21 V vs. SCE in MeCN) regenerates photocatalyst **2** and deuterated thiol **8a** after protonation by D_2O [39].

To test this mechanistic hypothesis, we began by exploring deuteration reactions of 2-naphthaldehyde (**1a**) under various conditions (Table 1). First, several thiol catalysts were screened in the presence of 4CzIPN (5 mol %) as the HAT photocatalyst and Na_2CO_3 as the base in 1:1 (v/v) ethyl acetate/D_2O under irradiation with a blue LEDs. To our delight, 2-naphthaldehyde (**9a**) with 93% deuterium incorporation was obtained when triisopropylsilanethiol (**5a**, 40 mol %) was used as the thiol catalyst (entry 1). Under the same conditions, other thiols gave considerably lower deuterium incorporation percentages (entries 2–4). This result may have been due to the fact that the gap between the BDE of the C(=O)H bond of the aldehyde (94 kcal mol^{-1}) and the BDEs of the S–H bonds of **5b**–**5d** (80–86 kcal mol^{-1}) prevented direct abstraction of the formyl hydrogen by the thiol radical. The use of *N*-methyl-2-pyrrolidinone, dichloromethane, or chloroform as the cosolvent instead of ethyl acetate also resulted in lower deuterium incorporation (entries 5–7). Reducing the amount of either thiol **5a** or Na_2CO_3 slightly decreased the deuterium incorporation percentage (entries 8 and 9). Control experiments showed that the reaction failed to proceed in the absence of the photocatalyst, light, the thiol catalyst, or Na_2CO_3 (entries 10–13).

Table 1
Optimization of conditions for photoredox catalytic deuteration of aldehydes[a].



entry	deviation from standard conditions	Deuteration (%)[b]
1	none	93
2	**5b** instead of **5a**	45
3	**5c** instead of **5a**	26
4	**5d** instead of **5a**	19
5	NMP instead of EA	8
6	DCM instead of EA	46
7	$CHCl_3$ instead of EA	38
8	20 mol % of **5a**	70
9	20 mol% of Na_2CO_3	86
10	no 4CzIPN	18
11	no light	7
12	no **5a**	13
13	no Na_2CO_3	24



[a] Reaction conditions, unless otherwise noted: 2-naphthaldehyde (**1a**, 0.3 mmol), photocatalyst 4CzIPN (0.015 mmol), thiol **5a** (0.12 mmol), Na_2CO_3 (0.12 mmol), and 1:1 (v/v) EA/D_2O (3.0 mL) under Ar atmosphere.
[b] Deuterium incorporation was determined by integration of the residual formyl proton in the ^1H NMR spectrum of the product. EA = ethyl acetate, NMP = *N*-methyl-2-pyrrolidinone.

Having optimized the protocol, we explored the substrate scope. These experiments revealed the protocol to be a mild, general approach for the synthesis of a wide array of deuterated aldehydes in good yields (up to 93%) and with uniformly high levels of deuterium incorporation (90–100%, Table 2). Deuterated 2-naphthaldehyde **9a** was isolated in 88% yield after purification by column chromatography, indicating that decomposition and side-product formation were minimal. Benzaldehydes bearing substituents with various electronic and steric properties afforded deuterated products **9b**–**9q**. We were particularly interested in halogenated substrates because halogenated molecules account for approximately 50% of the market-leading drugs, owing to their lower susceptibility to oxidation by cytochrome P450 [41]. Furthermore, they offer a valuable platform for generating molecular complexity by means of cross-coupling reactions [42,43]. Surprisingly, we found that fluoro-, chloro-, bromo-, and iodo-substituted benzaldehydes gave the corresponding products (**9b**–**9e**) with higher deuterium incorporation (90–96%) than our previously reported method. Notably, benzaldehydes with electronically neutral functional groups, such as *t*-butyl and methyl, worked well under the optimal conditions, giving moderate to high yields and up to 99% deuterium incorporation (**9f**–**9i**). Moreover, electron-rich aldehydes were also suitable, giving the desired products (**9j**–**9n**) with 98–99% deuterium incorporation. Intriguingly, relatively sensitive yet versatile functional groups, a boronic ester (**9o**) and a OH group (**9p**) tolerated the deuteration conditions well. As mentioned above, our previously reported method was unsuitable for ortho-substituted aldehydes [33]. In contrast, this new HIE method afforded ortho-substituted deuterated aldehyde **9q** with excellent deuterium incorporation. Because heteroaromatic moieties are present in the scaffolds of many pharmaceutical compounds, we were pleased to find that *N*-heterocycles were also tolerated under our deuteration conditions; **9r** and **9s** were obtained with 99% deuterium incorporation. In addition, the reaction was amenable to scale up; when it was carried out on a 8-mmol scale, **9j** was isolated in 83% yield with no decrease in deuterium incorporation.

Aliphatic aldehydes are also of interest because they constitute an even greater proportion of known –CHO compounds. Gratifyingly, aliphatic aldehydes were suitable substrates for our protocol, affording the deuterated products **9t**–**9v** in 74–85% yields and 99–100% deuterium incorporation. Notably, no products of CO dissociation were observed, and deuterium was not incorporated at other acidic C–H positions, particularly at enolizable α-positions. However, in our previously reported method, deuteration also takes place at the α-positions of formyl [33]. In addition, reaction of adapalene, an antiacne drug, afforded deuterated aldehyde **9w** with high deuterium incorporation. These reactions confirm the potential utility of our protocol for late-stage modification of pharmaceutical intermediates and for generating libraries of deuterated compounds.

Having explored the substrate scope and utility of the reaction, we carried out some experiments in support of the proposed mechanism shown in Scheme 2. When the radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was present in the reaction mixture, deuterium incorporation decreased markedly (to 2%), and radical-trapping product 2,2,6,6-tetramethyl-1-(((triisopropylsilyl)thio)oxy)piperidine (**10**) was observed by mass spectrometry (Scheme 3A). When 2,6-di-tert-butyl-4-methylphenol was used as the radical scavenger, 2,6-di-tert-butyl-4-methylphenyl 2-naphthoate (**11**) was observed by mass spectrometry (Scheme 3B). When 1,1-diphenylethylene was the radical scavenger, radical-trapping products 1-(naphthalen-2-yl)-3,3-diphenylprop-2-en-1-one (**12**) and ((2,2-diphenylvinyl)thio)triisopropylsilane (**13**) were observed by mass spectrometry (Scheme 3C). 1,2-di(naphthalen-2-yl)ethane-1,2-dione (**14**) was observed by mass spectrometry after reaction (Scheme 3D). These results suggest that thiol radical **6a** and acyl radical **7a** were generated. Furthermore, light on/off experiments indicated that the reaction stopped completely in the absence of light but began again when irradiation was recommenced (Figure S12). This result indicates that light was essential for the transformation and that any chain-propagation process was short-lived.

3. Conclusion

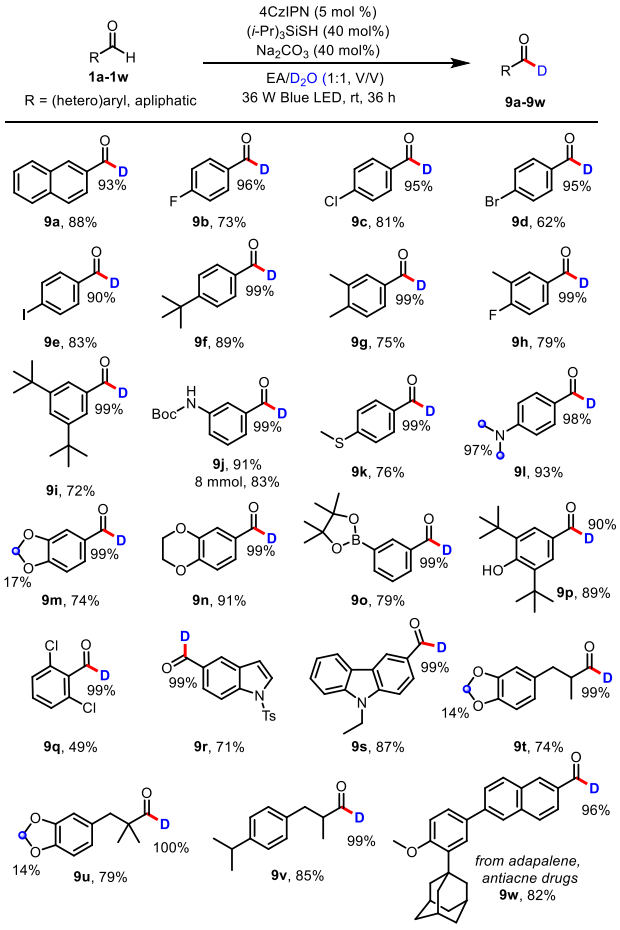
In conclusion, we have developed a protocol for visible-light-mediated HIE reactions that directly convert readily accessible aldehydes to their 1-deutero counterparts in D_2O with synergistic visible-light photoredox catalysis and thiol catalysis. Unlike established photoredox catalytic HIE reactions, this protocol is suitable for ortho-substituted aldehydes, and deuterium incorporation is higher. We anticipate that this protocol will facilitate access to a wide range of deuterated compounds, which are highly valuable in the fields of biological, medicinal, and organic chemistry [44].

4. Experimental section

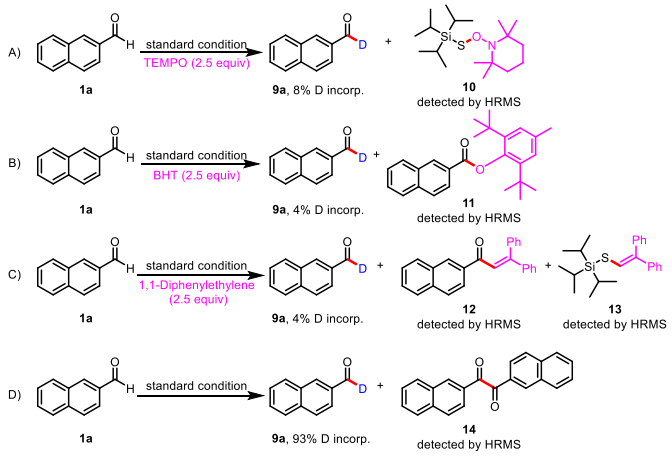
4.1. General experimental information

^1H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded on Bruker Avance 400 Ultrashield NMR spectrometers. Chemical shifts (δ) were given in parts per million (ppm) and were measured downfield from internal tetramethylsilane. HRMS were made by means of ESI/EI-FTMS. The melting points were determined on an X-4 microscope melting point apparatus and are uncorrected. Conversion was monitored by thin layer chromatography

Table 2
Exploration of substrate scope[a].



[a]Reactions were performed on a 0.3 mmol scale, unless otherwise noted. [b]Compounds **9l**, **9m**, **9t**, and **9u** contained deuterium atoms at sites other than C-1 (as shown in their structures). Isolated yields are given. See the Supporting Information for experimental details. Deuterium incorporation was determined by integration of the residual formyl proton in the ^{1}H NMR spectra of the products.



Scheme 3. Experiments in support of the proposed mechanism.

(TLC). Flash column chromatography was performed over silica gel (100–200 mesh). Blue LED (36 W, λ_{max} = 470 nm) purchased from JIADENG (LS) was used for blue light irradiation. A fan attached to the apparatus was used to maintain the reaction temperature at room temperature, the internal temperature is 30 °C. The photocatalyst 4CzIPN was synthesized according to literature report [45]. The spectral data of the photocatalyst is consistent with the literature data. The other photocatalysts (Eosin Y, Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$, Ir(dtbbpy)(ppy)$_2$PF$_6$, [Ru(bpy)$_3$]Cl$_2$·6H$_2$O, and Ru(bpy)$_3$(PF$_6$)$_2$ are commercially available.

4.2. General procedure for the formyl-selective deuteration of aldehydes

To a 10 mL glass vial was added 4CzIPN (11.8 mg, 0.015 mmol, 5 mol %), aldehyde (0.3 mmol, 1.0 equiv), thiol **5a** (22.8 mg, 0.12 mmol, 40 mol %), Na_2CO_3 (12.7 mg, 0.12 mmol, 40 mol %), and EA/D_2O (1:1, v/v; 3.0 mL). The reaction mixture was degassed by bubbling with Ar for 15 s with an outlet needle and the vial was sealed with PTFE cap. The mixture was then stirred rapidly and

irradiated with a 36 W Blue LED (approximately 2 cm away from the light source) at room temperature for 36 h. The reaction mixture was diluted with 10 mL of aqueous 1 M $NaHCO_3$ solution, and extracted with DCM (3 × 20 mL). The combined organic extracts were washed with brine (40 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification of the crude product by flash chromatography on silica gel using the indicated solvent system afforded the desired product.

*4.2.1. 2-naphthaldehyde-formyl-d_1 (**9a**)*

According to the *general procedure*. The spectral Data is consistent with the literature data [33]. White solid (41.4 mg, 88%). Mp: 86–87 °C. R_f 0.40 (Petroleum ether/EtOAc, 40/1). D incorporation by 1H NMR: 93%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.16 (s, 0.07H), 8.33 (s, 1H), 8.11–7.82 (m, 4H), 7.76–7.46 (m, 2H). **HRMS** (ESI-FTMS) *m*/*z*: $[M + H]^+$ Calcd for $C_{11}H_8DO$ 158.0711; Found 158.0712.

*4.2.2. 4-fluorobenzaldehyde-formyl-d_1 (**9b**)*

According to the *general procedure*. The spectral Data is consistent with the literature data [33]. Colorless oil (27.4 mg, 73%). R_f 0.40 (Petroleum ether/EtOAc, 40/1). D incorporation by 1H NMR: 96%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 0.04H), 7.99–7.87 (m, 2H), 7.26–7.15 (m, 2H).

*4.2.3. 4-chlorobenzaldehyde-formyl-d_1 (**9c**)*

According to the *general procedure*. The spectral Data is consistent with the literature data [33]. White solid (34.3 mg, 81%). Mp: 44–45 °C. R_f 0.40 (Petroleum ether/EtOAc, 40/1). D incorporation by 1H NMR: 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 0.05H), 7.84 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H).

*4.2.4. 4-bromobenzaldehyde-formyl-d_1 (**9d**)*

According to the *general procedure*. The spectral Data is consistent with the literature data [33]. White solid (34.4 mg, 62%). Mp: 76–77 °C. R_f 0.40 (Petroleum ether/EtOAc, 40/1). D incorporation by 1H NMR: 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.98 (s, 0.05H), 7.76 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H).

*4.2.5. 4-iodobenzaldehyde-formyl-d_1 (**9e**)*

According to the *general procedure*. The spectral Data is consistent with the literature data [33]. White solid (58.0 mg, 83%). Mp: 98–99 °C. R_f 0.40 (Petroleum ether/EtOAc, 40/1). D incorporation by 1H NMR: 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.98 (s, 0.1H), 7.94 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H).

*4.2.6. 4-(tert-butyl)benzaldehyde-formyl-d_1 (**9f**)*

According to the *general procedure*. The spectral Data is consistent with the literature data [33]. Colorless oil (43.5 mg, 89%). R_f 0.50 (Petroleum ether/EtOAc, 40/1). D incorporation by 1H NMR: 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.98 (s, 0.01H), 7.82 (d, J = 8.0 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H), 1.36 (s, 9H).

*4.2.7. 3,4-dimethylbenzaldehyde-formyl-d_1 (**9g**)*

According to the *general procedure*. The spectral Data is consistent with the literature data [33]. Colorless oil (30.4 mg, 75%). R_f 0.40 (Petroleum ether/EtOAc, 40/1). D incorporation by 1H NMR: 99%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 0.01H), 7.80–7.52 (m, 2H), 7.28 (d, J = 7.6 Hz, 1H), 2.46–2.19 (m, 6H).

*4.2.8. 4-fluoro-3-methylbenzaldehyde-formyl-d_1 (**9h**)*

According to the *general procedure*. The spectral Data is consistent with the literature data [33]. Colorless oil (32.9 mg, 79%). R_f 0.40 (Petroleum ether/EtOAc, 40/1). D incorporation by 1H NMR: 99%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 0.01H), 7.80–7.69 (m, 2H), 7.15 (t, J = 8.8 Hz, 1H), 2.35 (d, J = 2.0 Hz, 3H).

*4.2.9. 3,5-di-tert-butylbenzaldehyde-formyl-d_1 (**9i**)*

According to the *general procedure*. Colorless oil (47.3 mg, 72%). R_f 0.40 (Petroleum ether/EtOAc, 40/1). D incorporation by 1H NMR: 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, 0.01H), 7.77–7.69 (m, 2H), 7.26 (s, 1H), 1.37 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 129.1, 124.3, 35.1, 31.5. **HRMS** (EI-FTMS) *m*/*z*: $[M]^{+\cdot}$ Calcd for $C_{15}H_{21}DO$ 219.1733; Found 219.1726.

*4.2.10. tert-butyl (3-formylphenyl)carbamate-formyl-d_1 (**9j**)*

According to the *general procedure*. The spectral Data is consistent with the literature data [33]. White solid (60.6 mg, 91%). Mp: 88–89 °C. R_f 0.40 (Petroleum ether/EtOAc, 10/1). D incorporation by 1H NMR: 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.98 (s,0.01H), 7.94 (s, 1H), 7.64 (d, J = 7.6 Hz, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.45 (t, J = 7.6 Hz, 1H), 6.78 (s, 1H), 1.53 (s, 9H).

*4.2.11. 4-(methylthio)benzaldehyde-formyl-d_1 (**9k**)*

According to the *general procedure*. The spectral Data is consistent with the literature data [25]. Colorless oil (34.9 mg, 76%). R_f 0.40 (Petroleum ether/EtOAc, 10/1). D incorporation by 1H NMR: 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, 0.01H), 7.77 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 2.53 (s, 3H).

*4.2.12. 4-(dimethylamino)benzaldehyde-formyl-d_1 (**9l**)*

According to the *general procedure*. The spectral Data is consistent with the literature data [25]. White solid (43.5 mg, 93%). Mp: 67–69 °C. R_f 0.40 (Petroleum ether/EtOAc, 10/1). D incorporation by 1H NMR: 98%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 0.02H), 7.73 (d, J = 8.8 Hz, 2H), 6.68 (d, J = 8.8 Hz, 2H), 3.09–3.02 (m, 0.18H).

*4.2.13. benzo[d] [1,3]dioxole-5-carbaldehyde-formyl-d_1 (**9m**)*

According to the *general procedure*. The spectral Data is consistent with the literature data [25]. Colorless oil (33.5 mg, 74%). R_f 0.40 (Petroleum ether/EtOAc, 20/1). D incorporation by 1H NMR: 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 0.01H), 7.42 (d, J = 8.0 Hz, 1H), 7.34 (s, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.13–6.01 (m, 1.66H).

*4.2.14. 2,3-dihydrobenzo[b] [1,4]dioxine-6-carbaldehyde-formyl-d_1 (**9n**)*

According to the *general procedure*. The spectral Data is consistent with the literature data [28]. Yellow solid (45.0 mg, 91%). Mp: 44–45 °C. R_f 0.40 (Petroleum ether/EtOAc, 20/1). D incorporation by 1H NMR: 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 0.01H), 7.40 (dd, J = 4.4, 2.4 Hz, 2H), 6.98 (d, J = 8.8 Hz, 1H), 4.36–4.32 (m, 2H), 4.31–4.27 (m, 2H).

*4.2.15. 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzaldehyde-formyl-d_1 (**9o**)*

According to the *general procedure*. The spectral Data is consistent with the literature data [33]. Colorless oil (55.2 mg, 79%). R_f 0.40 (Petroleum ether/EtOAc, 20/1). D incorporation by 1H NMR: 98%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (s, 0.02H), 8.31 (s, 1H), 8.06 (d, J = 7.2 Hz, 1H), 8.03–7.95 (m, 1H), 7.53 (t, J = 7.6 Hz, 1H), 1.37 (s, 12H).

*4.2.16. 2,6-di-tert-butyl-4-hydroxybenzaldehyde-formyl-d_1 (**9p**)*

According to the *general procedure*. White solid (62.7 mg, 89%). Mp: 136–137 °C. R_f 0.40 (Petroleum ether/EtOAc, 20/1). D incorporation by 1H NMR: 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (s, 0.1H), 7.74 (s, 2H), 5.88 (s, 1H), 1.48 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8 (t, J = 26.5 Hz), 159.7, 136.6, 128.7 (t, J = 3.5 Hz), 127.7,

34.4, 30.1. **HRMS** (EI-FTMS) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{15}H_{21}DO_2$ 235.1683; Found 235.1675.

4.2.17. 2,6-dichlorobenzaldehyde-formyl-d_1 (**9q**)

According to the *general procedure*. White solid (25.7 mg,49%). Mp: 54–55 °C. R_f 0.40 (Petroleum ether/EtOAc, 40/1). D incorporation by 1H NMR: 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (s, 0.01H), 7.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 133.6, 129.8. **HRMS** (EI-FTMS) *m/z*: $[M - D]^{+\cdot}$ Calcd for $C_7H_3Cl_2O$ 172.9555; Found 172.9555.

4.2.18. 1-tosyl-1H-indole-5-carbaldehyde-formyl-d_1 (**9r**)

According to the *general procedure*. The spectral Data is consistent with the literature data [33]. White solid (63.9 mg, 71%). Mp: 120–121 °C. R_f 0.40 (Petroleum ether/EtOAc, 5/1). D incorporation by 1H NMR: 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.03 (s, 0.01H), 8.11 (d, J = 8.4 Hz, 1H), 8.07 (s, 1H), 7.86 (dd, J = 8.4, 1.2 Hz, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 3.6 Hz, 1H), 7.26 (d, J = 8.0 Hz, 2H), 6.78 (d, J = 3.6 Hz, 1H), 2.35 (s, 3H).

4.2.19. 9-ethyl-9H-carbazole-3-carbaldehyde-formyl-d_1 (**9s**)

According to the *general procedure*. The spectral Data is consistent with the literature data [28]. White solid (58.5 mg, 87%). Mp: 84–85 °C. R_f 0.40 (Petroleum ether/EtOAc, 5/1). D incorporation by 1H NMR: 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.04 (s, 0.01H), 8.53 (d, J = 3.6 Hz, 1H), 8.15–8.05 (m, 1H), 8.00–7.91 (m, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.39 (dd, J = 9.2, 5.6 Hz, 2H), 7.29 (t, J = 7.6 Hz, 1H), 4.41–4.22 (m, 2H), 1.49–1.35 (m, 3H).

4.2.20. 3-(benzo[d] [1,3]dioxol-5-yl)-2-methylpropanal-formyl-d_1 (**9t**)

According to the *general procedure*. The spectral Data is consistent with the literature data [33]. Colorless oil (42.8 mg, 74%). R_f 0.40 (Petroleum ether/EtOAc, 20/1). D incorporation by 1H NMR: 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (d, J = 1.6 Hz, 0.01H), 6.73 (d, J = 8.0 Hz, 1H), 6.66 (d, J = 1.6 Hz, 1H), 6.61 (dd, J = 8.0, 1.6 Hz, 1H), 5.93 (s, 1.72H), 3.00 (dd, J = 13.6, 5.6 Hz, 1H), 2.67–2.47 (m, 2H), 1.08 (d, J = 6.8 Hz, 3H).

4.2.21. 3-(benzo[d] [1,3]dioxol-5-yl)-2,2-dimethylpropanal-formyl-d_1 (**9u**)

According to the *general procedure*. Colorless oil (49.1 mg, 79%). R_f 0.40 (Petroleum ether/EtOAc, 40/1). D incorporation by 1H NMR: 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (d, J = 7.6 Hz, 1H), 6.64 (s, 1H), 6.58 (d, J = 7.6 Hz, 1H), 5.91 (s, 1.72H), 2.38 (s, 2H), 0.88 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 145.6, 135.7, 121.9, 109.6, 108.0, 100.8, 45.2, 30.0 (t, J = 19 Hz), 22.3. **HRMS** (EI-FTMS) *m/z*: $[M - CO]^{+\cdot}$ Calcd for $C_{11}H_{13}DO_2$ 179.1051; Found 179.1050.

4.2.22. 3-(4-isopropylphenyl)-2-methylpropanal-formyl-d_1 (**9v**)

According to the *general procedure*. The spectral Data is consistent with the literature data [33]. Colorless oil (48.7 mg, 85%). R_f 0.40 (Petroleum ether/EtOAc, 40/1). D incorporation by 1H NMR: 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (d, J = 1.6 Hz, 0.01H), 7.16 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H), 3.04 (dt, J = 11.2, 5.6 Hz, 1H), 2.88 (dt, J = 13.6, 6.8 Hz, 1H), 2.67 (dt, J = 12.8, 6.8 Hz, 1H), 2.61–2.51 (m, 1H), 1.24 (d, J = 6.8 Hz, 6H), 1.09 (d, J = 6.8 Hz, 3H).

4.2.23. 6-(3-((3r,5r,7r)-adamantan-1-yl)-4-methoxyphenyl)-2-naphthaldehyde-formyl-d_1 (**9w**)

According to the *general procedure*. The spectral Data is consistent with the literature data [33]. White solid (97.7 mg, 82%). Mp: 236–237 °C. R_f 0.40 (Petroleum ether/EtOAc, 20/1). D incorporation by 1H NMR: 96%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.14 (s, 0.04H), 8.33 (s, 1H), 8.02 (d, J = 7.6 Hz, 2H), 7.96 (s, 2H), 7.83 (dd, J = 8.4, 1.2 Hz, 1H), 7.61 (d, J = 2.4 Hz, 1H), 7.55 (dd, J = 8.4, 2.4 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 3.90 (s, 3H), 2.18 (s, 6H), 2.11 (s, 3H), 1.80 (s, 6H).

4.3. Gram-scale reaction

To an oven dried Schlenk tube was added 4CzIPN (316 mg, 0.4 mmol, 5 mol %), tert-butyl (3-formylphenyl)carbamate **1j** (8 mmol, 1.0 equiv), thiol **5a** (0.61 g, 3.2 mmol, 40 mol %), Na_2CO_3 (339 mg, 3.2 mmol, 40 mol %), and EA/D_2O (1:1, v/v; 80 mL). The tube was evacuated and backfilled with Ar (this process was repeated three times). The mixture was then stirred rapidly and irradiated with two 36 W blue LEDs (approximately 2 cm away from the light source) at room temperature for 48 h. The reaction mixture was diluted with 100 mL of aqueous 1 M $NaHCO_3$ solution, and extracted with DCM (3 × 50 mL). The combined organic extracts were washed with brine (150 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification of the crude product by flash chromatography on silica

gel using the indicated solvent system afforded the desired product **9j** in 83% yield (1.474 g) and 99% D incorporation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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