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# Deuteration of Formyl Groups via a Catalytic Radical H/D Exchange Approach

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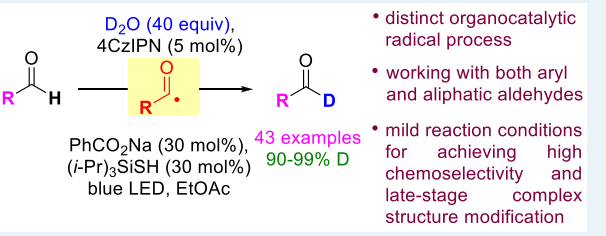
**ABSTRACT:** H/D exchange at formyl groups represents the straightforward approach to C-1 deuterated aldehydes. This transformation has been recently realized by transition metal and NHC carbene catalysis. Mechanistically, all of these processes involve an ionic pathway. Herein, we report a distinct photoredox catalytic, visible light mediated neutral radical approach. Selective control of highly reactive acyl radical in the energy barrier surmountable, reversible reaction enables driving the formation of deuterated products when an excess of $D_2O$ is employed. The power of the H/D exchange process has been demonstrated for not only aromatic aldehydes but also aliphatic substrates, which have been difficult in transitional metal catalyzed H/D exchange reactions, and for selective late-stage deuterium incorporation into complex structures with uniformly high deuteration level (>90%).




**KEYWORDS:** *aldehyde, deuteration, H/D exchange, photoredox, radical reaction*



Among isotopes, deuterium perhaps has the broadest impact on almost every subdiscipline in the life, chemical, material, and nuclear sciences and beyond.[1] The recent surge in applications of deuterated pharmaceutical agents has been witnessed by the FDA approval of the first deuterated drug, Austedo (deutetrabenazine), in 2017[2] and the large number of emerging deuterated drug candidates.[1c,d,2,3] This has spurred considerable interest in developing synthetic methods that enable efficient generation of deuterated building blocks.[4,5]

Given the broad availability and synthetic versatility of aldehydes, C-1 deuterated aldehydes can provide quick access to a wide range of highly valued and structurally diverse deuterated building blocks and to pharmaceutically relevant structures.[6] Several methodologies have been reported for their synthesis (Scheme 1). Conventional methods rely on the reduction and/or oxidation sequence but use expensive deuterated reducing agents such as $LiAlD_4$[7] and $Cp_2ZrDCl$.[8] Recently, more cost-effective approaches using cheap, safe, and readily handled $D_2O$ as the deuterium source have been elegantly realized from aryl iodides,[9] carboxylic acids,[10] or benzyl halides[11] by Denmark, Xie, and Sheng, respectively (Scheme 1a). Direct hydrogen−deuterium exchange (HDE) processes with aldehydes without requiring additional functional group transformation represent an even more synthetically efficient strategy. Tuttle and Newman[12] independently reported Ir and Ru catalyzed HDE reactions (Scheme 1b). Despite these impressive studies, it is recognized that significant synthetic challenges are associated with the difficulty of controlling chemoselectivity of nonselective deuteration of aromatic rings and the unsatisfactory deuteration level (14−84%). Furthermore, the reported protocols (Schemes 1a and b) mainly work for aromatic aldehydes. More recently, we[13] and Bertrand and Yan[14] have developed more efficient NHC carbene promoted HDE processes (Scheme 1c). Mechanistically, all of these HDE transformations rely on the ionic reaction pathway.

A radical process for direct HDE offers an alternative route. Implementing the distinct neutral radical process for direct HDE requires the *in situ* generation of an aldehyde derived acyl radical. A process using acyl radical as a key intermediate has been nicely realized by Xie and coworkers for the synthesis of C-1 deuterated aldehydes (Scheme 1a).[10] In their studies, acyl radicals are produced from carboxylic acid precursors using visible light mediated photoredox deoxygenation with phosphines. Furthermore, direct abstraction of formyl hydrogen with photoredox strategy has been successfully used by Glorius and us for new bond formation recently.[15,16] These processes, involving new bond connection, are generally kinetically controlled and irreversible. It is recognized that the realization of the reversible acyl radical[17] involved chemistry for HDE process must overcome the challenge that the control of intrinsic reversibility enables manipulation of the equilibrium to achieve synthetically useful yields of the desired product. Moreover, achieving the thermodynamic control process could be complicated by an undesired

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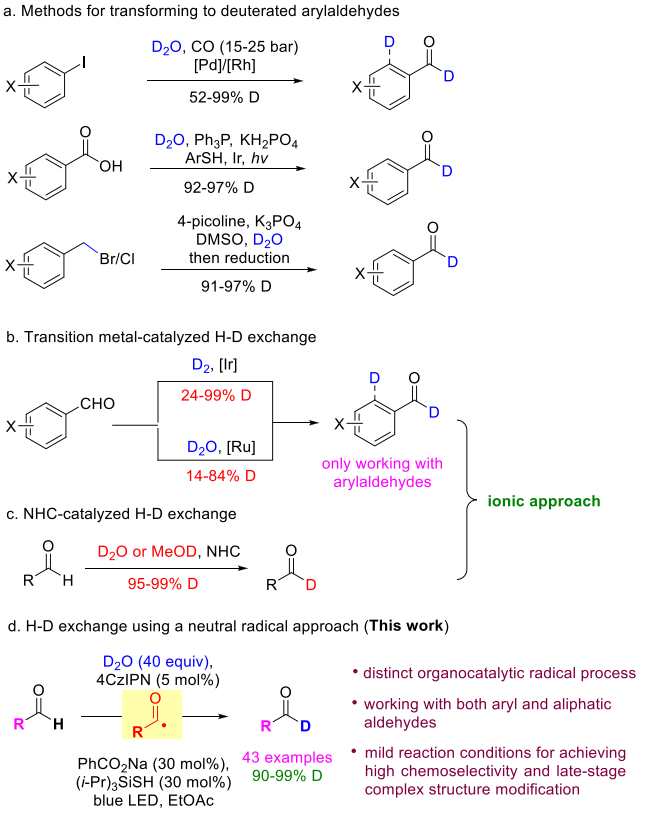
**Scheme 1. Methods for the Synthesis of C-1 Deuterated Aldehydes**




decarbonylation process (Scheme 2).[18,19] Studies indicate that the decarbonylation process is unfavored.[20] With these in mind, it is possible to realize the strategy of combining a thermodynamic approach with the use of one of the reaction components in a large excess. Furthermore, the stronger C−D bond (bond dissociation energy (BDE) of C−H as 338 kJ/mol and C−D as 341.4 kJ/mol) also could enhance the C−D bond formation. The investigation from MacMillan and coworkers of an elegant photoredox mediated hydrogen isotope exchange (HIE) for selective deuteration and tritiation of $\alpha$-C−H bonds of amines made our new HDE with a formyl group possible.[5b]

Herein, we report the results of the study which lead to a visible light mediated photoredox catalytic H/D exchange at formyl groups (Scheme 1d). In the preparation of this manuscript, a similar work was reported by Wang and coworkers.[21]

Our investigation began with a model deuteration reaction of *p*-tolualdehyde with $D_2O$ in the presence of a photocatalyst and a hydrogen atom transfer (HAT) catalyst. 9,10-Phenanthrenequinone **2a** used as a HAT photocatalyst in our previous study[16] gave 23% deuterium incorporated product **3a** (Table 1, entry 2). Switching to the photoredox catalytic system of 4CzIPN as photosensitizer (PS) and methyl 2-mercaptoacetate **2b** as HAT gave slightly improved deuterium incorporation (40%, Table S1), but the results were not reproducible. In our extensive reaction optimization effort (Table S1), we accidently found that an impurity of sodium dodecyl sulfate (SDS) from the detergent contaminated reaction flask could generate reproducible results (40% D incorporation). We surmised that SDS might serve as a more effective HAT. Glorius et al. found that benzoyloxy radical PhCOO•, produced from $PhCO_2Na$ in the presence of

**Scheme 2. A Plausible Mechanism**

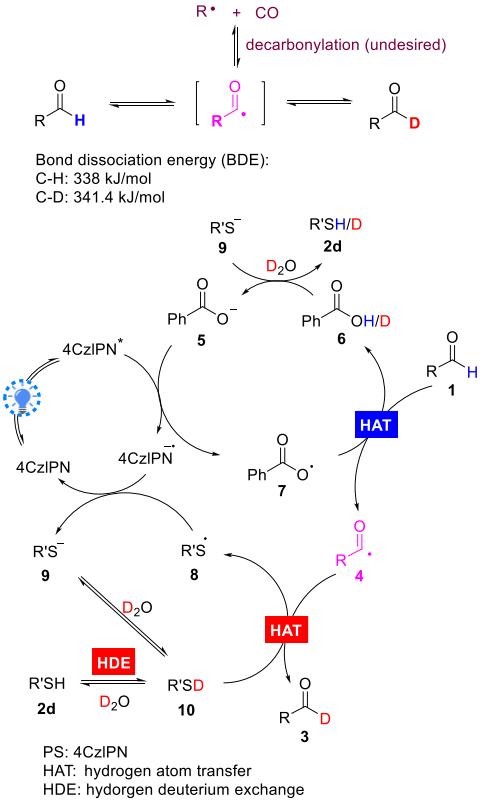
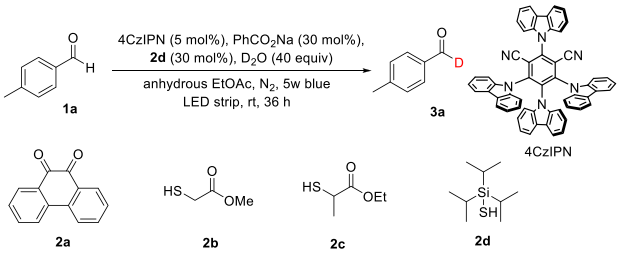



**Table 1. Optimization of the Reaction Conditions**




| entry | variation of standard conditions[e] | yield (%)[b] | D ratio (%)[d] |
|---|---|---|---|
| 1[a] | none | 95 (91[c]) | 97 |
| 2 | **2a** instead of 4CzIPN and $PhCO_2Na$ | 89 | 23 |
| 3 | **2b** instead of **2d** | 87 | 95 |
| 4 | **2c** instead of **2d** | 91 | 82 |
| 5 | MeCN instead of EtOAc | 93 | 16 |
| 6 | DMF instead of EtOAc | 94 | <5 |
| 7 | without $PhCO_2Na$ | 93 | <5 |
| 8 | without **2d** | 93 | <5 |
| 9 | no light or no photocatalyst | 95 | <5 |
| 10 | open to air | <5 | ND |

[a]Standard reaction conditions: **1a** (0.2 mmol), 4CzIPN (5 mol %), sodium benzoate (30 mol %), **2d** (30 mol %), $D_2O$ (40 equiv), anhydrous EtOAc (0.2 M), 5 W blue LED strip, $N_2$, 36 h. Isotope exchanged **2d** of 1 M anhydrous EtOAc solution was prepared by following procedure: dissolve **2d** (1.0 mmol) in 1.0 mL of anhydrous EtOAc followed by adding $D_2O$ (10 mmol, 1/10 molar ratio of **2d**/$D_2O$); after 1 h stirring, the top EtOAc layer was separated and used in the reaction. [b]$^1$H NMR yield. [c]Isolated yield. [d]D (deuteration) % determined by $^1$H NMR. [e]All solvents are anhydrous. ND: not detected.



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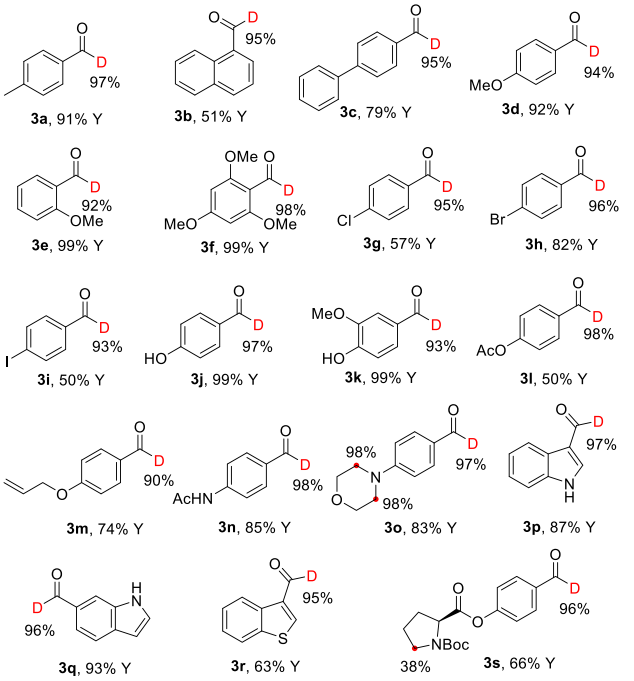
a PS, could selectively and efficiently abstract the hydrogen atom from the formyl group.[15] Therefore, we probed $PhCO_2Na$. To our delight, a level of 95% D-incorporation and 87% yield were obtained (entry 3). Without $PhCO_2Na$, almost no deuteration product was detected (entry 7). Screening of thiol HAT catalysts revealed triisopropylsilanethiol **2d** to be optimal one (entry 1 vs 3 and 4) and variation of reaction media led to the choice of ethyl acetate (entry 1 vs 5 and 6). In control studies, HAT **2d** (entry 8), light, and photocatalyst (entry 9) are necessary for the deuteration process. When the reaction is open to air, *p*-tolualdehyde was oxidized to benzoic acid (entry 10). The efforts on the optimization of the reaction led to the optimal reaction conditions as follows: 4CzIPN (5 mol %) as photoredox promoter, $PhCO_2Na$ (30 mol %) and triisopropylsilanethiol (**2d**, 30 mol %) as HAT and $D_2O$ (40 equiv) in anhydrous EtOAc (0.2 M) by 5 W blue LED strip under $N_2$ at rt. To reduce the introduction of extra protium in the reaction as much as possible, isotope exchanging of **2d** was performed by stirring **2d** solution of anhydrous EtOAc with 10 equiv $D_2O$ for 1 h.

Based on these results, a possible reaction mechanism is proposed (Scheme 2). Irradiation of photocatalyst 4CzIPN by visible light generates the excited state 4CzIPN*, which oxidizes sodium benzoate **5** to give benzoyloxy radical **7** for a subsequent HAT. The key acyl radical **4** is formed by abstraction of a hydrogen from aldehyde precursor **1**. Then, the second HAT process between resulting acyl radical **4** and deuterated thiol **10** delivers deuterated aldehyde product **3** and concurrent generation of thiyl radical **8**. Finally, the thiyl radical is reduced by the $4CzIPN^{\bullet-}$ to give the thiolate **9** and 4CzIPN to complete the redox cycle. The more basic thiolate anion **9** serves as an internal base to deprotonate the benzoic acid ($pK_a$ = 10) to regenerate HAT catalysts **5** and **2d**. The latter HAT catalyst can be transformed to deuterated thiol **10** by HDE with $D_2O$. It is also possible that **9** can be directly protonated to give **10**.

With the optimized protocol in hand, the scope of the deuteration process was probed. The methodology serves as a mild, general approach for the synthesis of a wide array of deuterated aromatic aldehydes in good yields (up to 99%) and with uniformly high levels (90−98%) of deuterium incorporation (Scheme 3). In general, the substrates of aromatic ring containing electron donating groups (MeO, AcO, AcHN, morpholine) gave slightly better results. It is believed that their enhancement in the nucleophilicity of acyl radical provides higher reactivity in the electrophilic HAT process. Notably, various functional groups such as free hydroxy (**3j** and **3k**), halogen substituents (**3g**, **3h**, **3i**), ester (**3l**, **3s**), and allylic (**3m**) can be tolerated by the deuteration protocol. Moreover, heteroaromatic aldehydes underwent deuteration smoothly to afford desired products (**3p**, **3q**, **3r**).

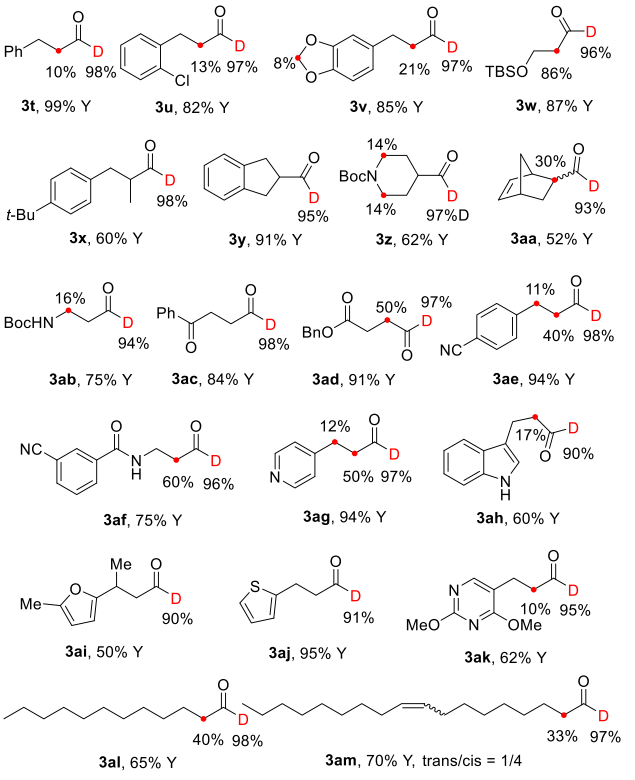
Having demonstrated the capacity of the aromatic aldehydes to participate in this radical engaged deuteration process, we turned our attention to aliphatic aldehyde substrates, which have remained an unsolved synthetic challenge for their C-1 deuteration (Scheme 4). Gratifyingly, aliphatic aldehydes are competent substrates, affording the corresponding C-1 deuterated products (**3t**−**3aa**) in 52−99% yields and with uniformly high level of D-incorporation (93−98%) under the optimized mild reaction conditions (Scheme 3). It is noteworthy that under the mild reaction conditions, the formation of decarbonylated side products is minimized.

**Scheme 3. Reaction Scope for Aromatic Aldehydes**[a]




[a]See the Supporting Information for detailed reaction conditions. Isolated yields (Y); D% determined by $^1H$ NMR spectroscopy.

**Scheme 4. Reaction Scope for Aliphatic Aldehydes**[a]




[a]See the Supporting Information for detailed reaction conditions. Isolated yields (Y); D% determined by $^1H$ NMR spectroscopy.

Nonetheless, in many cases, D-incorporation into other acidic C−H positions, in particular the enolizable $\alpha$-position, is observed. Again, a wide array of functional groups such as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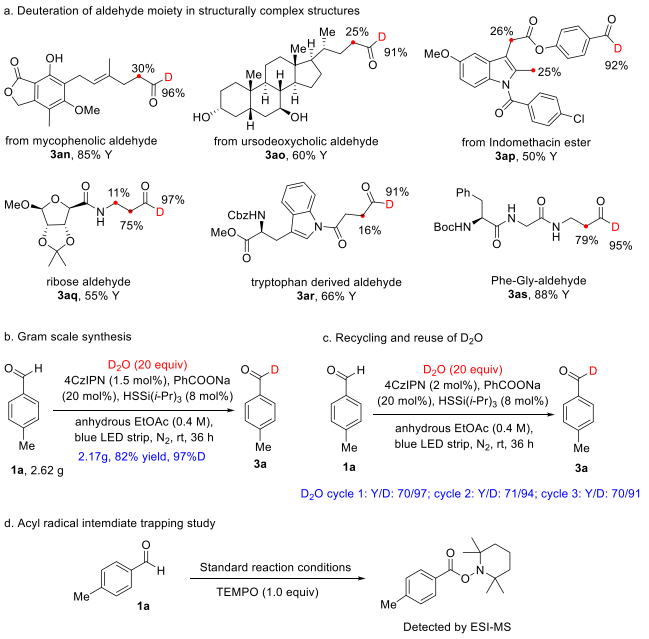
radical sensitive C═C (**3aa**, **3am**), amide (**3ab**), ketone (**3ac**), ester (**3ad**), and cyanide (**3ae** and **3af**) are tolerated. Moreover, the reaction can be applied to generate aliphatic deuterated aldehydes, which contain synthetically and biologically relevant heterocycles, including pyridine (**3ag**), indole (**3ah**), furan (**3ai**), thiophene (**3aj**), and pyrimidine (**3ak**). Finally, aliphatic aldehydes bearing long chain also work smoothly (**3al** and **3am**). It is found that isomerization of the *cis* C═C double bond in **3am** is observed.

The capacity of the mild deuteration methodology is also demonstrated in selective C-1 deuteration of aldehyde functionality in complex pharmaceutically relevant structures (Scheme 5a). Native ursodeoxycholic aldehyde, mycophenolic aldehyde, and marketed drug indomethacin derived aldehydes are selectively deuterated in good yield and with high deuteration (**3an**−**3ap**). Furthermore, ribose amino acid tryptophan and dipeptide Phe-Gly aldehyde derivatives can be labeled by deuterium with high level deuterium decoration (91−96%, **3aq**−**3as**).

**Scheme 5. Deuteration of Aldehyde Moiety in Structurally Complex Structures, Gram Scale Synthesis, Recycling and Reuse of $D_2O$, and Intermediate Trapping Study**[a]




[a]See the Supporting Information for detailed reaction conditions. Isolated yields (Y); D% determined by $^1H$ NMR spectroscopy.

The method can be used in a gram-scale synthesis of C-1deuterated aldehydes. In comparison to the small-scale process, as shown using *p*-tolualdehyde **1a** as an example, the gram-scale counterpart **3a** is formed in a similar yield and with a comparable level of D-incorporation, although reduced amounts of reagents and catalysts (only 20 equiv of $D_2O$, 1.5 mol % 4CzIPN, 20 mol % $PhCO_2Na$, and 8 mol % triisopropylsilanethiol) are used (Scheme 5b). Furthermore, the recovered $D_2O$ containing solvent can be used in a second and third reaction without causing a significant decrease in yield and D-incorporation level (Scheme 5c). These studies demonstrate that the cost for the synthesis of deuterated aldehyde products can be further reduced. Finally, to verify the proposed mechanism, the formed acyl radical was trapped by TEMPO. The product was confirmed by ESI-MS analysis of the crude reaction mixture (Scheme 5d) (SI, Section 6).

In summary, we developed a visible light mediated, organocatalyzed HDE process for directly converting readily accessible aldehydes to their 1-deutero counterparts using $D_2O$ as the deuterium pool. Distinct from the established transition metal catalyzed ionic HDE processes, this organophotoredox catalytic radical strategy was successfully realized. Notably, this approach not only enables direct HDE of aromatic aldehydes without deuteration on the aromatic ring but also for aliphatic aldehydes and selective late-stage deuterium incorporation into complex structures with uniformly high level (>90%) of deuterium incorporation. We anticipate that the approach will enable facile access to a wide range of deuterated structures, which are highly valuable in the fields of biological, medicinal, and organic chemistry.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.9b05300.

General information and procedures, cost calculations, further experimental results, and characterization data for compounds **3** (PDF)

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### Notes

The authors declare no competing financial interest.

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