Synergistic Catalysis

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Deoxygenative Deuteration of Carboxylic Acids with D_2O

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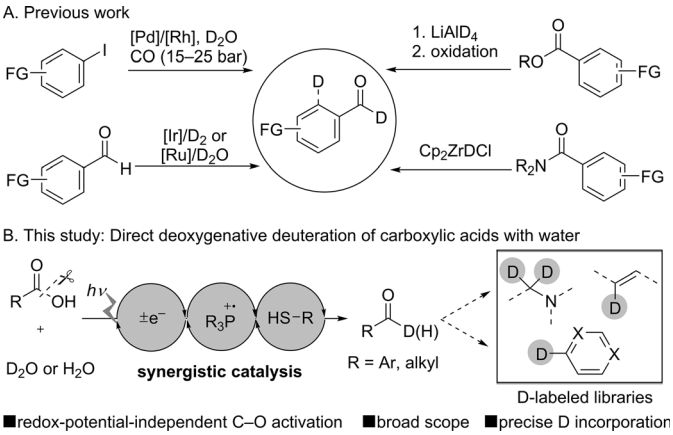
Abstract: *We report a general, practical, and scalable means of preparing deuterated aldehydes from aromatic and aliphatic carboxylic acids with D_2O as an inexpensive deuterium source. The use of Ph_3P as an O-atom transfer reagent can facilitate the deoxygenation of aromatic acids, while Ph_2POEt is a better O-atom transfer reagent for aliphatic acids. The highly precise deoxygenation of complex carboxylic acids makes this protocol promising for late-stage deoxygenative deuteration of natural product derivatives and pharmaceutical compounds.*

Deuteration as a labeling technique has long been regarded as an important tool in the analysis of drug metabolism[1] and the investigation of reaction mechanisms[2] as well as nuclear magnetic resonance spectroscopy[3] and mass spectrometry.[4] The incorporation of a deuterium atom can dramatically enhance the metabolism and pharmacokinetic properties of parent drugs and drug candidates.[5] In 2017, FDA permission for the entry to market of the first deuterated drug, deutetrabenazine,[6] has significantly motivated the development of synthetic methods for deuteration,[7] and will certainly accelerate the discovery and development of deuterium-labeled drugs.

Aromatic aldehydes are very useful building blocks in organic synthesis.[8] The development of a highly efficient protocol to construct aromatic aldehydes deuterated at the formyl position should enhance the availability of deuterated lead compounds. Several methodologies that access deuterated aromatic aldehydes have been reported. Representative strategies include Pd/Rh-cocatalyzed reductive carbonylation of aryl halides,[9] Ru- and Ir-catalyzed hydrogen isotope exchange (HIE),[10] and careful reduction of carboxylic acid derivatives with deuterated reductants[11] (Scheme 1 A). Given the importance of deuterated aromatic aldehydes, a convenient and step-economical synthetic approach is still highly desired. Moreover, the late-stage introduction of deuterium into structurally complex aldehydes remains a challenge in organic synthesis.



Scheme 1. Summary of previous and current studies. FG = functional group.

Very recently, our research group developed a direct synthesis of ketones from abundant aromatic acids and alkenes in aqueous solution by phosphoranyl-radical-assisted deoxygenation enabled by visible-light photoredox catalysis.[12] We questioned whether the generation of acyl radicals from aromatic acids had the potential to produce deuterated aldehydes with D_2O. However, the strong bond dissociation energy (BDE) of D–O–D bonds (118 kcal mol^{-1}) prohibits direct deuterium-atom transfer (HAT) from D_2O.[13] Recently, successful radical deuteration with D_2O was reported by the research groups of MacMillan[14a] and Renaud,[14b] who used a HAT catalyst to bridge the energy gap. Our experience in synergistic thiol catalysis and photoredox catalysis[15] suggested that the thermodynamic properties of thiols were an important factor in the success of such reactions. The use of a suitable thiol catalyst may be able to tune the equilibrium with D_2O as well as the HAT rate and possibly furnish deuterated aldehydes. With these considerations in mind, we developed a general and practical radical deoxygenative deuteration of carboxylic acids with D_2O as enabled by synergistic thiol catalysis, photoredox catalysis, and phosphoranyl radical chemistry (Scheme 1 B).

A synergistic mechanism for the direct deoxygenative deuteration of carboxylic acids is proposed in Scheme 2. Density functional theory (DFT) calculations indicate that the pK_a values of thiols **2a–d** range from 10 to 17, and the proton of a thiol catalyst can exchange with excess D_2O (pK_a = 32)[16] to furnish a deuterium-labeled thiol **4**, which serves as the source of deuterium. The photoexcited complex *[Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ [$^{1/2}E_{red}$ (*Ir^{II}I/Ir^{II}) = +1.21 V vs. SCE; τ = 2.3 μs][17] is a strong oxidant, which can achieve

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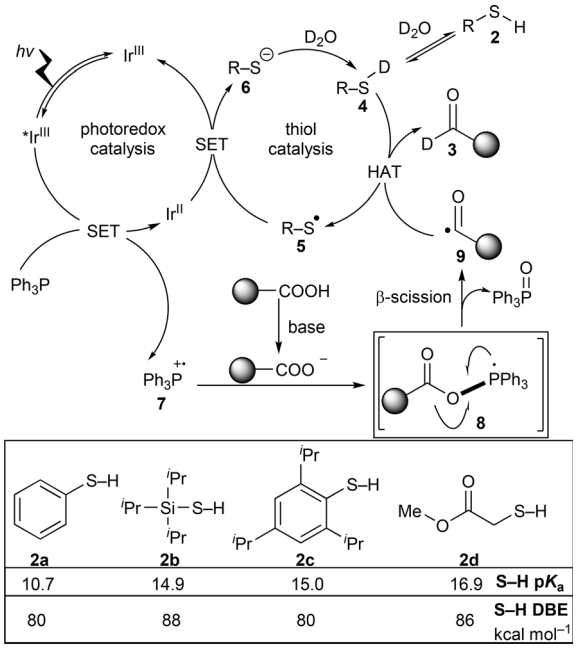
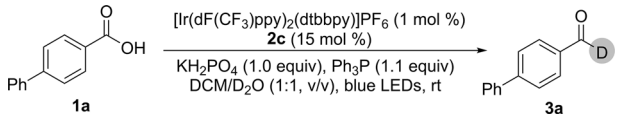


Scheme 2. Mechanistic proposal.

Table 1: Optimization of the reaction conditions.[a]



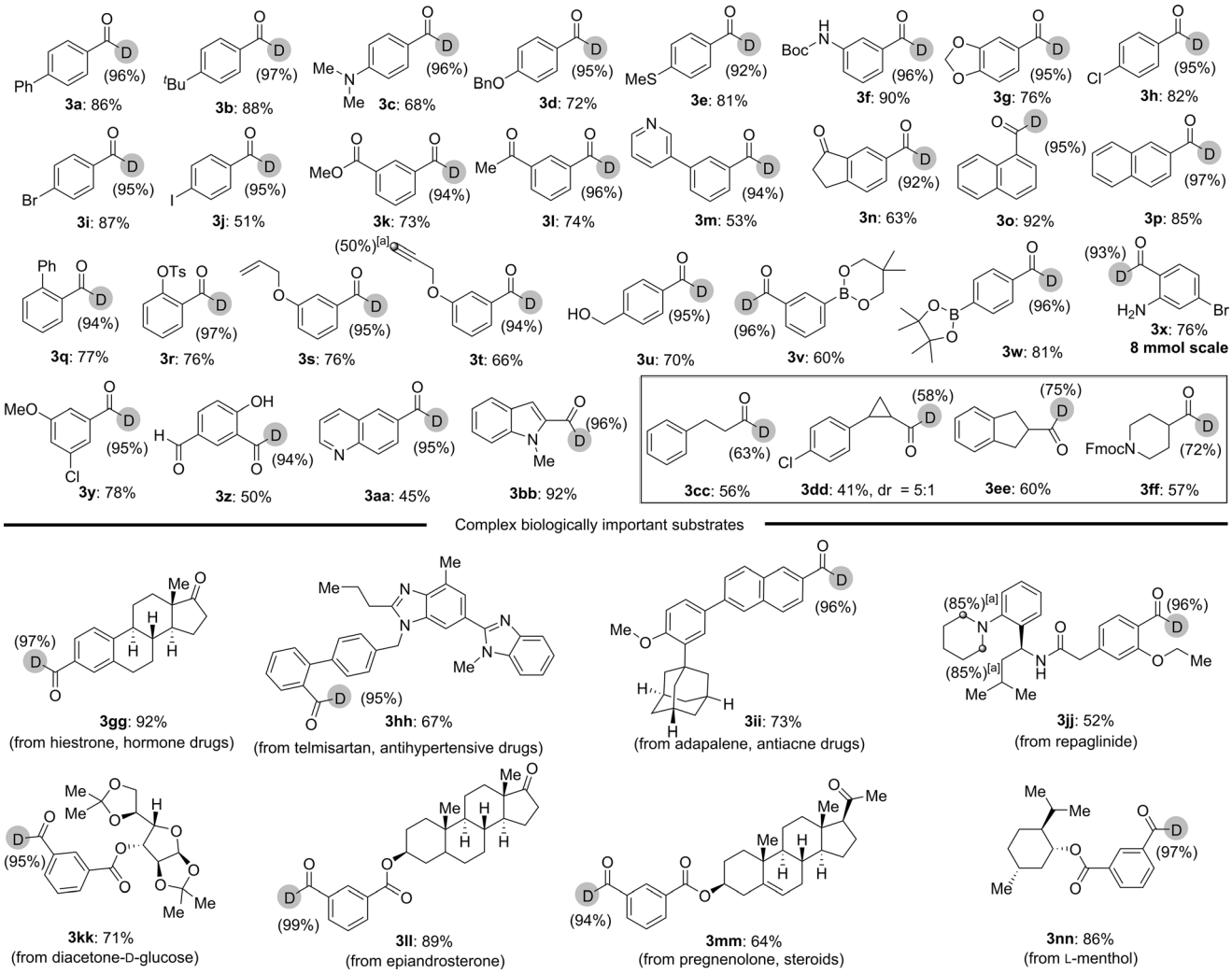
Entry	Variation of standard conditions	Yield [%][b]	D incorp. [%][c]
1	none	86	96
2	Ph_2POEt instead of Ph_3P	12	95
3	$P(OEt)_3$ instead of Ph_3P	n.d.	n.d.
4	no Ph_3P	n.d.	n.d.
5	2a instead of 2c	65	95
6	2b instead of 2c	38	96
7	2d instead of 2c	20	94
8	$[Ir(dF(Me)ppy)_2(dtbbpy)]PF_6$	80	92
9	no light or no photocatalyst	n.d.	n.d.

[a] Standard conditions: 1a (0.2 mmol), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (1 mol%), 2c (15 mol%), Ph_3P (1.1 equiv), K_2HPO_4 (1.0 equiv), and DCM/D_2O (1:1, v/v; 2 mL), 5 W blue LEDs, 36 h. [b] Yield of the isolated product. [c] Deuterium incorporation was determined by ^1H NMR spectroscopy. n.d. = not detected. DCM = dichloromethane, dF(CF$_3$)ppy = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine, dtbbpy = 4,4′-di-tert-butyl-2,2′-dipyridyl.

single-electron oxidation of triphenylphosphine ($^{1/2}E_{red} = +0.98$ V vs. SCE)[18] to generate a triphenylphosphine radical cation **7**. This radical cation reacts with a carboxylate ion to form an intermediate **8**, which can undergo β-scission[19] to produce triphenylphosphine oxide and a reactive acyl radical **9** as a result of the strong affinity between phosphines and oxygen atoms. The DFT calculations also demonstrate that although the S–H bond in thiols **2a–d** varies significantly, the BDE for C–H of an aldehyde (94 kcal mol^{-1}) is still much higher than that of the S–H bond of these thiols **2a–d** (80–88 kcal mol^{-1}). The BDE gap between C–H and S–H bonds would be an important driving force for HAT processes (**4**→**5** and **9**→**3**). In this context, the nucleophilic acyl radical **9**[20] can readily undergo HAT from the thiol **4** to form a deuterated aldehyde, a reaction which is controlled by a polarity-matching effect.[21] The generated electrophilic thiyl radical **5** subsequently accepts one electron from reducing Ir^{II} species to complete the photoredox cycle, and the generated thiol anion **6** abstracts one deuteron from D_2O to restart the thiol catalysis.

Our investigation began with optimization of the deoxygenative deuteration of 4-phenylbenzoic acid with D_2O (Table 1). The optimized reaction conditions include $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (1 mol%) as the photocatalyst, 2,4,6-triisopropylbenzenethiol (**2c**, 15 mol%) as the HAT catalyst, Ph_3P (1.1 equiv) as an oxygen-atom transfer reagent, and DCM/D_2O (1:1, v/v) as the solvent (entry 1). The desired deuterated product **3a** was obtained in 86% yield with 96% D incorporation using commercially inexpensive D_2O as an ideal deuterium source. The use of other relatively electron poor trivalent phosphorus compounds, such as Ph_2POEt and $P(OEt)_3$, led to decreased reaction yields (entries 2 and 3), suggesting that the choice of O-transfer reagent was crucial for the success of the reaction (entries 2–4). When other thiols were employed under the same conditions, the reaction yield significantly decreased, although D incorporation remained at a high level (entries 5–7). The use of a lower-oxidation-potential photocatalyst, $[Ir(dF(Me)ppy)_2(dtbbpy)]PF_6$ [$^{1/2}E_{red}$ ($^*Ir^{III}/Ir^{II}$) = +0.97 V vs. SCE; $\tau = 1.2$ μs],[22] resulted in a slightly deccreased yield and D incorporation (entry 8). Control experiments demonstrated that the deoxygenative deuteration reaction could not occur in the absence of either light or a photocatalyst (entry 9).

Having optimized the reaction conditions, we investigated the scope of the transformation with respect to the carboxylic acid substrate (Scheme 3). In principle, the developed phosphoranyl-radical-assisted deoxygenation could overcome the limitation of the redox potential of carboxylic acids, and thus a wide variety of aromatic carboxylic acids should be competent substrates. A diverse range of electron-donating (Ph, ^{t}Bu, NMe_2, BnO, SMe, and NBoc) and electron-withdrawing functional groups (COOMe, COMe, and pyridinyl) at the *ortho*, *meta*, and *para* positions of a phenyl ring attached to the carboxylic acid group were entirely compatible. Such substrates uniformly delivered the desired deuterated aryl aldehydes **3a–r** in moderate to good (up to 92%) yield with high D incorporation (92–97% D) exclusively at the formyl position. Both 1-naphthoic acid and 2-naphthoic acid were efficient substrates (products **3o**, **3p**). Reactive terminal alkene and alkyne units remained intact (products **3s**, **3t**). Intriguingly, several relatively sensitive yet versatile functional groups, such as a free hydroxy (product **3u**) or amino group (product **3x**), halogen substituents (products **3i**, **3j**), boronic esters (products **3v**, **3w**), an aldehyde (product **3z**), and a ketone (product **3n**), tolerated the deoxygenative deuteration conditions well, which suggests promising broad-ranging applications in synthetic and medicinal chemistry. Furthermore, the reaction can be scaled up conveniently: product **3x** was obtained in 76% yield with a high level of D incorporation when the reaction was carried out on an 8 mmol scale. The robustness of the reaction is illustrated by

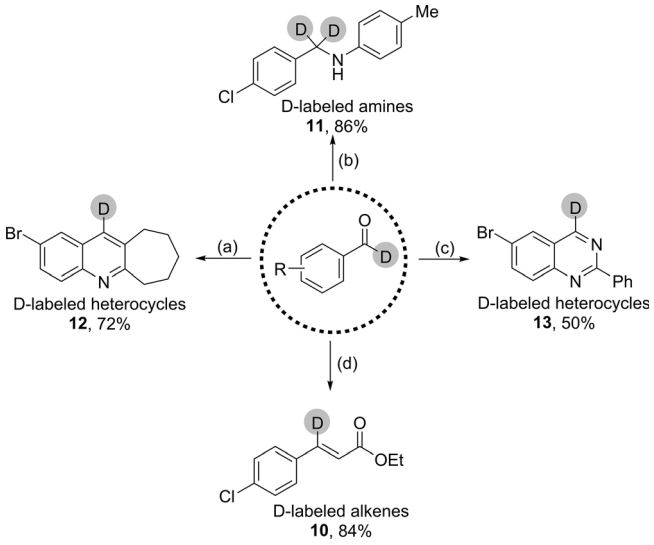


Scheme 3. Reaction scope (see the Supporting Information for detailed reaction conditions). Yields are for the isolated product after column chromatography on SiO_2; the D content was determined by ^1H NMR spectroscopy. [a] Proton/deuterium exchange ratio of acidic protons with D_2O. Bn = benzyl, Boc = tert-butoxycarbonyl, Fmoc = fluorenylmethoxycarbonyl, Ts = p-toluenesulfonyl.

the precise synthesis of monodeuterated *meta*-phthalaldehyde derivative **3z**. Quinoline and indole heteroaromatic acids underwent this deoxygenative deuteration smoothly to give **3aa** and **3bb**. Besides aromatic acids, aliphatic carboxylic acids were also good substrates and afforded deuterated aliphatic aldehydes **3cc**–**ff** in moderate yields with a moderate level of D incorporation under modified reaction conditions.[23] In such cases, the combination of $[Ir(dF(Me)ppy)_2(dtbbpy)]PF_6$ as a photocatalyst and Ph_2POEt as an O-atom transfer reagent is a key factor for control of deoxygenation as opposed to the well-studied decarboxylation.[24]

This excellent functional-group tolerance enables the potential application of the reaction in the synthesis of complex deuterated aldehydes by late-stage functionalization of biologically active natural products, pharmaceuticals, and agrochemicals (Scheme 3, lower part). The deoxygenative deuteration of pharmaceuticals such as hiestrone (product **3gg**), telmisartan (product **3hh**), and adapalene (product **3ii**) was successfully achieved in 67–92% yield with 95–97% D incorporation. In complex carboxylic acids containing a tertiary amine motif, for example, repaglinide, besides the expected deoxygenative deuteration, visible-light-induced HIE was observed at α-C(sp^3)–H positions of tertiary amines (product **3jj**).[14a] Derivatives of diacetone-D-glucose (product **3kk**), epiandrosterone (product **3ll**), pregnenolone (product **3mm**), and L-menthol (product **3nn**) underwent radical deuteration in 64–89% yield with high D incorporation (up to 99% D), exclusively at the formyl position. These examples indicate that this protocol enables practical late-stage modification in synthetic medicinal chemistry.

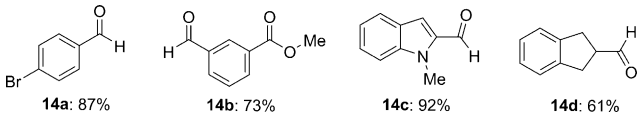
The versatility of aldehydes in organic transformations allows practical access to an enhanced library of deuterated compounds (Scheme 4). For example, the deuterium-labeled aldehydes obtained in this way can be readily elaborated through Horner–Wadsworth–Emmons olefination and reductive amination to deliver β-deuterated, α,β-unsaturated esters **10** and highly valuable deuterated amines[7a] **11**. The reaction of aminobenzaldehydes with deuterium-labeled aldehydes provides an efficient route to deuterium-labeled nitrogen-



Scheme 4. Downstream transformations (see the Supporting Information for detailed reaction conditions).

containing heterocyclic compounds, such as quinazolines **12** and quinolines **13**.

The mild reduction of carboxylic acids to aldehydes is one of the most important and challenging functional-group conversions in organic synthesis.[25] Just by replacing D_2O with H_2O,[26] our synergistic deoxygenation can serve as a powerful and general strategy for the selective reduction of carboxylic acids to aldehydes under mild conditions with good selectivity and functional-group compatibility (Scheme 5).



Scheme 5. Selective transformation of carboxylic acids into aldehydes.

To gain insight into the mechanism of this reaction, we performed radical-inhibitor experiments by the addition of 2,2,6,6-tetramethyl-1-piperidyloxy (TEMPO) and 2,6-di-*tert*-butyl-*p*-cresol (BHT) to the model reaction (see the Supporting Information for details). Both these radical traps completely inhibited the deoxygenative deuteration, thus suggesting the possibility of a radical process. The trapping of acyl radicals by TEMPO further supports this claim. ^{18}O-Labeling experiments demonstrated that the oxygen atom in triphenylphosphine oxide comes from carboxylate group rather than from H_2O (see the Supporting Information for details). Accordingly, the proposed mechanism in Scheme 2 is a promising candidate.

In conclusion, we have developed the first deoxygenative deuteration of both aromatic and aliphatic carboxylic acids with D_2O as an inexpensive deuterium source by synergistic photoredox catalysis and organocatalysis in conjunction with phosphoranyl radical chemistry. A wide arrange of deuterated aldehydes were obtained in moderate to good yields with high levels of D incorporation. This reaction also provides a simple and promising method for the transformation of carboxylic acids to aldehydes using H_2O as a medium.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: aldehydes · carboxylic acids · deoxygenation · deuteration · synergistic catalysis

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Communications

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