Deoxyrogenative Deuteration of Carboxylic Acids with D$_2$O

Muliang Zhang, Xiang-Ai Yuan, Chengjian Zhu, and Jin Xie*

Abstract: We report a general, practical, and scalable means of preparing deuterated aldehydes from aromatic and aliphatic carboxylic acids with D$_2$O as an inexpensive deuterium source. The use of Ph$_3$P as an O-atom transfer reagent can facilitate the deoxygenation of aromatic acids, while Ph$_3$POEt 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 deoxyrogenative 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 1A). 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.

Very recently, our research group developed a direct synthesis of ketones from abundant aromatic acids and alkenes in aqueous solution by phosphoryl-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$_2$O. However, the strong bond dissociation energy (BDE) of D$_2$O-N bonds (118 kcal mol$^{-1}$) prohibits direct deuterium-atom transfer (HAT) from D$_2$O.[13] Recently, successful radical deuteration with D$_2$O 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$_2$O as well as the HAT rate and possibly furnish deuterated aldehydes. With these considerations in mind, we developed a general and practical deoxyrogenative deuteration of carboxylic acids with D$_2$O as enabled by synergistic thiol catalysis, photoredox catalysis, and phosphoryl radical chemistry (Scheme 1B).

A synergistic mechanism for the direct deoxyrogenative 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$_2$O ($pK_a = 32$)[16] to furnish a deuterium-labeled thiol 4, which serves as the source of deuterium. The photoexcited complex $^{1}$[Ir(dF(C$_3$)ppy)$_2$(dibbpy)]PF$_6$ $^{[12]E_{red} (\text{Ir}^3/\text{Ir}^2) = +1.21 \text{ V vs SCE}}; \tau = 2.3 \mu \text{s}\) is a strong oxidant, which can achieve
single-electron oxidation of triphenylphosphine \((1/2E_{\text{red}} = +0.98 \text{ V vs. SCE})\)\(^{[19]}\) 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 thioles \(2a-d\) varies significantly, the BDE for C–H of an aldehyde \((94 \text{ kcal mol}^{-1})\) is still much higher than that of the S–H bond of these thioles \(2a-d\) \((80–88 \text{ kcal mol}^{-1})\). The BDE gap between C–H and S–H bonds would be an important driving force for HAT processes \(4–5\) and \(9–9\). 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 thyl radical \(5\) subsequently accepts one electron from reducing Ir\(^{III}\) species to complete the photoredox cycle, and the generated thiol cation \(7\) readily accepts one electron from reducing Ir\(^{II}\) species for the success of the reaction (entries 2–4). When other thioles 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, \([\text{Ir}(\text{dF(Me)}\text{ppy})_2(\text{dtbbpy})]PF_6\) \((1 \text{ mol} \%), \quad 2c\) \((15 \text{ mol} \%), \quad \text{Ph}_3\text{P} \quad (1 \text{ mol} \%), \quad \text{K}_2\text{HPO}_4 \quad (1.0 \text{ equiv}.), \quad \text{and DCM/DCO} \quad (1.0 \text{ equiv}), \quad \text{and} \quad \text{DCM/D}_2\text{O} \quad (1.0 \text{ equiv}.), \quad 5 \text{ W blue LEDs, } 36 \text{ h.}\)\(^{[b]}\) Yield of the isolated product.\(^{[b]}\) Deuterium incorporation was determined by \(^1\)H 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.

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 phosphonanyl-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 and electron-withdrawing functional groups (COOMe, COMe, and pyridyl) 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 alkenic and alkynic units remained intact (products 3s, 3t). Intriguingly, several relatively sensitive yet versatile functional groups, such as a free hydroxyl (product 3u) or amino group (product 3x), halogen substitutes (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

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**Table 1:** Optimization of the reaction conditions.\(^{[a]}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Variation of standard conditions</th>
<th>Yield [%](^{[b]})</th>
<th>D incorp. [%](^{[c]})</th>
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<tr>
<td>1</td>
<td>none</td>
<td>86</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>Ph$_3$POEt instead of Ph$_3$P</td>
<td>12</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>P(OEt)$_3$ instead of Ph$_3$P</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>4</td>
<td>no Ph$_3$P</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>5</td>
<td>2a instead of 2c</td>
<td>65</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>2b instead of 2c</td>
<td>38</td>
<td>96</td>
</tr>
<tr>
<td>7</td>
<td>2d instead of 2c</td>
<td>20</td>
<td>94</td>
</tr>
<tr>
<td>8</td>
<td>[Ir(dF(Me)ppy)$_2$(dtbbpy)]PF$_6$</td>
<td>80</td>
<td>92</td>
</tr>
<tr>
<td>9</td>
<td>no light or no photocatalyst</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

[a] Standard conditions: 1a \((0.2 \text{ mmol})\), [Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ \((1 \text{ mol} \%), \quad 2c\) \((15 \text{ mol} \%), \quad \text{Ph}_3\text{P} \quad (1 \text{ mol} \%), \quad \text{K}_2\text{HPO}_4 \quad (1.0 \text{ equiv}.), \quad \text{and} \quad \text{DCM/D}_2\text{O} \quad (1.0 \text{ equiv}), \quad 5 \text{ W blue LEDs, } 36 \text{ h.}\)\(^{[b]}\) Yield of the isolated product.\(^{[b]}\) Deuterium incorporation was determined by \(^1\)H 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.

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**Scheme 2:** Mechanistic proposal.
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. In such cases, the combination of [Ir(dF(Me)ppy)2(dtbbpy)]PF6 as a photocatalyst and Ph2POEt as an O-atom transfer reagent is a key factor for control of deoxygenation as opposed to the well-studied decarboxylation. 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(sp3)–H positions of tertiary amines (product 3jj). Derivatives of diacetone-Ω-glucose (product 3kk), epiandrosterone (product 3il), 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 and highly valuable deuterated amines. The reaction of aminobenzaldehydes with deuterium-labeled aldehydes provides an efficient route to deuterium-labeled nitrogen-
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.[23] Just by replacing D₂O with H₂O,[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).

To gain insight into the mechanism of this reaction, we performed radical-inhibitor experiments by the addition of 2,2,6,6-tetramethyl-1-piperidylx (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. ¹⁸O-Labeling experiments demonstrated that the oxygen atom in triphenylphosphine oxide comes from carboxylate group rather than from H₂O (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 deuteriation of both aromatic and aliphatic carboxylic acids with D₂O 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 H₂O as a medium.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

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

References


[23] The preparation of deuterated aliphatic carboxylic acids from the corresponding aliphatic carboxylic acids with D₂O in the first step is necessary because aliphatic acids are prone to undergo radical decarboxylation in aqueous solution; see the Supporting Information for detailed reaction conditions.


[26] Aliphatic carboxylic acids can deliver the corresponding aldehydes under modified conditions without the addition of H₂O. After submission of this manuscript, a study with similar conditions was reported, see: E. E. Stache, A. B. Ertel, T. Rovis, A. G. Doyle, ACS Catal. 2018, 8, 11134.
Deoxygenative Deuteration of Carboxylic Acids with D$_2$O

**Drink of water**: A general, practical, and scalable means of preparing deuterated aldehydes from aromatic and aliphatic carboxylic acids has been developed with D$_2$O as an inexpensive deuterium source (see scheme). The transformation, enabled by synergistic photoredox catalysis, thiol catalysis, and phosphoranyl radical chemistry, shows broad scope and good functional-group tolerance and can be used for late-stage deoxygenative deuteration.