

# Rhodium-Catalyzed Deuterated Tsuji–Wilkinson Decarbonylation of Aldehydes with Deuterium Oxide

Xiang-Ting Min, Yong-Kang Mei, Bing-Zhi Chen, Li-Bowen He, Ting-Ting Song, Ding-Wei Ji, Yan-Cheng Hu, Boshun Wan, and Qing-An Chen\*



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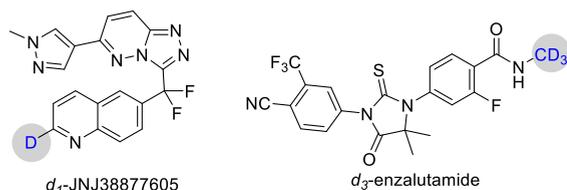
Supporting Information

**ABSTRACT:** The recent surge in the applications of deuterated drug candidates has rendered an urgent need for diverse deuterium labeling techniques. Herein, an efficient Rh-catalyzed deuterated Tsuji–Wilkinson decarbonylation of naturally available aldehydes with D<sub>2</sub>O is developed. In this reaction, D<sub>2</sub>O not only acts as a deuterated reagent and solvent but also promotes Rh-catalyzed decarbonylation. In addition, decarbonylative strategies for the synthesis of terminal monodeuterated alkenes from  $\alpha,\beta$ -unsaturated aldehydes are within reach.

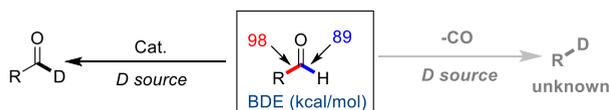
Since Austedo received FDA approval,<sup>1</sup> there are many other deuterated drug candidates under clinical testing, such as *d*<sub>1</sub>-JNJ38877605,<sup>2</sup> *d*<sub>3</sub>-enzalutamide (Scheme 1a).<sup>3</sup> Deuterium-labeled molecules are expected to prolong the half-life of metabolism, enhance the efficacy, and decrease side effects owing to the better stability of C–D bonds compared to that of C–H bonds.<sup>4</sup> In particular, deuterium-containing

## Scheme 1. Decarbonylation and Deuteration of Aldehydes

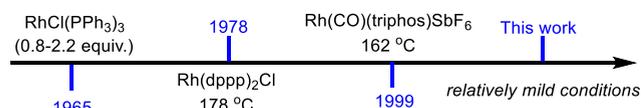
a) Representative deuterium-containing drugs



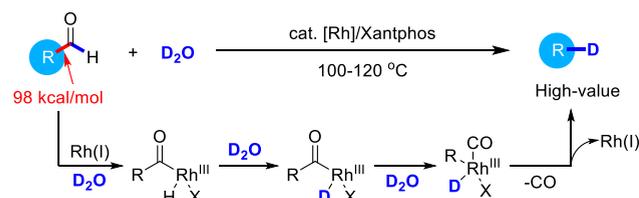
b) Selective deuteration of aldehydes



c) Development of Tsuji–Wilkinson decarbonylation under Rh catalysis



d) This work: Deuterated Tsuji–Wilkinson decarbonylation with D<sub>2</sub>O



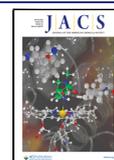
molecules have been widely used in mechanistic studies<sup>5</sup> and NMR analyses.<sup>6</sup> Therefore, it is of great interest to develop efficient deuterated methods.<sup>7–9</sup>

Given the tremendous availability of aldehydes, the development of an efficient deuterated protocol for editing aldehydes can be expected to increase the accessibility and chemical space of deuterated compounds.<sup>10</sup> Currently, several methods for the formyl-selective deuteration of aldehydes have been developed under transition metal catalysis,<sup>11</sup> NHC catalysis,<sup>12</sup> enzymes catalysis,<sup>13</sup> or photoredox catalysis.<sup>14</sup> In terms of C–H/C–C bond dissociation energy (BDE),<sup>15</sup> the decarbonylative deuteration of aldehydes will be more challenging and remains unknown (Scheme 1b). Since its discovery in 1965,<sup>16</sup> Tsuji–Wilkinson decarbonylative reaction has been developed and recognized as an important method for C–C bond cleavage under transition metal catalysis.<sup>17</sup> To realize the efficient Rh-catalytic version, elevated reaction temperatures (typically >160 °C) were indispensable (Scheme 1c).<sup>17,18</sup> Therefore, exploiting a catalytic protocol under relatively mild conditions for decarbonylation/deuteration reaction of aldehydes will be of great significance.

Given that most of the active metal–carbon bonds are moisture sensitive, traditional transition metal catalysis is required to be performed under anhydrous conditions.<sup>19</sup> In continuation of our ongoing interest in developing decarbonylative functionalization,<sup>20</sup> we envisioned that the decarbonylation of aldehydes could be facilitated by water as a strong polar solvent through dispersing the charge of high-valent metal intermediates.<sup>19a</sup> Meanwhile, deuterium oxide (D<sub>2</sub>O) is an ideal deuterium source in terms of its availability and cost.<sup>21</sup>

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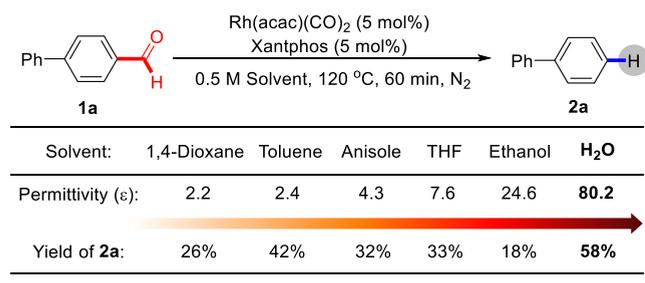
Published: June 16, 2022



Herein, we report an efficient Rh-catalyzed deuterated version of the Tsuji–Wilkinson decarbonylation of aldehydes with D<sub>2</sub>O (Scheme 1d).

To verify our proposal, we began our study by exploring a decarbonylative reaction using 4-biphenylcarboxaldehyde as model substrates in the presence of Rh(acac)(CO)<sub>2</sub> and Xantphos with different solvents (Scheme 2). When oxygen-

### Scheme 2. Solvent Effects on Rh-Catalyzed Decarbonylation



containing solvents such as 1,4-dioxane, anisole, and THF were used, the yield of diphenyl increased from 26% to 33% as the polarity of the solvent increased.<sup>22</sup> Probably owing to its π–π interaction ability, the use of toluene displayed better reactivity. With respect to the yield, water emerged as the best choice from the examination of solvents with higher permittivity.

Encouraged by these results, a more interesting decarbonylative deuteration of aldehyde was carried out (Table 1). To our delight, the decarbonylative deuteration product **2a** was obtained in 57% yield with >95% deuterium incorporation after stirring at 100 °C for 90 min (entry 1). No significant improvement was observed when the reaction was performed at higher temperature with a prolonged reaction time (entry 2). The investigation on the additives showed that PhNO<sub>2</sub> was the best additive and delivered product **2a** in 87% yield (entries 3–8).<sup>23</sup> Besides [Rh(cod)OH]<sub>2</sub>, [Rh(cod)OMe]<sub>2</sub> showed comparable reactivity. Other catalyst precursors such as [Rh(cod)Cl]<sub>2</sub>, Rh(acac)(CO)<sub>2</sub> and [Ir(cod)OMe]<sub>2</sub><sup>24</sup> were not efficient at 100 °C. Notably, other decarbonylative catalysts, such as RhCl(PPh<sub>3</sub>)<sub>3</sub> and RhCl<sub>3</sub>·3H<sub>2</sub>O<sup>18d</sup> and Ni(cod)<sub>2</sub><sup>25</sup> did not afford any desired product at 100 °C (entries 9–12 and Table S2 in Supporting Information). No better result was observed from the evaluation of other bisphosphine or monophosphine ligands (Table S2 in Supporting Information (SI)). Corresponding control experiments confirmed the essential roles of the rhodium catalyst and the phosphine ligand (entries 13–14). In terms of yields, the optimized amount of PhNO<sub>2</sub> was 20 mol % (entries 15–16). The yield of **2a** could be increased to 97% by slightly prolonging the reaction time and increasing the temperature (entries 17–18).

With the optimized reaction conditions in hand, a wide range of available aldehydes were evaluated (Scheme 3). Aldehydes with varied skeletons (diphenyl, naphthalene, fluorene, anthracene and pyrene) were efficiently converted to the corresponding deuterated products (**2a**–**2h**). It was also found that mono-, dialkoxy substituted benzaldehydes, which mostly were naturally available substrates, were tolerated and successfully afforded deuterium-containing molecules (**2i**–**2m**). In addition, aldehydes with nitrogen-containing groups (**1n** and **1o**) also proved to be competent partners in affording the desired product in decent yields. Higher deuterium

Table 1. Selected Optimization Studies

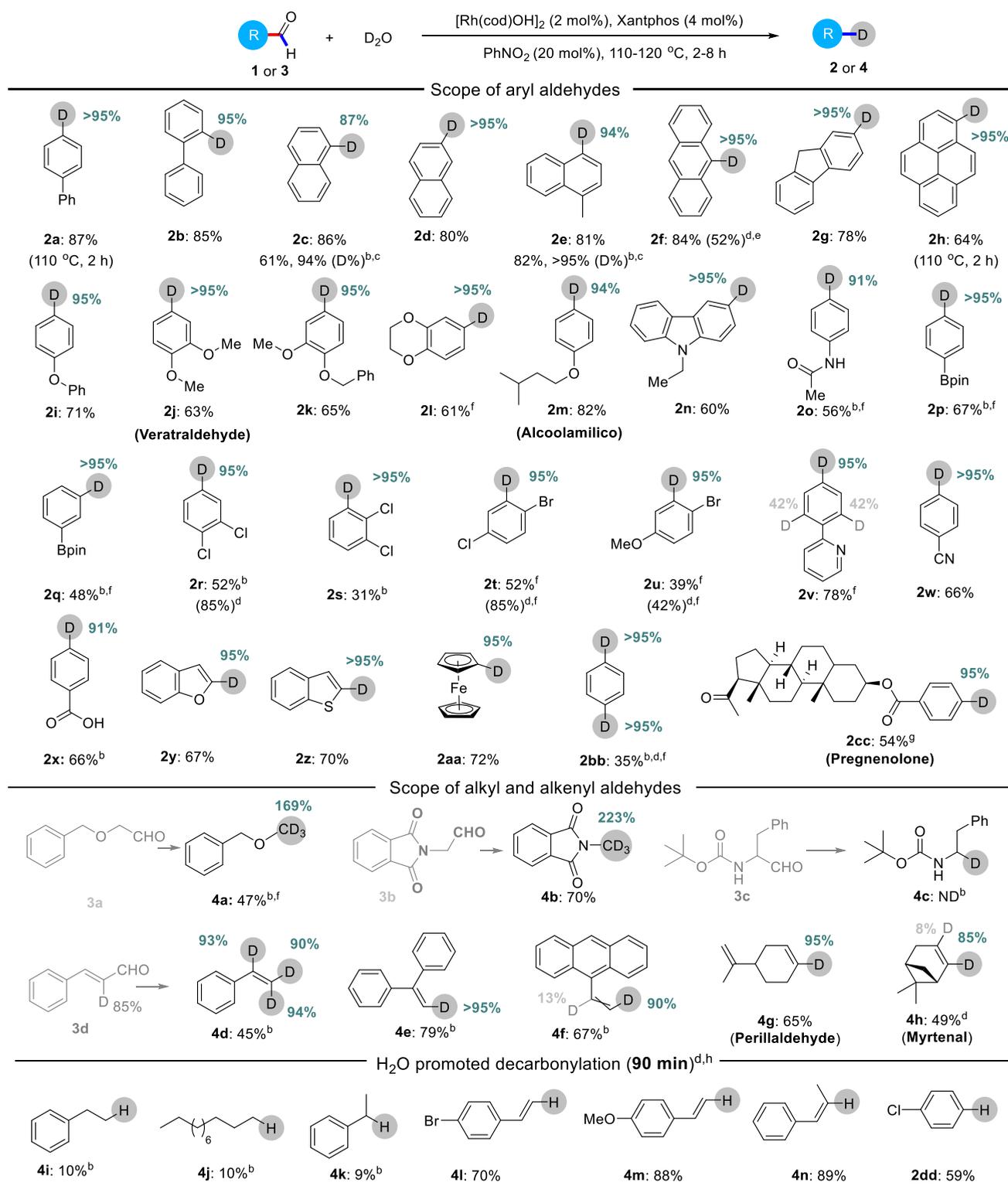
entry	ML <sub>n</sub>	additives (4 mol%)	<b>2a</b> (D%) <sup>a</sup>
1	[Rh(cod)OH] <sub>2</sub>	None	57% (>95%)
2	[Rh(cod)OH] <sub>2</sub>	None	62% (>95%) <sup>b</sup>
3	[Rh(cod)OH] <sub>2</sub>	PhCO <sub>2</sub> H	56% (–)
4	[Rh(cod)OH] <sub>2</sub>	4-MeO-C <sub>6</sub> H <sub>4</sub> -NO <sub>2</sub>	76% (>95%)
5	[Rh(cod)OH] <sub>2</sub>	4-F-C <sub>6</sub> H <sub>4</sub> -NO <sub>2</sub>	67% (>95%)
6	[Rh(cod)OH] <sub>2</sub>	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> -CO <sub>2</sub> H	80% (>95%)
7	[Rh(cod)OH] <sub>2</sub>	PhNO <sub>2</sub>	87% (>95%)
8	[Rh(cod)OH] <sub>2</sub>	MeNO <sub>2</sub>	55% (–)
9	[Rh(cod)OMe] <sub>2</sub>	PhNO <sub>2</sub>	80% (95%)
10	Rh(acac)(CO) <sub>2</sub>	PhNO <sub>2</sub>	58% (–)
11	[Ir(cod)OMe] <sub>2</sub>	PhNO <sub>2</sub>	18% (–)
12	Ni(cod) <sub>2</sub>	PhNO <sub>2</sub>	ND
13	None	PhNO <sub>2</sub>	ND
14	[Rh(cod)OH] <sub>2</sub>	PhNO <sub>2</sub>	ND <sup>c</sup>
15	[Rh(cod)OH] <sub>2</sub>	PhNO <sub>2</sub> (20 mol%)	91% (>95%)
16	[Rh(cod)OH] <sub>2</sub>	PhNO <sub>2</sub> (30 mol%)	85% (>95%)
17	[Rh(cod)OH] <sub>2</sub>	PhNO <sub>2</sub> (20 mol%)	93% (>95%) <sup>d</sup>
18	[Rh(cod)OH] <sub>2</sub>	PhNO <sub>2</sub> (20 mol%)	97% (>95%) <sup>d,e</sup>

<sup>a</sup>Conditions: **1a** (0.20 mmol), ML<sub>n</sub> (dimer 0.004 mmol or monomer 0.008 mmol), Xantphos (0.008 mmol, 4 mol %), PhNO<sub>2</sub> (0.008 mmol, 4 mol %), D<sub>2</sub>O (1.0 M), N<sub>2</sub> atmosphere, 90 min and 100 °C. Yield was determined by GC-FID with mesitylene as the internal standard. Deuterium incorporation was determined by <sup>1</sup>H NMR spectroscopy. <sup>b</sup>4 h, 110 °C. <sup>c</sup>Without Xantphos. <sup>d</sup>110 °C. <sup>e</sup>120 min.

incorporations (e.g., **2c**, **2e**) could be achieved using more D<sub>2</sub>O.

Given potential further elaborations, a range of functionalized derivatives, including Bpin-, Cl-, and Br-substituted aldehydes, underwent decarbonylative deuteration selectively to provide the corresponding products **2p**–**2u** with ≥95% deuterium incorporations. Besides, substrates with potentially coordinating pyridine (**1v**) or CN (**1w**) groups were also suitable in this reaction, leading to deuterated products **2v** and **2w** in 78% and 66% yields, respectively. The deuterium incorporation at the ortho positions of phenyl group on **2v** indicated that directed C–H activation<sup>26</sup> and decarbonylation occur simultaneously (Scheme S2 in SI). Interestingly, 4-formylbenzoic acid could be transformed into benzoic-4-d acid (**2x**) in 66% yield and 91% deuterium incorporation. The heteroarylaldehydes and highly electron-rich ferrocene-carboxaldehyde also participated in this deuteration well, giving rise to **2y**, **2z**, and **2aa** with 67–72% yields. Notably, cheap terephthalaldehyde could be transformed to the corresponding expensive benzene-1,4-*d*<sub>2</sub> (**2bb**) in 35% yield with >95% deuterium incorporation. This deuterated method could also be used for the late-stage functionalization of aldehydes derived from natural products or pharmaceuticals. For example, estrone derived aldehyde could be selectively deuterated to furnish **2cc** in 54% yield.

Scheme 3. Substrates Scope of Rh-Catalyzed Decarbonylative Deuteration of Aldehydes

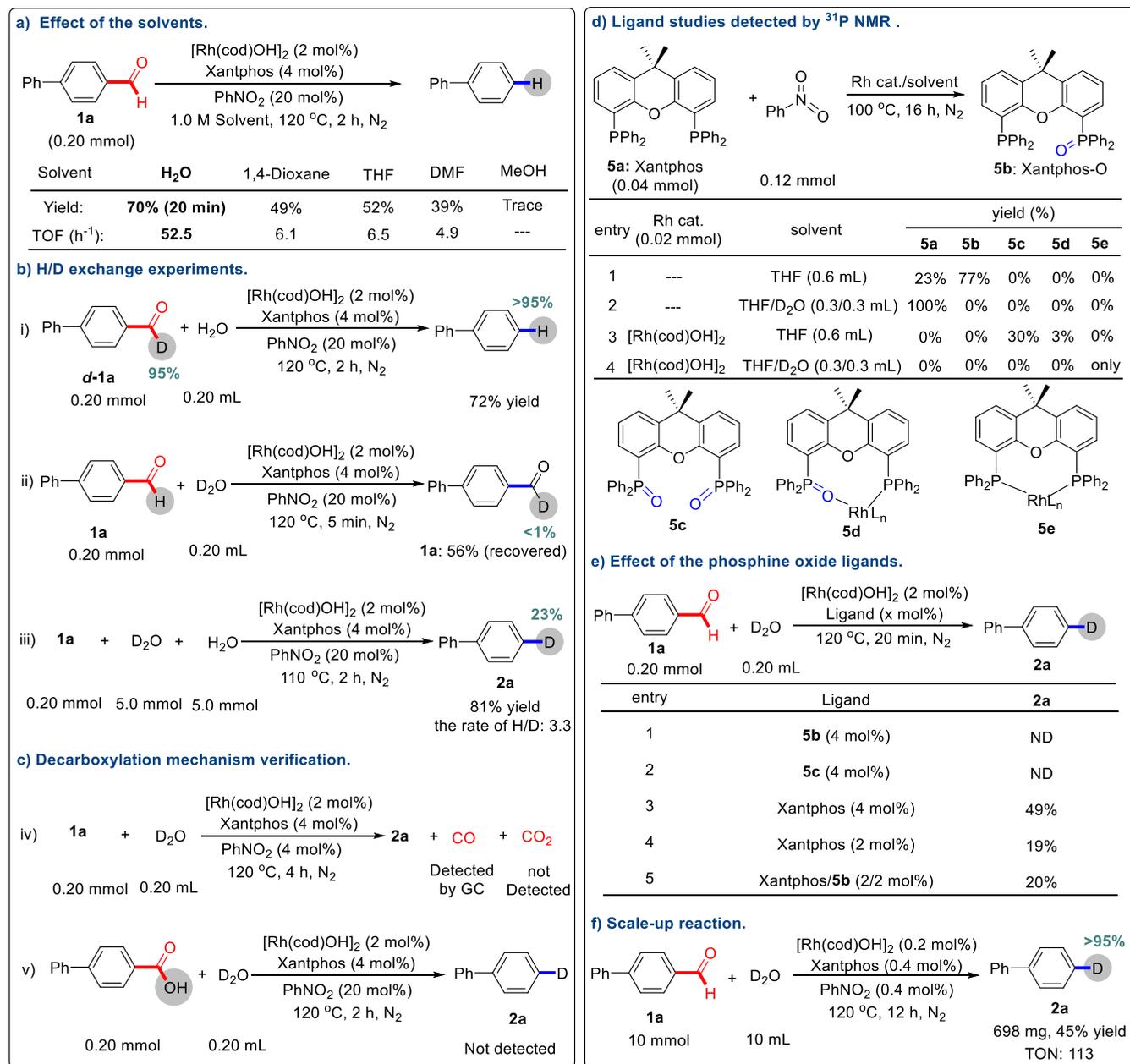


<sup>a</sup>Conditions are as follows: 1 or 3 (0.20 mmol, 1.0 equiv), [Rh(cod)(OH)]<sub>2</sub> (2 mol %), Xantphos (4 mol %), PhNO<sub>2</sub> (20 mol %), D<sub>2</sub>O (1.0 M), 120 °C, 8 h, N<sub>2</sub> atmosphere. Isolated yield was given. Deuterium incorporation was determined by <sup>1</sup>H NMR spectroscopy. <sup>b</sup>Aldehyde (0.40 mmol). <sup>c</sup>D<sub>2</sub>O (0.4 M), PhNO<sub>2</sub> (4 mol %), 16 h. <sup>d</sup>Yield was determined by GC-FID with mesitylene as the internal standard. <sup>e</sup>Without PhNO<sub>2</sub>. <sup>f</sup>3-NO<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>CO<sub>2</sub>H (4 mol %) was used as additives. <sup>g</sup>Aldehyde (0.10 mmol). <sup>h</sup>H<sub>2</sub>O (1.0 M), 90 min.

It is noteworthy that aliphatic aldehyde (3a) could also undergo decarbonylative deuteration with 47% and 169% D-

incorporation. A super incorporation of deuterium (223% D, 4b) was observed for alkyl-substituted aldehyde 3b. This is

## Scheme 4. Control Experiments and Mechanistic Studies



probably due to Rh-catalyzed H/D exchanges of the starting material **3b** rather than that of the product **4b** (Scheme S3 in SI).

Tertiary aldehydes, such as *N*-Boc-*L*-phenylalaninal (**3c**), gave no desired decarbonylative deuteration product. One of the most significant synthetic challenges for current deuterated methods was the precise construction of monodeuterium substituted alkenes.<sup>27</sup> In this respect, we were particularly interested in decarbonylative deuteration of  $\alpha,\beta$ -unsaturated aldehydes. Delightfully, styrene- $\alpha,\beta,\beta$ -*d*<sub>3</sub> (**4d**) was obtained with 45% yield from  $\alpha$ -deuterocinnamaldehyde (**3d**).<sup>28</sup> This unexpected  $\alpha$ -deuterium incorporation probably resulted from a reversible H/D exchange of styrene under Rh catalysis.<sup>29</sup> Gratifyingly, several deuterated alkenes could successfully be obtained with excellent deuterium incorporation (**4e–4h**), highlighting the potential utility of this protocol. Only small amounts of desired decarbonylation products (**4i–4k**) were

obtained for the aliphatic aldehydes bearing  $\beta$ -H. Probably due to the  $\beta$ -H elimination issues of alkyl-Rh intermediate,<sup>2,3a</sup> the corresponding alkenes were more easily produced (**3i–3k**). This Rh-catalyzed decarbonylation can serve as a powerful and general strategy for the selective decarbonylation of aryl-, alkyne-aldehydes (**1dd** and **3l–3n**) within 90 min.

To gain insight into the D<sub>2</sub>O/H<sub>2</sub>O induced Rh-catalyzed decarbonylation, preliminary mechanistic investigations have been conducted (Scheme 4). First, with H<sub>2</sub>O as the solvent, diphenyl was formed in 70% yield with TOF 52.5 h<sup>-1</sup>. The use of other organic solvents such as 1,4-dioxane, THF, DMF, and MeOH displayed a lower TOF (Scheme 4a). Performing the reaction with formyl deuterated aldehydes delivered the product in 72% yield, which indicated that D/H exchange was also a feasible pathway. No deuterium incorporation on formyl group was observed from the recovery of starting material **1a**. It excludes the possibility of direct D/H exchange

between aldehyde **1a** and  $D_2O$ . Next, when the decarbonylation was carried out in a mixture of  $H_2O$  and  $D_2O$ , the ratio for the formation rate of normal and deuterated products was 3.3/1, which indicated that a C–H bond cleavage or formation step is probably the rate-determining step (Scheme 4b). Furthermore, only CO was detected through the analysis of the gas phase component of the reaction mixture by GC (Scheme 4c). The inertness of *p*-phenylbenzoic acid under standard conditions rules out a decarboxylative reaction pathway (Scheme 4c).<sup>20a,30</sup> An unexpected ligand oxidation phenomenon has been observed during the characterization of active Rh species for this deuterated Tsuji–Wilkinson decarbonylation (Scheme 4d). First, monophosphine oxidized Xantphos **5b** could be selectively obtained in 77% yield under  $PhNO_2/THF$  conditions. Interestingly, **5b** or **5c** was not formed in the presence of  $D_2O$  (entry 2). The addition of  $[Rh(cod)OH]_2$  could promote the bisoxidation of Xantphos (entry 3). It was also found that  $D_2O$  could inhibit the oxidation of Xantphos (entry 4). To further confirm whether the mono-O-Xantphos **5b** or bis-O-Xantphos **5c** was the hidden ligand for this reaction, corresponding control experiments on the ligand were performed (Scheme 4e). It was found that this reaction could only occur when Xantphos acted as a ligand. Oxidized phosphine ligands **5b** and **5c** could not promote this reaction at all. It also suggests  $PhNO_2$  should not be added too much owing to the potential consumption of Xantphos through oxidation. To demonstrate the scalability and efficiency of this methodology, a scale-up reaction has been performed with a low catalyst loading (0.2 mol %  $[Rh(cod)OH]_2$ ) to afford 0.698 g of **2a** (Scheme 4f). It represents the best TON (113) for decarbonylation of aldehydes under  $\leq 120$  °C conditions.<sup>18a,c–f,24</sup>

Based on the above results and literature precedents on decarbonylative reactions,<sup>31</sup> a possible catalytic cycle is shown in Scheme 5. Initially, a ligand exchange between  $Rh-OH$  **A** with  $D_2O$  generates  $Rh^I-OD$  species **B** which undergoes a subsequent oxidative addition with aldehyde **1** to yield  $Rh^{III}-H$  species **C**. This high-valent rhodium species **C** can be more easily formed and stabilized with water via dispersing the

accumulative charge of rhodium complex. Meanwhile,  $Rh^{III}-H$  **C** converts into  $Rh^{III}-D$  complex **D** via H/D exchange in  $D_2O$ . The presence of the OD group on  $Rh^{III}-H$  complex **C** could promote the desired ligand exchange (H to D) through the formation of hydrogen bonding via transition state  $TS_1$  or  $TS_2$ . The positive effect of the addition of  $PhNO_2$  could probably result from its ability on the facilitating this ligand exchange through different hydrogen bonding. Acyl-Rh **D** undergoes ligand dissociation to give  $Rh(III)$  species **E** with a vacant coordination site. This spared space is beneficial for the reinsertion of carbon monoxide to give  $Rh^{III}$ -complex **F**. Finally, a reductive elimination produces the deuterated decarbonylation product **2** and regenerates Rh catalyst **B**. Based on the observed high deuterium incorporation and dramatic kinetic isotope effect (KIE, Scheme 4b), it suggests the final reductive elimination might be the rate-determining step.

In summary, an efficient Rh-catalyzed deuterated Tsuji–Wilkinson decarbonylation reaction between  $D_2O$  and naturally available aldehydes has been achieved under relatively mild conditions. This protocol showed a broad scope and good to excellent deuterium incorporation.  $D_2O$  not only acts as a deuterated reagent and solvent but also promotes Rh-catalyzed decarbonylation via dispersing the accumulative charge of high-valent rhodium species. This decarbonylation deuteration can provide an opportunity to conveniently obtain numerous previously poorly available deuterated compounds from inexpensive aldehydes. It is believed that this bifunctional strategy could become a complementary approach to the traditional Tsuji–Wilkinson decarbonylation and may be of great interest to the chemists in both academia and industry.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.2c04422>.

Experimental procedures, characterization data, and NMR spectra (PDF)

## ■ AUTHOR INFORMATION

### Corresponding Author

Qing-An Chen – Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China; University of Chinese Academy of Sciences, Beijing 100049, China; [orcid.org/0000-0002-9129-2656](https://orcid.org/0000-0002-9129-2656); Email: [qachen@dicp.ac.cn](mailto:qachen@dicp.ac.cn)

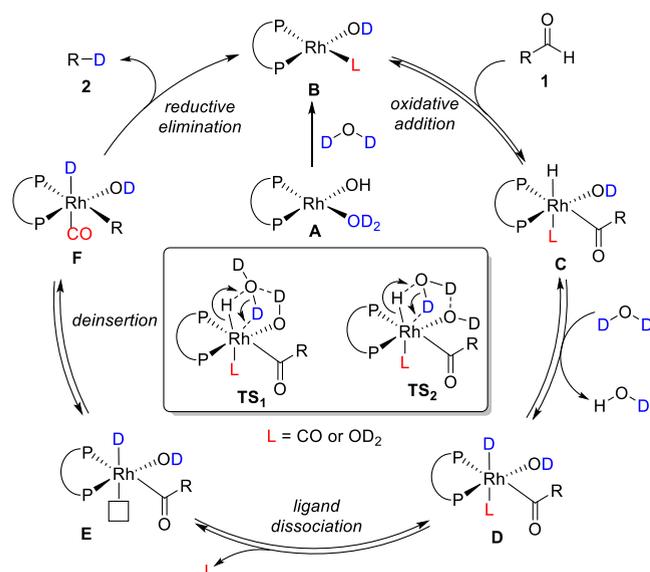
### Authors

Xiang-Ting Min – Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China  
Yong-Kang Mei – Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China; University of Chinese Academy of Sciences, Beijing 100049, China

Bing-Zhi Chen – Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China; University of Chinese Academy of Sciences, Beijing 100049, China

Li-Bowen He – Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China; University of Chinese Academy of Sciences, Beijing 100049, China

**Scheme 5. Proposed Mechanism for Decarbonylative Deuteration**



Ting-Ting Song – Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China  
Ding-Wei Ji – Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China  
Yan-Cheng Hu – Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China; [orcid.org/0000-0002-8731-4445](https://orcid.org/0000-0002-8731-4445)  
Boshun Wan – Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China; [orcid.org/0000-0002-7001-6214](https://orcid.org/0000-0002-7001-6214)

Complete contact information is available at:  
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## Notes

The authors declare no competing financial interest.

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