# ORGANOMETALLICS

## Harnessing the Reactivity of Iridium Hydrides by Air: Iridium-Catalyzed Oxidation of Aldehydes to Acids in Water

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**Supporting Information** 

**ABSTRACT:** An iridium-catalyzed oxidation of aldehydes to acids was realized by using air as the oxidant and water as the solvent in the presence of base. Interestingly, the same type of catalysts were also used for the reduction of aldehydes under acidic conditions. A common iridium hydride intermediate is proposed for both redox reactions. The oxidation has a number of advantages such as high yields, great functionality tolerance, and easy purification without chromatography.

xidation of aldehydes to carboxylic acids represents one of the most fundamental reactions in academic laboratories,<sup>1</sup> industrial productions,<sup>2</sup> and biomimetic studies.<sup>3</sup> Numerous reagents and methods have been developed for this useful transformation. Traditionally, Cr(IV)-,<sup>4</sup> Mn(VII)-,<sup>5</sup> Ag(I)-,<sup>6</sup> and Cu(I)-based reagents<sup>7</sup> produce copious amount of transition metal pollutants. Metal-free oxidants such as hypochlorites,<sup>8</sup> chlorites,<sup>9</sup> hydrogen peroxide,<sup>10</sup> *tert*-butyl hydroperoxide,<sup>11</sup> and oxone,<sup>12</sup> in combination with numerous catalysts or stoichiometric additives, have been also used to oxidize aldehvdes to acids. However, oxidation of aldehvdes with ultimate green oxidant molecular oxygen or even air, especially the latter, in water represents the most ideal solution.<sup>13</sup> To date, most methods for the aerobic oxidation of aldehydes to acids were performed in organic solvents.<sup>14</sup> Recently, Li and his co-workers developed elegant catalytic systems that could promote aerobic oxidation of aldehydes to acids in water by using molecular oxygen as the oxidant.<sup>1</sup>

In our recent studies, we found that iridium hydride A-H generated from formic acid<sup>16</sup> could be successfully trapped by aldehydes to afford alcohols in excellent yields in water (Scheme 1a).<sup>17</sup> Accidentally, we also found that benzoic acids were formed from benzaldehydes under reduction conditions when the reaction was run under air (Scheme 1b). Initially, benzaldehyde 1a was mixed with excessive formic acid and 0.1 mol % of catalyst A1 in water at 80 °C in an open flask for its reduction. Among the screened catalysts (for details, see Supporting Information), we were surprised to find that A1 showed good activity toward the aerobic oxidation of benzaldehydes. On a 10 mmol scale at 0.1 mol % catalyst loading, the oxidation was completed within 10 min (Scheme 1b, condition i). After decreasing the catalyst loading to 0.01 mol %, it took 6.5 h to complete the oxidation (Scheme 1b, condition ii).



Scheme 1. Redox Reactivity of Iridium Hydrides for the Reduction and Oxidation of Aldehydes



However, the optimal conditions (Scheme 1b, condition i) were only applicable to benzaldehyde substrate. For other aldehydes, the alcohol reduction products were formed exclusively (see Supporting Information). It is necessary to reoptimize the conditions for other substrates. In Li's recent work on Ag(I)- and Cu(II)-catalyzed aerobic oxidation of aldehydes with molecular oxygen (1 atm) in water,<sup>15</sup> metal hydrides (L<sub>n</sub>AgH and L<sub>n</sub>CuH, L = ligand) were proposed as key intermediates. Therefore, we envisioned that iridium hydrides (A–H) could be generated under similar conditions and oxidized to iridium hydroperoxide intermediate [L-IrOOH]<sup>+</sup> by molecular oxygen,<sup>18</sup> which could then facilitate the aerobic oxidation of aldehydes (Scheme 1c).<sup>19</sup>

Piperinal 1b was selected as the model substrate to further optimize the oxidation conditions (for more details, see



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Supporting Information). Different iridium catalysts A1–A13<sup>17</sup> were screened in aqueous sodium hydroxide solution at 80 °C. Catalysts A1–A3 gave piperonyl acid 2b in 48, 29, and 21% yields, together with reduction product 3b in 8, 5, and 5% yields, respectively (Table 1, entries 1–3). The introduction of





3	A3	21	5	74		
4	A4	14	0	86		
5	A5	37	0	63		
6	A6	26	0	74		
7	A7	15	4	81		
8	A8	21	1	78		
9	A9	7	4	89		
10	A10	4	<1	96		
11	A11	28	20	52		
12	A12	34	22	44		
13	A13	55	41	4		
Variation of Temperature and Catalyst Loading <sup>c</sup>						
14 <sup>d</sup>	A5	80 $(78)^{e}$	0	20		
15 <sup>f</sup>	A5	76	5	19		
16 <sup>g</sup>	A5	53	14	33		

<sup>*a*</sup>The yields were obtained by <sup>1</sup>H NMR analysis of the reaction mixture after acidification with HCl (2 mol/L) and extraction with ethyl acetate. <sup>*b*</sup>Conditions: **1b** (0.5 mmol), catalysts **A** (1 mol %), NaOH (0.5 mmol), water (1 mL), 80 °C, 7 h, air. <sup>*c*</sup>Conditions: **1b** (0.25 mmol), **A5** (2 mol %), NaOH (0.25 mmol), water (2 mL), 12 h, air. <sup>*d*</sup>At 80 °C. <sup>*e*</sup>Isolated yields. <sup>*f*</sup>At 60 °C. <sup>*g*</sup>Room temperature.

an N-methyl group at the 4,5-dihydro-1*H*-imidazole moiety (A4), or modification of the pyridine component at 6-positions with methoxy (A5) and methyl (A6) suppressed the reduction, and the desired acid was exclusively generated in 14, 37, and 26% yields, respectively (entries 4–6). Using catalyst A7 with 2,2'-biimidazole ligand and A8 with 1,1'-dimethyl-2,2'-biimidazole ligand, 2b was produced in 15 and 21% yields, respectively, together with a trace amount of 3b in both cases (entries 7 and 8). Catalysts derived from 2,2'-bypridine (A9) or 1,10-phenanthroline (A10) did not behave well in the aerobic oxidation (entries 9 and 10). Although catalysts A11–A13, bearing ethylenediamine-type ligands, produced acid 2b in 28,

34, and 55% yields, byproduct **3b** was also formed in 20, 22, and 41% yields, respectively (entries 11-13). It appeared that **A5** gave the best chemoselectivity for aerobic oxidation (entry 5). It was then employed for further optimization. Increasing the amount of water to 2 mL and the catalyst loading to 2 mol %, as well as prolonging the time to 12 h gave the highest yield of **2b** (80%, entry 14). Interestingly, decreasing the temperature promoted the formation of reduction product **3b** (entries 15 and 16).

A series of structurally diverse aldehydes were submitted to the optimal conditions, and the results were summarized in Table 2. We note that no column chromatography purification





<sup>*a*</sup>Isolated yields without column chromatography.

is needed for purification. In addition to 1a and 1b, aldehyde 1c also underwent aerobic oxidation to afford 97% yield of product (entry 3). Alkyl substituted benzaldehydes were also converted to carboxylic acids in high yields (entries 4 and 5). However, 2,4,6-trimethylbenzaldehyde (1f) was reluctant to the oxidation, giving acid 2f in only 30% yield, presumably because of the large steric hindrance of the 2,6-dimethyl groups (entry 6). The halogen atoms on aromatic rings remained intact during the aerobic oxidation, as demonstrated by substrates 1g-11. These aldehydes were oxidized into the corresponding acids in 72–98% yields (entries 7–12). The acetyl group in 1m was not affected (entries 13). Electron-deficient aldehydes such as 1n and 10 produced acids 2n and 20 in 92 and 97% yields,

respectively (entries 14 and 15). Other aromatic aldehydes 1p, 1q, and 1r were readily oxidized into the corresponding acids (entries 16–18). The C=C double bond of  $\alpha,\beta$ -unsaturated (*R*)-myrtenal (1s) could be tolerated during oxidation (entry 19). Aliphatic acids 2t, 2u, and 2v were obtained in 81, 95, and 77% yields, respectively, from the corresponding aldehydes (entries 20–22). Ketones such as acetophenones are inert toward aerobic oxidation under the reaction conditions.

In a gram-scale aerobic oxidation, 1.06 g of benzaldehyde (1a) was converted into benzoic acid (2a) in 99% yield with lower 0.1 mol % of A5 after heating at 80 °C for 24 h (Scheme 2). To understand the aerobic oxidation mechanism, three

Scheme 2. Gram-Scale Synthesis of Benzol
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<b>0.1 mol% A5</b> , NaOH (1 equiv.)						
Ph-CHO -		Ph-COOH				
<b>1a</b> , 10 mmol,	water (10 mL), air, 80 <sup>o</sup> C, 24 h	<b>2a,</b> 1.22 g,				
1.06 g		99%				

Scheme 3. Evidence for the Formation of Iridium Hydride Intermediates



experiments were conducted for 1b (Scheme 3, top), and neither acid 2b nor alcohol 3b was observed in all cases. The absence of catalyst indicates that acid 2b in Table 1 was not generated by the autoxidation of aldehydes; alcohol 3b was not generated by the Canizarro reaction of 1b under basic conditions. The presence of sodium hydroxide and air is also essential.

The formation of alcohol **3b** in Table 1 indicates the formation of iridium hydrides during the reaction. Iridium hydrides are highly reductive species and have been involved in transfer hydrogenation<sup>20</sup> and borrowing hydrogen processes,<sup>21</sup> but rarely found in the aerobic oxidation. To further confirm its formation, we selected terephthalaldehyde (**1w**) as the substrate (Scheme 3, bottom). One aldehyde group of **1w** was anticipated as hydride donor, and the other as hydride acceptor. As we expected, the reaction of **1w** delivered the hydride-trapped 4-hydroxymethylbenzoic acid **2wa** in 56% yield, demonstrating the formation of iridium hydride species in the aerobic oxidation.

The plausible mechanism is proposed in Figure 1. First, iridium chloride **A** reacts with hydroxide anions to give iridium hydroxides **B** as the active catalyst, which undergoes formal hydroxyiridation across the C=O bond of aldehydes 1 via transition state **C** to deliver intermediate **D**. Subsequent  $\beta$ -H elimination of **D** produces carboxylic acid **2** and iridium hydride **E**. Given that iridium hydride **E** is highly reductive, it reduces aldehydes to alcohols in some cases (Table 1, entries 1–3, 15,



Figure 1. Proposed catalytic mechanism for the iridium-catalyzed aerobic oxidation of aldehydes.

16; Scheme 3, bottom equation); however, it is oxidized by oxygen to form iridium hydroperoxide  $\mathbf{F}$ .<sup>18</sup> On the basis of Rauchfuss's report,<sup>18</sup> the reaction between hydroperoxide  $\mathbf{F}$  and hydride  $\mathbf{E}$  regenerated active catalyst  $\mathbf{B}$ . The overall mechanism is quite different from those proposed by Li and co-workers in their Ag(I)- and Cu(II)-catalyzed aerobic oxidations using molecular oxygen.<sup>15a,b</sup> The difference lies in the regeneration mode of active catalysts. One unique feature of our aerobic oxidation is the unexpected involvement of highly reductive iridium hydrides. In addition, the chemoselectivity is dependent on the ligands (Table 1, entries 1–13) and further affected by reaction temperature (Table 1, entries 14–16).

A similar iridium complex,  $[Cp*Ir(bpy)OH_2][OTf]_2$ , has been used to catalyze the conversion of aldehydes to carboxylic acids (aldehyde–water shift).<sup>22</sup> Both aldehyde–water shift and aerobic oxidation involve iridium hydrides. However, the hydrides in the former react with protons to release hydrogen, while those in the latter capture oxygen to give iridium hydroxides. Our work demonstrates that aerobic oxidation can also be a convenient alternative to realize such a transformation.

In conclusion, by harnessing the reactivity of iridium hydrides by air, we developed an efficient iridium-catalyzed method to oxidize aldehydes to carboxylic acids using air as the oxidant and water as the solvent. Both aromatic and aliphatic aldehydes could be oxidized in good to excellent yields with great functional group tolerance. In addition, column chromatography is not necessary for the purification of products. Interestingly, the aerobic oxidation involves highly reductive iridium hydrides species.

#### ASSOCIATED CONTENT

#### **S** Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organo-met.7b00634.

Further reaction condition optimizations, detailed experimental procedures, copies of <sup>1</sup>H NMR spectra of the reaction mixture, and <sup>1</sup>H and <sup>13</sup>C NMR spectra of products (PDF)

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#### Notes

The authors declare no competing financial interest.

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