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Iridium-catalyzed highly efficient chemoselective reduction of aldehydes in water using formic acid as the hydrogen source[†]

Zhanhui Yang, (¹)^{‡^{a,b}} Zhongpeng Zhu, ^{‡a,c} Renshi Luo,^{a,d} Xiang Qiu,^a Ji-tian Liu,^a Jing-Kui Yang (¹)^c and Weiping Tang (¹)^{*a,e}

A water-soluble highly efficient iridium catalyst is developed for the chemoselective reduction of aldehydes to alcohols in water. The reduction uses formic acid as the traceless reducing agent and water as a solvent. It can be carried out in air without the need for inert atmosphere protection. The products can be purified by simple extraction without any column chromatography. The catalyst loading can be as low as 0.005 mol% and the turn-over frequency (TOF) is as high as 73 800 mol mol⁻¹ h⁻¹. A wide variety of functional groups, such as electron-rich or deficient (hetero)arenes and alkenes, alkyloxy groups, halogens, phenols, ketones, esters, carboxylic acids, cyano, and nitro groups, are all well tolerated, indicating excellent chemoselectivity.

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Introduction

The reduction of aldehydes to alcohols is a fundamentally important reaction in organic chemistry. For example, hydroformylation of alkenes followed by aldehyde reduction constitutes one of the most important industrial processes for the manufacture of alcohols.¹ Different strategies have been developed for the reduction of aldehydes to alcohols, such as electron-transfer reduction,² reduction with metal hydrides such as NaBH₄ and LiAlH₄,³ transition-metal catalysed hydrogenation,⁴ and transfer hydrogenation (TH).⁵ Among them, transition metal-catalysed hydrogenation is the most atomeconomical and cleanest reduction method. However, it generally requires a high pressure of hydrogen gas, which causes safety issues. The TH has the potential to become an ideal green method for reduction. Various reducing agents for the transition metal-catalysed TH reduction of aldehydes under neutral or basic conditions in organic solvents have been developed, such as iso-propanol,⁶ 1,4-butanediol,⁷ hydrosilane⁸ and ammonium formate⁹ (Scheme 1a). However, an operationally simple and green reduction method that works for chemists in both academia and industry is still highly desirable.¹⁰ For example, organic solvents are employed in most of the above processes and water would be a more ideal solvent for TH.¹⁰ The waste generated from hydrogen donors can be further reduced. Being able to conduct the reactions in air and



Scheme 1 Reduction of aldehydes to alcohols by transfer hydrogen (TH) reactions.

^aSchool of Pharmacy, University of Wisconsin–Madison, Madison, WI, 53705, USA. E-mail: weiping.tang@wisc.edu

^bFaculty of Science, Beijing University of Chemical Technology, Beijing, 100029, P. R. China

^cSchool of Chemistry and Chemical Engineering, University of Chinese Academy of Sciences, Beijing, P. R. China

^dSchool of Pharmacy, Gannan Medical University, Ganzhou, Jiangxi Province, P. R. China

^eDepartment of Chemistry, University of Wisconsin–Madison, Madison, WI, 53706, USA

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without complex purification procedures will deliver a greener procedure.

In 2000, Bryson reported an aqueous TH reduction of aldehydes with sodium formate at high temperature and high pressure in low to moderate yields (Scheme 1b).¹¹ In 2004, Ajjou realized a Rh-catalyzed aqueous TH of aldehydes with isopropanol as a hydrogen donor and 0.2 equivalents of sodium carbonate as an additive under a nitrogen atmosphere (Scheme 1c).¹² A breakthrough was made in 2006 by Xiao and co-workers by using iridium catalysts (**Ir-1** or **Ir-2**) with *N*-sulfonyl ethylenediamine as the ligand (Scheme 1d).¹³ In their work, the aldehydes were reduced in high efficiency (TOF of up to 50 000 mol mol⁻¹ h⁻¹) in water and in air under neutral conditions by using 5 equivalents of sodium formate as the hydrogen source. Imperfectly, the use of sodium formate generates sodium bicarbonate salt as the waste.

We envision that if sodium formate can be replaced by formic acid while retaining other advantages, it will yield a greener procedure since formic acid is a traceless reducing agent and no waste will be left in the reaction system after the reduction. The development of a new catalyst is then necessary because the activity of existing catalysts is decreased under acidic conditions as noted by Xiao and co-workers.¹³ Numerous catalysts have been developed for the decomposition of formic acid to hydrogen and carbon dioxide.¹⁴ The decomposition mechanism involves the generation of an iridium hydride intermediate,¹⁴ which may be trapped by aldehydes before forming hydrogen gas. Herein, we report that a greener reduction of aldehydes in air and water under acidic conditions can be realized by employing novel catalysts Ir-3 or Ir-4 and formic acid as the hydrogen source (Scheme 1e). The reduction with Ir-4 features not only high efficiency (TOF of up to 73 800 mol mol⁻¹ h⁻¹) and low catalyst loading (0.005 mol%), but also the minimal production of waste and excellent chemoselectivity.

Results and discussion

The reaction conditions were optimized by using 4-methoxybenzaldehyde 1a as the model substrate. Catalyst screening was first performed at a 0.02 mol% level with 4 equivalents of formic acid at 80 °C. Although catalysts (Ir-1 and Ir-2) were very effective under neutral conditions,¹³ they gave low conversions under the current acidic conditions (pH = 2.2) (Table 1, entries 1 and 2). In contrast, 4-substituted pyridyl catalysts Ir-3, Ir-4, Ir-5, and Ir-6 showed excellent activity toward the reduction, and complete conversion was obtained in less than 15 min (entries 3-6). 6-Substituted pyridyl catalysts Ir-7 and Ir-8 showed different activities; the former only needs 10 min while the latter requires 60 min to promote the reaction to completion (entries 7 and 8). The bipyridyl-based catalyst Ir-9 and phenanthroline-based catalyst Ir-10 exhibited poor activity (entries 9 and 10). Lowering the amount of formic acid to two equivalents and decreasing the catalyst loading to 0.01 mol% only slightly decelerated the reaction rates (entries 11 and 12). At 0.005 mol% catalyst loading, it took 120 min to obtain 58%

Table 1 Optimization of reaction conditions



Entry	[Ir]	x	Conv. ^{<i>a</i>} (%)	Time ^b (min)	$\begin{array}{c} \text{TOF} \\ (\text{mol mol}^{-1} \text{ h}^{-1}) \end{array}$
1	Ir-1	4	4.3	120	107
2	Ir-2	4	2.9	120	73
3	Ir-3	4	100	10	30 000
4	Ir-4	4	100	8	37 500
5	Ir-5	4	100	15	20 000
6	Ir-6	4	100	15	20 000
7	Ir-7	4	100	10	30 000
8	Ir-8	4	100	60	5000
9	Ir-9	4	7.4	120	185
10	Ir-10	4	5.7	120	143
11	Ir-4	2	100	12	25 000
12^{c}	Ir-4	4	100	25	12 000
13^d	Ir-4	4	58	120	1450
14^e	Ir-4	4	100	15	20 000

^{*a*} The conversions in entries 1, 2, 9, 10 and 13 were determined by ¹H NMR of the crude reaction mixture, while the rest were estimated by TLC. ^{*b*} The reactions were detected by TLC every 1 min within 10 min, every 5 min after 10 min, every 10 min after 0.5 h, and every 30 min after 1 h. ^{*c*} The catalyst loading was 0.01 mol%. ^{*d*} The catalyst loading was 0.005 mol%. ^{*e*} The temperature was 60 °C.

conversion (entry 13). Lowering the temperature to 60 °C also decelerates the rate of the reaction (entry 14). The optimal conditions are listed in entry 4. Notably, all catalysts from **Ir-3** to **Ir-10** are well soluble in water.

As presented in Fig. 1, the catalytic activity is closely associated with the pH values of the aqueous solution. Under acidic conditions (pH < 4), the catalyst showed higher activity (TOF > $25\,000$ mol mol⁻¹ h⁻¹), and the highest activity (TOF = $30\,000$ h⁻¹) was obtained when pH = 3.0. The catalytic activity decreased significantly as the pH increases from 4.0. We also compared our catalyst **Ir-4** with previously reported catalyst **Ir-2** at different pH values. It is clear that **Ir-4** excelled **Ir-2** under more acidic conditions (pH < 5.0), while **Ir-2** showed higher TOF under weakly acidic, neutral or basic conditions (pH > 5).

We also evaluated the catalyst reactivity with time and the highest TOF value was recorded as 73 800 mol mol^{-1} h⁻¹ after 2 min (Table 2).

A number of structurally diverse aldehydes were examined under optimal conditions (Table 3). In most cases they were



Fig. 1 Activity comparison between our catalyst (**Ir-4**, a) and known catalyst (**Ir-2**, b). (a) The TOF against the initial solution pH values in the complete reduction: *p*-methoxybenzaldehyde (2 mmol), **Ir-4** catalyst (0.02 mol%), HCOOH (4 equiv.), water (2 mL), 60 °C. The initial pH value was determined by varying the HCOOH/NaOH molar ratios. (b) See ref. 13.

Table 2	2 TO	F against	reaction	time ^a
Table 1	2 10	i agamso	reaction	unic

Time (min)	1	2	4	6
Conversion ^{b} (%)	21.9	49.2	87.1	99.4
TOF (mol mol ^{-1} h ^{-1})	63 500	73 800	65 325	49500

^{*a*} The reduction of *p*-methoxybenzaldehyde (2 mmol) with **Ir-4** catalyst (0.02 mol%) and HCOOH (4 equiv.) in water (2 mL) at 80 °C. ^{*b*} Determined by ¹H NMR of the crude reaction mixture.

reduced to alcohols in excellent yields (91–99%) within 30 min. Upon completion, simple extraction with a greenchemistry-preferred solvent such as ethyl acetate^{10d,g} followed by concentration under vacuum delivered pure alcohol products. Column chromatography is not necessary for purification. Moreover, the reduction displayed very high efficiency and functionality tolerance.

In addition to 4-methoxybenzaldehyde (1a), other electronrich aldehydes such as 4-hexyloxybenzaldehyde (1b), 4-allyloxybenzaldehyde (1c), 2,5-dimethoxybenzaldehyde (1d), and 2,4,6trimethoxy-benzaldehyde (1e), were readily reduced to the corresponding alcohols efficiently (entries 1-5). Notably, the allylic group in 2c and the very electron-rich phenyl rings in 2d and 2e survived from the reduction under acidic conditions. Benzaldehyde (1f) and its alkyl-substituted homologues (1g-1j) also underwent reduction readily and delivered excellent yields of alcohols (entries 6-9). It was notable that at 0.05 mol% catalyst loading, the reduction of benzaldehyde 1f was completed in only 2 min, with TOF as high as 60 000 mol mol⁻¹ h⁻¹ (entry 6). Halogen atoms were well tolerated, as demonstrated by high yields of the fluoro-, bromo-, and chloro-substituted aromatic alcohols (2j-2m, entries 10-13). For the reaction of 3-cyanobenzaldehyde, the cyano group remained intact in 2n (entry 14). No product derived from the reduction or hydrolysis of the cyano group was detected. The two carbonyl groups in 1,4-phthalaldehyde (10) were reduced





^{*a*} The reactions were detected by TLC every 5 min within 0.5 h, every 10 min after 0.5 h, and every 30 min after 1 h. ^{*b*} Isolated yields by extracting with ethyl acetate, drying over Na₂SO₄, and concentrating under vacuum. ^{*c*} 1.5 mL of water and 0.5 mL of ethanol were used as solvents. ^{*d*} Catalyst loading at 0.05 mol%.

simultaneously (entry 15), while only the aldehyde carbonyl group of 4-acetylbenzaldehyde (1**p**) was reduced (entry 16), demonstrating excellent chemoselectivity. Although it was reported that the ketone groups could be reduced under similar iridium-catalyzed hydrogen transfer reduction,¹⁵ we are glad that the ketone moiety of 2**p** was not affected under our conditions (entry 16). The ester group in aldehyde 1**q**

(entry 17), the nitro groups in aldehydes **1r** and **1s** (entries 18 and 19), and the trifluoromethyl group in **1t** (entry 20) were immune to the reduction. Fused aryl aldehyde **1u** (entry 21) and heteroaryl aldehydes **1v**, **1w** and **1x** (entries 22–24) also underwent the reduction to yield the desired products in more than 95% yields. The electron-deficient C=C double bonds in cinnamaldehydes **1y** and **1z** (entries 25 and 26) remained untouched during the reduction, indicating the highly chemoselective reduction of aldehyde groups.

By using Xiao's catalyst, the reduction of aldehydes containing acidic protons such as carboxylic acid 1ad (Table 4) was not successful.¹³ Xiao and co-workers did not report the reductions of 2-, 3-, or 4-hydroxybenzaldehydes under their conditions.¹³ When we tried to reduce aldehydes 1aa, 1ac, and 4-hydroxy benzaldehydes on a 1 mmol scale under their standard conditions (0.02 mol% Ir-2, 1 mL of deionized water, in air, 80 °C) for 1 h, no reduction products were detected by TLC. Similarly, under the same conditions, 2- and 3-carboxybenzaldehydes 1ae and 1af could not be reduced. Gratifyingly, by using our catalyst under acidic conditions, most of these aldehydes could be reduced to alcohols in high yields (Table 4). For instance, ortho- and meta-hydroxy benzaldehydes 1aa, 1ab and 1ac were readily reduced in excellent yields (entries 1-3). To our surprise, although 4-hydroxy benzaldehydes were completely consumed, only complex mixtures were obtained. More acidic para- and meta-carboxybenzaldehydes 1ad and 1ae also showed excellent reactivity toward the reduction (entries 4 and 5). ortho-Carboxybenzaldehyde 1af



^{*a*} The reactions were detected by TLC every 5 min within 0.5 h, every 10 min after 0.5 h, and every 30 min after 1 h. ^{*b*} Isolated yields by extracting with ethyl acetate, drying over Na_2SO_4 , and concentrating under vacuum. ^{*c*} 1.5 mL of water and 0.5 mL of ethanol were used as solvents.

was completely reduced within 10 minutes; however, reduced product **2af** and intramolecularly esterified product **3af** were both observed. Heating for additional 2 hours afforded **3af** exclusively in 91% isolated yield (entry 6).

Under Xiao's basic conditions, aliphatic aldehydes with acidic α -protons were prone to undergo aldol condensation. Therefore, their reduction was drastically inhibited. For example, under their standard conditions, octanal was reduced to only 3% yield after 18 h.¹³ Lowering the aldehyde concentration and slow addition of aldehydes were required to overcome the inhibition.¹³ In contrast, under our acidic conditions, aliphatic aldehvdes can be easily reduced. Alcohols 2ag-2ai were prepared in good to excellent yields (entries 7-9) in a short period of time. In addition, the reductions of aldehyde 1b (entry 2, Table 3) as well as 1ai (entry 9, Table 4) took a longer time than others, presumably because of their lower solubility in reaction media. The success of these two examples and those substrates bearing acidic protons also indicates that our reduction occurs on water, while Xiao's reduction appeared to occur in water.13

The current reduction can be easily scaled up. As shown in Scheme 2, 13.6 grams of 4-methoxybenzaldehyde (1a) are converted to (4-methoxyphenyl)methanol (2a) in >99% yields (13.8 g) at 0.005 mol% catalyst loading. Again, the product was obtained in high purity by simple extraction.







Fig. 2 Proposed catalytic mechanism.

The proposed mechanism for the reduction is shown in Fig. 2. The formate anion exchanged with the chloride ligand on iridium catalyst **Ir-4** to yield active catalyst **A**, which extruded carbon dioxide to give rise to iridium hydride **B**.¹⁴ Hydride **B** could be trapped by aldehydes **1**, possibly *via* transition state **C**, to deliver alkoxide **D**. Protonation then afforded alcohol **2** and the active catalyst **A** was regenerated. Hydride **B** could also be protonated to release hydrogen gas directly.¹⁴ Under our conditions, it appeared that the addition of Ir-hydride to aldehydes was preferred over direct protonation.

Kinetic studies from Himeda's^{14b-d} and Li's^{14e} groups and DFT calculations from Himeda's group^{14c,d} indicated that the formation of the iridium hydrides from formate anions was often a rate-determining step for the decomposition of formic acids. We have found that the rates of reductions are independent of the electronic properties of benzaldehydes. This suggests that the formation of iridium hydride is also the rate-determining step for the reduction of aldehydes.

Conclusions

We have developed an efficient iridium catalyst for the chemoselective reduction of aldehydes in water under acidic conditions. The reduction uses formic acid as the traceless reducing agent. It does not require inert atmosphere protection or purification by column chromatography, offering an operationally simple and green procedure. The catalyst efficiency is extremely high, and the instant TOF value can be as high as 73 800 mol mol⁻¹ h⁻¹. Of significance is the good tolerance of a wide variety of functional groups, such as electron-rich or deficient aryls and alkenes, alkyloxy groups, halogens, phenols, ketones, esters, carboxylic acids, cyano, and even nitro groups.

Experimental

General procedure for reduction of aldehydes

To a mixture of formic acid (0.30 mL, 8 mmol) and aldehydes (2 mmol) in deionized water (2 mL) at 80 °C was added the aqueous solution of catalyst **Ir-4** (80 μ L, 0.005 mol⁻¹ L). For poorly soluble aldehydes as indicated in Tables 3 and 4, 1.5 mL of water and 0.5 mL of ethanol were used. The resulting solution was stirred for the time indicated in Tables 3 and 4. When complete conversion of aldehydes was achieved as detected by TLC, water (10 mL) was added to dilute the mixture, followed by the addition of ethyl acetate (10 mL) to extract the alcohol products. Drying the organic phase over Na₂SO₄, filtration, and the removal of the solvent under vacuum gave the pure desired products in good yields.

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