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Cyclometalated iridium complexes for transfer hydrogenation of carbonyl groups in water†

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Cyclometalated iridium complexes are shown to be excellent catalysts for transfer hydrogenation of carbonyl compounds in water using formate as a hydrogen source. A wide range of ketones and aldehydes have been reduced at 0.05% catalyst loading with no need for any organic solvents. Solution pH is found to play a critical role, with acidic conditions needed for fast transfer hydrogenation.

Introduction

Catalysis in water is an important direction of green chemistry.[1] As a solvent for organic reactions, water bears a number of attractive physicochemical properties over traditional organic solvents. It is non-flammable, non-explosive, non-toxic and non-carcinogenic. Consequently its use can bring about significant gains in environmental, economic and safety terms. Unsurprisingly, a great number of aqueous phase catalytic reactions have been documented,[2,3] including transfer hydrogenation.[4,5]

Transfer hydrogenation has recently emerged as a powerful, practical and versatile tool for the reduction of carbonyl compounds.[6] The method is attractive as an alternative to hydrogenation because it requires neither the hazardous hydrogen gas nor pressure vessels, and it is easy to execute. Ever since the seminal work of Noyori, Ikariya and co-workers,[6b,7] a great number of catalysts have been reported, with vast majority of these catalysts featuring metal–ligand bifunctional abilities.[6b–i] Moreover, many of these catalysts have been shown to enable efficient transfer hydrogenation in water.[4,5] The aqueous reduction can be carried out with either unmodified or tailor-made catalysts, using mild, readily available formate salt as a reductant with no organic solvents required, thus providing a simple, economic and green pathway for alcohol production. Successful transfer hydrogenation catalysts lacking metal–ligand bifunctional ability are rare, however.[8] Recently, we discovered that cyclometalated iridium complexes are versatile catalysts for transfer hydrogenative reductive amination reactions.[9–12] These iridium catalysts have no metal–ligand bifunctionality but afford very fast imine reduction and highly chemoselective reductive amination of ketones, *i.e.* with little reduction of the carbonyl groups in reductive amination, providing a new class of transfer hydrogenation catalysts.[12] Herein, we disclose that, counter-intuitively, ketone reduction is also viable with these cyclometalated iridium catalysts, and the reduction can be easily conducted in neat water using cheap and safe formate as a hydrogen source, provided that the solution pH is controlled.

Results and discussion

In reductive amination, complex **1** showed very good activity and selectivity towards the C=N double bond using HCOOH as a hydrogen source in MeOH.[12a] Ketone reduction is very slow under these conditions. Our previous work[4] on aqueous ketone reduction has revealed that water can accelerate ketone reduction, and the solution pH has a dramatic effect on both the catalytic activity and enantioselectivity, when using the M-TsDPEN (M = Rh or Ir, TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine) type catalysts.[7] This effect of solution pH on transfer hydrogenation of ketones was also observed by Joò, Ogo, Himeda and co-workers.[5,13] We envisioned that transfer hydrogenation of ketones with the cyclometalated iridium complexes may also be feasible in water; but the reduction rate may vary with the solution pH.

Using formate as a reductant, we first investigated the reduction of acetophenone with precatalysts **1** and **2** in water. As is shown in Scheme 1, the hydrogenation does take place, even at a high S/C (substrate to catalyst) ratio of 2000, but only

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†Electronic supplementary information (ESI) available: Experimental procedures, characterization data, ^{1}H, ^{13}C, IR, and HMRS spectra. See DOI: 10.1039/c2gc36619c

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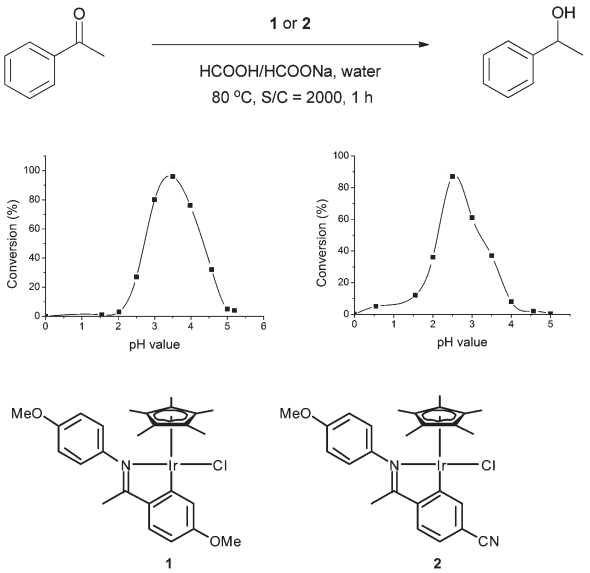
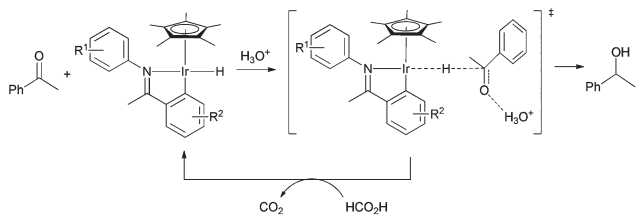


Scheme 1 Effect of solution pH on the transfer hydrogenation of acetophenone (5 mmol) with precatalysts **1** (left) and **2** (right) (0.0025 mmol) in aqueous HCOOH–HCOONa solution (4 mL) at 80 °C (1 h reaction time). The pH values were measured prior to the hydrogenation and the conversion was determined by GC. Further details are found in the ESI.†

under certain acidic conditions. The highest reaction rate was observed at pH 3.5 for the precatalyst **1** and pH 2.5 for **2**.[14] Deviating from these optimal pH values by *ca.* 1.5 units led to much lower conversion for both catalysts. These optimal values are quite distinct from those observed with the M-TsDPEN catalysts, which show best performance at neutral pH.[4c]

The difference in optimal solution pH between the two types of catalysts can be rationalized by the difference in catalyst structure and the related catalytic mechanism. With the M-TsDPEN type catalyst, the ketone substrate is activated *via* hydrogen bonding between the oxygen atom of the ketone and the proton from the acidic NH_2 group in the TsDPEN ligand.[7] As a result, no external activation is required, and the reaction performs best at around neutral conditions. However, with complexes **1** and **2**, no hydrogen bonding interaction can be formed between the ketone and the catalyst ligand. Ketone reduction presumably occurs *via* a pathway shown in Scheme 2, where the carbonyl group is activated through hydrogen bonding with hydroxonium ions. This type of interaction is expected to lower the LUMO energy of the ketone,



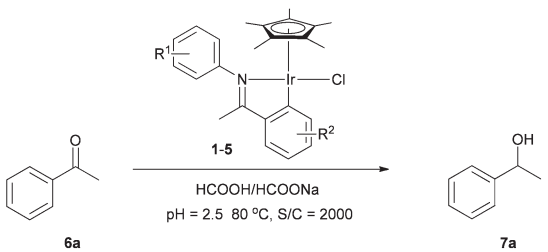
Scheme 2 Possible pathway for the transfer hydrogenation of ketones in water under acidic conditions.

rendering the hydride addition easier. Hence an acidic condition is necessary for the reduction to proceed. Activation of carbonyl groups by protons or hydrogen bond donors is well known,[5c,13,15] and a similar mechanism has been suggested by Ogo, Fukuzumi and co-workers for the $[Cp^*Ir(bpy)(OH_2)]^+$ catalysed transfer hydrogenation of ketones with HCOOH in water.[5c]

The variation of the hydrogenation rate with pH may stem from two competing reactions. Once the iridium hydride is formed from decarboxylation of foramte, it can react with either the ketone (Scheme 2) or protons from the reaction medium.[5c] At low pH values, the activation of ketones by hydrogen-bonding with hydroxonium ions leads to a high reduction rate.[15] However, the rate of the reaction of iridium hydride with proton is also expected to be fast at low pH values; this reduces the concentration of active catalytic species and so the hydrogenation rate. Hence, there should be an optimal pH value to balance the two competing reactions. Interestingly, precatalyst **1** bearing an electron donating methoxyl group and precatalyst **2** with an electron withdrawing cyano group require different pH values for achieving their best activities. The higher optimal pH value for **1** is likely to result from its higher hydricity conferred by the methoxyl group.

We also examined other precatalysts by varying the substituents on the imino ligand for the reduction of acetophenone. pH 2.5 was chosen instead of 3.5 for the reaction, as acidic conditions may allow for a wider substrate scope. The results obtained with all the catalysts are summarized in Table 1. At pH 2.5, complex **2** achieved 87% conversion in 1 h at an S/C ratio of 2000, while only 27% yield was obtained with complex **1**. By replacing the electron donating methoxyl group with hydrogen on the *N*-aryl ring, the catalytic activities of the corresponding iridium complexes increase slightly. Complex **3** with a ligand derived from aniline and 4-cyanoacetophenone provided a slightly higher conversion of 89%. As expected, electron rich groups on the ligand lead to lower conversions (Table 1, complexes **4** and **5**).

Table 1 Reduction of acetophenone with different catalysts[a]



Complex	R^1	R^2	Conversion[b] (%)
1	4-OMe	5-OMe	27
2	4-OMe	5-CN	87
3	H	5-CN	89
4	H	5-OMe	32
5	H	5-Me	17

[a] Reaction conditions: acetophenone (5 mmol), catalyst (0.0025 mmol), pH 2.5 aqueous HCOOH–HCOONa solution (4 mL), 80 °C, 1 h. [b] Determined by GC.

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With the optimised reaction conditions in hand, the substrate scope of the cyclometalated iridium complex-catalysed ketone reduction was examined with complex **3** at pH 2.5. The results are shown in Table 2. A range of aromatic ketones could be reduced with good to excellent isolated yields in 4–12 h (Table 2, entries 1–15). Substrates with *para*-electron donating substituents showed lower activities (Table 2, entry 2) than *para*-electron withdrawing substituents (Table 2, entries 4 and 5). However, the ketone with a *para*-cyano group showed relatively low activity, probably due to the coordination ability of the cyano group (Table 2, entry 6).[16] Similarly, *para*-halogen atoms on the phenyl ring render the substrates less reactive than acetophenone (Table 2, entries 7–9). *meta*- and *ortho*-Substituents afforded similar or slightly worse activity than *para*-substituents (Table 2, entries 10–14), while ketones with a naphthyl group showed good activity (Table 2, entry 15). Aliphatic ketones are also viable substrates (Table 2, entries 16–18). Full conversions were observed for cyclohexanone and 2-octanone in 12 h (Table 2, entries 17 and 18).

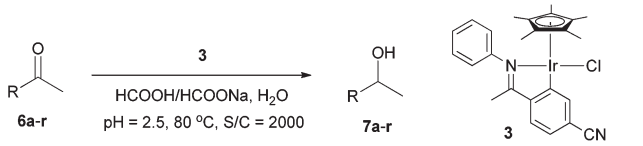
To demonstrate the practical applicability of the catalyst, a larger scale reduction of acetophenone was carried out under the conditions shown in Table 2. Scheme 3 shows the transfer hydrogenation of acetophenone at a 6 g scale, where phenethanol was obtained in 97% isolated yield.

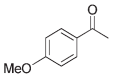
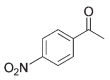
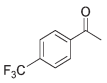
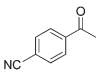
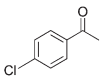
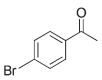
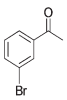
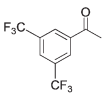
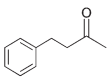
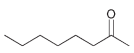
With the success in ketone reduction, the reduction of aldehydes was also explored under the optimal conditions for ketones. The results are given in Table 3. Aldehydes are less reactive than ketones under these conditions, generally requiring a lower S/C and 12 h reaction time. This may be due to the aldehyde existing mainly in its hydrate form. Nonetheless, a series of aromatic aldehydes were reduced to afford aromatic alcohols in moderate to excellent yields at S/C = 1000 (Table 3, entries 1–8). In particular, a high 96% isolated yield was obtained for benzaldehyde. However, the influence of electron withdrawing and donating substituents on the catalytic activity is not obvious under the conditions used (Table 3, entries 2–8). Thus, whilst electron-rich aldehydes only afforded moderate isolated yields (Table 3, entries 2 and 3), the same is also true for the 4-NO_2 and 2,4-Cl substituted aldehydes (Table 3, entries 4 and 8). However, high activities were observed for the 4-CF_3 and 4-F analogues (Table 3, entries 5 and 6). These results, together with those shown in Table 2, demonstrate the wide substrate scope of the transfer hydrogenation in water, showing the potential of the cyclometalated iridium catalysts in aqueous-phase organic synthesis.

Conclusion

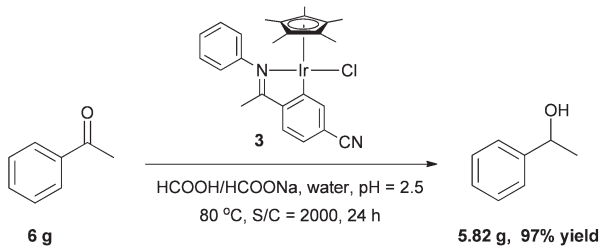
In summary, by controlling the solution pH, cyclometalated iridium complexes can be "switched on" to function as excellent catalysts for transfer hydrogenation of carbonyl compounds in water, with no need for organic solvents. These catalysts, which are highly effective for reductive amination, have simple and modular ligands and operate in a mechanism different from most of the current transfer hydrogenation

Table 2 Reduction of ketones with precatalyst **3**[a]



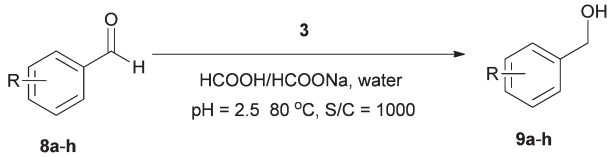
Entry	Substrate	Product	Time	Yield[b] (%)
1		**7a**	4	96
2[c]		**7b**	12	87
3[d]		**7c**	12	79
4		**7d**	4	97
5		**7e**	4	95
6		**7f**	12	91
7[c]		**7g**	12	89
8[e]		**7h**	12	89
9[e]		**7i**	12	94
10		**7j**	4	96
11[c]		**7k**	12	93
12[c]		**7l**	12	91
13[e]		**7m**	12	90
14[e]		**7n**	12	91
15		**7o**	4	89
16[e]		**7p**	12	97
17[c,f]		**7q**	12	100
18[c,f]		**7r**	12	100

[a] Reaction conditions: ketone (5 mmol), catalyst (0.0025 mmol), pH 2.5 aqueous HCOOH–HCOONa solution (4 mL), 80 °C. [b] Isolated yield. [c] S/C = 1000. [d] S/C = 200. [e] S/C = 500. [f] Determined by GC.



Scheme 3 A large scale transfer hydrogenation in water.

Table 3 Reduction of aromatic aldehydes with precatalyst **3**[a]



Entry	R	Product	Yield[b] (%)
1[c]	H	**9a**	96
2	3-CH_3	**9b**	79
3	4-OMe	**9c**	73
4	4-NO_2	**9d**	75
5	4-CF_3	**9e**	93
6[c]	4-F	**9f**	94
7	4-Cl	**9g**	80
8	2,4-Cl	**9h**	62

[a] Reaction conditions: aldehyde (2.5 mmol), catalyst (0.0025 mmol), pH 2.5 aqueous HCOOH–HCOONa solution (2 mL), 80 °C, 12 h. [b] Isolated yield. [c] S/C = 2000.

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catalysts, offer new opportunities for developing more enabling and versatile catalysts for hydrogenation and other reactions in water or conventional solvents.

Experimental section

General procedure for preparation of cyclometalated complexes[9a,12a]

$[Cp^*IrCl_2]_2$ (1 equiv.), an imine ligand (2.2 equiv.) and NaOAc (10 equiv.) were placed in a Schlenk tube. The tube was then degassed and recharged with argon three times. DCM was then added and the resulting mixture was stirred at room temperature overnight. The reaction mixture was then filtered through celite and dried over Na_2SO_4. Following the removal of the solvent under vacuum, the resulting solid was washed with diethyl ether and petroleum ether to afford the cyclometalated iridium complexes **1–5**.

Iridium complex **1**: yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm): 7.45 (d, J = 8.0 Hz, 1H), 7.36 (br, 1H), 6.93 (br, 2H), 6.58 (6.6–6.57, m, 1H), 3.90 (s, 3H), 3.85 (s, 3H), 2.38 (s, 3H), 1.44 (s, 15H); ^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ (ppm): 180.1, 170.4, 162.1, 157.6, 144.3, 141.3, 130.0, 124.5, 119.2, 112.8, 107.8, 89.0, 55.5, 55.0, 16.8, 8.6; HRMS (ESI) for $C_{26}H_{31}ClIrNO_2$ $[M - Cl]^+$, calc.: 582.1984, found: 582.1979.

Iridium complex **2**: red solid; ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ (ppm): 7.97 (s, 1H), 7.46 (d, J = 7.2 Hz, 1H), 7.22 (br, 3H), 6.91 (s, 2H), 3.79 (s, 3H), 2.38 (s, 3H), 1.37 (s, 15H); ^{13}C NMR (75 MHz, $CDCl_3$, 298 K) δ (ppm): 180.9, 167.6, 158.2, 151.9, 143.7, 138.3, 128.0, 124.4, 123.8, 119.5, 114.4, 89.9, 55.6, 17.1, 8.5; HRMS (ESI) for $C_{26}H_{28}ClIrN_2O$ $[M - Cl]^+$, calc.: 577.1831, found: 577.1818.

Iridium complex **3**: red solid; ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ (ppm): 7.92 (s, 2H), 7.44–7.36 (m, 3H), 7.19 (br, 2H), 6.90 (s, 1H), 2.41 (s, 3H), 1.41 (s, 15H); ^{13}C NMR (75 MHz, $CDCl_3$, 298 K) δ (ppm): 180.8, 170.5, 150.5, 146.5, 137.4, 129.8, 127.4, 126.5, 124.5, 123.0, 89.4, 17.0, 8.4; HRMS (ESI) for $C_{25}H_{26}ClIrN_2$ $[M - Cl]^+$, calc.: 547.1725, found: 547.1711.

Iridium complex **4**: orange solid; ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ (ppm): 7.49–7.35 (m, 4H), 7.23–7.20 (m, 3H), 6.59 (d, J = 7.9 Hz, 1H), 3.91 (s, 3H), 2.39 (s, 3H), 1.42 (s, 15H); ^{13}C NMR (75 MHz, $CDCl_3$, 298 K) δ (ppm): 179.8, 170.8, 162.2, 150.9, 141.0, 130.1, 126.0, 119.3, 107.9, 89.0, 55.0, 16.8, 8.5; HRMS (ESI) for $C_{25}H_{29}ClIrNO$ $[M - Cl]^+$, calc.: 552.1878, found: 552.1873.

Iridium complex **5**: orange solid; ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ (ppm): 7.64 (s, 1H), 7.41 (br, 3H), 7.25–7.21 (m, 2H), 6.84 (d, J = 7.2 Hz, 2H), 2.45 (s, 3H), 2.41 (s, 3H), 1.41 (s, 15H); ^{13}C NMR (75 MHz, $CDCl_3$, 298 K) δ (ppm): 180.8, 168.4, 150.8, 145.0, 142.1, 135.8, 128.4, 126.1, 122.6, 89.0, 22.0, 16.8, 8.4; HRMS (ESI) for $C_{25}H_{29}ClIrN$ $[M - Cl]^+$: calc.: 536.1929, found: 536.1925.

General procedure for preparing aqueous HCOOH–HCOONa solutions with different pH values

HCOOH–HCOONa solutions with different pH values were generally prepared by using a fixed amount of HCOONa and varying that of HCOOH and the volume of water added. For example, to prepare a solution of pH 2.5, 2 g of HCOONa (29.4 mmol), 3 mL of HCOOH (88 wt%) (70 mmol) and 2 mL of H_2O were mixed. For further details, see the ESI.†

General procedure for reduction of ketones with precatalyst 3

Ketone (5 mmol), complex **3** (0.0025 mmol; S/C = 2000) and a magnetic stir bar were placed in a pressure tube. To the mixture was injected 4 mL of aqueous HCOOH–HCOONa solution (pH = 2.5). The mixture was bubbled with argon for 15 min, and then stirred at 80 °C for 4 or 12 h as shown in Table 2. After cooling to room temperature, the reaction was quenched with aqueous $NaHCO_3$ solution, and extracted with ethyl acetate (7 × 3 mL). The organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The product was purified by flash chromatography using petroleum ether and ethyl acetate as eluent. The volume of aqueous HCOOH–HCOONa solution was 2 mL and 1 mL for S/C = 1000 and 500, respectively.

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