Green Chemistry

Accepted Manuscript

Volume 18 | Number 7 | 7 April 2016 | Pages 1821–2242

Green Chemistry

Cutting-edge research for a greener sustainable future
www.rsc.org/greenchem

ISSN 1463-9262

CRITICAL REVIEW
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Heterogeneous catalytic oxidation for lignin valorization into valuable chemicals: what results? What limitations? What trends?

175 YEARS

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ARTICLE

Iridium-catalyzed efficient reduction of ketones in water with formic acid as hydride donor at low catalyst loading

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A highly efficient and chemoselective transfer hydrogenation of ketones in water has been successfully achieved with our newly developed catalyst. Simple ketones, as well as α- or β-functionalized ketones are readily reduced. Formic acid is used as the traceless hydride source. At very low catalyst loading (S/C = 10,000 in most cases; S/C = 50,000 or 100,000 in some cases), the iridium catalyst is impressively efficient in reducing ketones in good to excellent yields. The TOF value can be as high as up to 26,000 mol mol^{-1} h^{-1}. A variety of functional groups is well tolerated, for example, heteroaryl, aryloxy, alkyloxy, halogen, cyano, nitro, ester, especially acidic methylene, phenol and carboxylic acid groups.

Introduction

Reduction of ketones to secondary alcohols is one of the most fundamental yet highly valued transformations in organic chemistry. Although numerous methods have been developed to realize the reduction, transfer hydrogenation (TH) outstands as an elegant one, due to the convenience, versatility, and ready accesses of hydrogen donors.[1] TH of ketones can be performed either in organic solvents or in water.[2] However, in association with the increasing concerns on the environmental and ecological issues, TH of ketones in water is greatly preferred, because of its green-chemistry characteristics.[3] It has received much attention since Sasson's,[4] Joo's[5] ,and Ogo's pioneering work.[6] In addition, numerous groups have reported the TH of ketones in water or water-containing media, including enantioselective versions, under the catalysis of various Ru-, Rh-, and Ir-catalysts.[2,7] However, the TH has still been plagued by the poor or modest catalyst efficiency. In most cases, the turnover frequencies (TOF) are far away from satisfactory, varying from a few to hundreds per hour. Recently, Xiao and co-workers made a breakthrough in improving the catalyst efficiency (Scheme 1, a).[8] By using an azairidacycle catalyst XC-1, the substrate/catalyst (S/C) ratios in the reduction of arylmethyl ketones were 2,000 in most cases.[8a] In their further reduction of α-functionalized ketones, the S/C ratios were 1,000 or 10,000 in most cases, by adopting

a structurally more complex catalyst XC-2.[8b] In a special case, the S/C ratio was as high as 50,000 under inert atmosphere. Despite of these advances endowed by *Xiao's catalysts* (XCs), diverse catalysts with high efficiency in water is still highly demanded for TH of ketones.
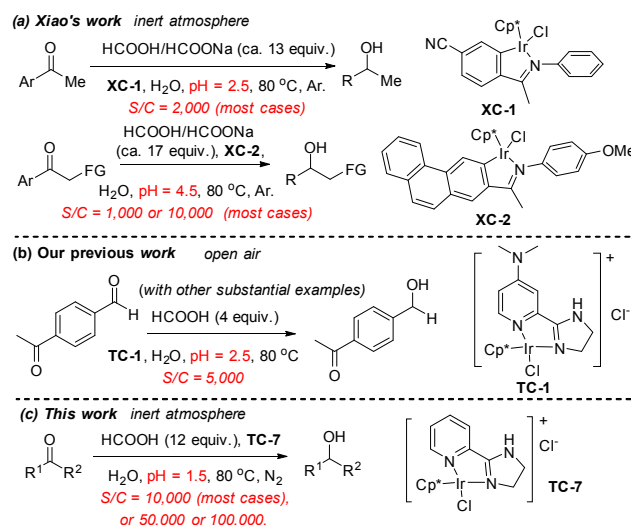
Scheme 1. Previous and present work in TH reduction of ketones in water.

In 2017, we reported a series of novel cationic iridium (III) complexes of substituted 2-(4,5-dihydro-1*H*-imidazol-2-yl)pyridines.[9] This work demonstrated that these new iridium complexes could serve as highly efficient catalysts for dehydrogenation of formic acid, TH of aldehydes, and aerobic oxidation of aldehydes. For convenience, these iridium complexes are termed as Tang's catalysts (TCs). In the above three transformations catalyzed by TCs, iridium hydrides were proposed as the key intermediates. During the chemoselective reduction of aldehydes in air, it was found that the ketone

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Electronic Supplementary Information (ESI) available: [Detailed experimental procedure, analytic data, copies of ^{1}H and ^{13}C NMR spectra of products]. See DOI: 10.1039/x0xx00000x

ARTICLE

moiety of 4-acetylbenzaldehyde was not affected at all (Scheme 1, b). In light of the high reactivity of iridium hydrides generated from **TC**s, we believe that a catalytic TH of ketones would also be feasible, if the reaction conditions are carefully tuned (Scheme 1, c). Herein, we present the Ir-catalyzed highly efficient TH of ketones, again using formic acid as a traceless reducing reagent and water as solvent.

Results and Discussion

Reaction condition optimization

The conditions were optimized by using acetophenone **1a** as the model substrate. Initial optimizations in open air did not give satisfactory results (see Table S1 in ESI), but they necessitated the inert atmosphere protection and revealed the optimal equivalents (12 equiv.) of formic acid. Further optimizations under nitrogen atmosphere were shown in Table 1. All the catalysts were screened at 10,000 S/C ratio. The 4-dialkylamino-substituted catalysts **TC-1** and **TC-2** gave 50% and 44% conversions, respectively (entries 1 and 2). The 4-, 5-, and 6-methoxy-substituted catalysts **TC-3**, **TC-4**, and **TC-5** delivered higher 67%, 78%, and 70% conversions (entries 3, 4 and 5), respectively, while the 3-methoxy-substituted one **TC-6** only gave 5% conversion (entry 6). Non-substituted catalyst **TC-7** has the highest activity, and an 88% conversion was obtained (entry 7). 4-Chloro-catalyst **TC-8** gave a conversion of 39% (entry 8). Subsequent optimization with **TC-7** showed that even at higher 100,000 S/C ratio, the reduction still occurred (entries 9-12), but longer time (12 h) was required to obtain a satisfactory conversion (entry 12). The TH did not take place at much lower catalyst loading (S/C = 1,000,000) (entry 14). The reduction could be completed within 0.5 h at 1,000 S/C ratio, 1 h at 5,000 S/C ratio, and 2 h at 10,000 S/C ratio (entries 15, 16, and 17). Notably, the TH is highly chemoselective, and alcohol **2a** was the only product.

Table 1. Optimization of reaction conditions.[a]

Entry	Cat.	S/C ratio	Time (h)	Conversion (%)[b]	TOF (mol mol^{-1} h^{-1})
1	**TC-1**	10,000	1	50	5,000
2	**TC-2**	10,000	1	44	4,400
3	**TC-3**	10,000	1	67	6,700
4	**TC-4**	10,000	1	78	7,800
5	**TC-5**	10,000	1	70	7,000
6	**TC-6**	10,000	1	5	500
7	**TC-7**	10,000	1	88	8,800
8	**TC-8**	10,000	1	39	3,900
9	**TC-7**	100,000	1	18	18,000
10	**TC-7**	100,000	2	52	26,000
11	**TC-7**	100,000	4	72	18,000
12	**TC-7**	100,000	12	92	7,770
13	**TC-7**	50,000	1	38	17,000
14	**TC-7**	1,000,000	12	trace	-
15	**TC-7**	1,000	0.5	99	2,000
16	**TC-7**	5,000	1	97	4,850
17	**TC-7**	10,000	2	99	5,000

[a]Reactions were performed on 1-mmol scale, using degassed formic acid and degassed water. [b]Determined by the ^{1}H NMR of the crude reaction mixtures, and calculated from the ratios of **1a** and **2a** (see Scheme S1 in ESI).

The TH reduction rates are dependent on the pH values of the reaction media (Figure 1, or Table S2 in ESI). In our study, catalyst **TC-7** behaves best at pH = 1.5, rendering an 88% conversion. The conversion decreases drastically against the increase of the pH values. When the pH value increases to greater than 3.0, very low catalyst efficiency is observed. Under neutral or basic conditions (for example, in HCOONa solution), even though iridium hydride is generated (see Figure S1, ESI), no reduction occurred. Thus, the dependence of the acidic conditions is probably due to the requirement of proton-mediated activation of ketones (Figure S2 in ESI).[8] In comparison, Xiao's catalysts showed highest efficiency at less acidic conditions (pH = 2.5 for **XC-1**, and pH = 4.5 for **XC-2**).
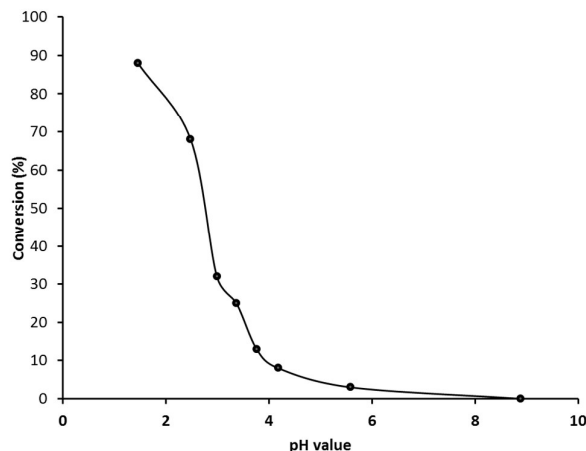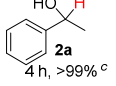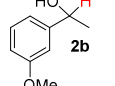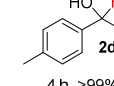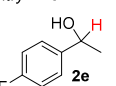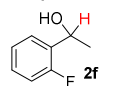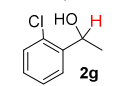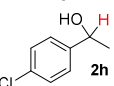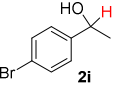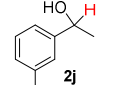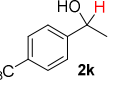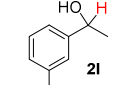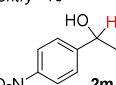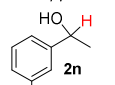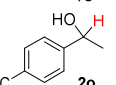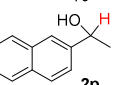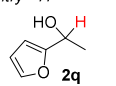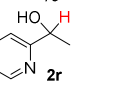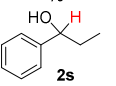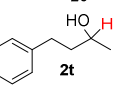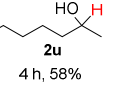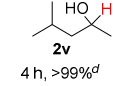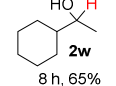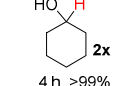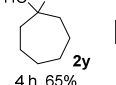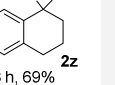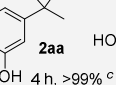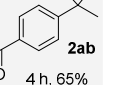

Figure 1. Effect of pH values on the TH conversions in 1 h. Reactions were performed with acetophenone (**1a**, 1 mmol), **TC-7** catalyst (S/C = 10,000), HCOOH-HCOONa (12 equiv. in total) solution in water at 80 ^{o}C for 1 h. The conversion was determined by the ^{1}H NMR of the crude reaction mixtures, and calculated from the ratios of **1a** and **2a** (see Scheme S1 in ESI). The initial pH value was determined by varying the HCOOH/HCOONa molar ratios.

Substrate scope

A number of ketones were tested at the 10,000 S/C ratio with catalyst **TC-7**. The results are summarized in Table 2. The reductions are highly selective, and no byproducts were observed. Besides acetophenone **1a** (entry 1), electron-rich 3-methoxy, 2-methoxy, and 4-methy analogues (**1b**, **1c**, **1d**) were facilely reduced in greater than 97% yields (entries 2-4). Haloaryl ketones, such as 4- and 2-fluoroacetophenones (**1e**

Journal Name ARTICLE

and **1f**), 2- and 4-chloroacetophenones (**1g** and **1h**), and 4- and 3-bromoacetophenones (**1i** and **1j**), were also susceptible to the TH, delivering the corresponding products **2e**-**j** in 67-95% yields (entries 5-10). The lower yield of **2i** was probably due to the poor solubility of **1i** in water (entry 9). These examples show that the halo atoms are well tolerated under the TH conditions. Electron-deficient ketones such as 4- and 3-trifluoromethyl aceophenones (**1k** and **1l**), 4- and 3-nitro aceophenones (**1m** and **1n**), and 4-cyano aceophenone (**1o**) were readily transfer-hydrogenated in 84-99% yields (entries 11-15). 1-(Naphthalen-2-yl)ethan-1-ol (**2p**) was obtained in 85% yield (entry 16).

Table 2. TH of simple ketones[a]

Reduction of heteroaryl methyl ketones such as 2-acetylfuran **1q** and 2-acetylpyridine **1r** to the corresponding alcohols **2q** and **2r** was easily realized in 98% and 86% yields, respectively, without affecting the heteroaryl groups (entries 17 and 18). However, the reduction of 2-acetylthiophene gave a very complex mixture. Propiophenone (**1s**), which is sterially larger than acetophenone (**1a**), was reduced in 57% yield (entry 19), indicating that the steric factor coul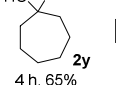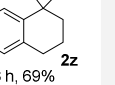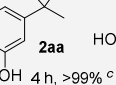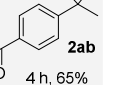d influence the TH reduction. Exposure of aliphatic ketones, including both linear (**1t-w**) and cyclic ones (**1x-z**), to the optimal conditions, afforded the reduced products (entries 20-26). In these cases, the TH was sensitive to the steric hindrance of ketones.[10] For example, reduction of sterically least hindered cyclohexanone **1x** gave quantitative yield (entry 24), while reduction of sterically more straining cycloheptanone (**1y**) and 1-tetralone (**1z**) only gave 65% and 69% yields (entries 25 and 26). Since the present TH with our iridium catalysts requires more acidic conditions than that with Xiao's catalysts,[8] we envisioned that acidic or base-sensitive groups should be well tolerable. Expectedly, 3-hydroxy acetophenone (**1aa**) and acetobenzoic acid (**1ab**) were reduced in >99% and 65% yields, respectively (entries 27 and 28). In the latter case, ketone **1ab** acted as a surfactant, and a lot of foam was formed, which prevented further reduction and presented a lower yield (entry 28).

Reduction of α-functionalized ketones is highly valuable in organic synthesis, because the products are prevalent building blocks or subunits in natural and synthetically bioactive compounds.[11] Exhilaratingly, such an important transformation could also be accomplished with our iridium catalyst (Table 3), and the high selectivity renders alcohols as the sole products. We found that at *S/C* = 10,000, **TC-7** was still very efficient in reducing the α-oxy ketones **3a-c**, and the desired products **4a-c** were isolated in 85-96% yields (entries 1-3). Reduction of α-cyano ketones **3d-f** occurred efficiently, and greater than 97% yields were obtained (entries 4-6). β-Ketoester **3g** was hydrogenated in 89% yield (entry 7), while the more electron-deficient **3h** was obtained in a quantitative yield (entry 8). Submitting α-ketoester **3i** to our reduction afforded **4i** in 83% yield (entry 9). Quantitative yields were also obtained in the reduction of α-fluoro and α,α,α-trifluoro acetophenones (**3j** and **3k**), as well as the 3-phenylpyruvic acid (**3l**) (entries 10-12). Notably, eve at *S/C* = 50,000, our catalyst **TC-7** still excelled well in reducing phenyloxyacetone (**3a**) and α-cyano ketones (**3e**) to the corresponding alcohols in 91% and 75% yields, respectively (entries 1 and 5).

Table 3. TH of functionalized ketones[a]

[a]Reactions were performed on 1-mmol scale, using degassed formic acid and degassed water under nitrogen atmosphere. [b]Isolated yields after column chromatography. [c]TLC indicated complete conversion, and the yields were obtained without chromatography (for detail, see ESI). [d]GC-MS identified complete conversion to product.
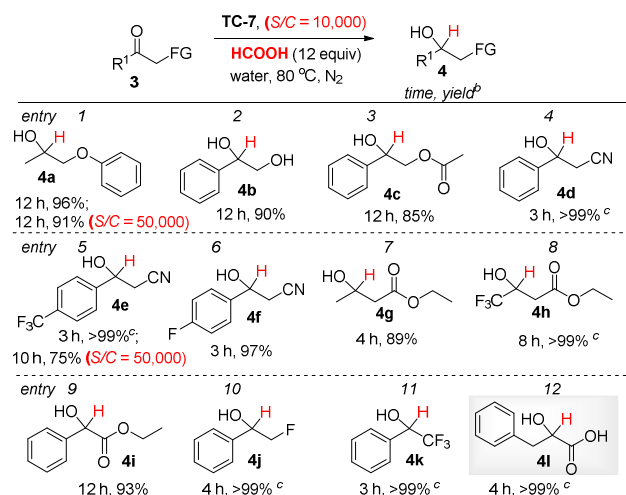
*a*Reactions were performed on 1-mmol scale, using degassed formic acid and degassed water under nitrogen atmosphere. *b*Isolated yields after column chromatography. *c*TLC indicated complete conversion, and the yields were obtained without chromatography (for detail, see ESI).

Our Iridium catalysts *versus* Xiao's catalysts

The TH reduction of methyl ketones and cyclohexanone was also realized by Xiao and co-workers with iridacycle **XC-1** at *S/C* = 2000 in most cases under inert atmosphere.[8a] Apparently, our catalyst **TC-7** was proved more efficient at lower catalyst loading (*S/C* = 10,000 in most cases). In addition, the high compatibility to the acidic groups such phenol and carboxylic acid also makes our catalysts more attractive. For the reduction of α-functionalized ketones, Xiao's catalyst **XC-1** appeared to be not applicable. Thus, Xiao and co-workers presented a modified iridacycle **XC-2** and achieved the reduction at pH = 4.5 (*S/C* = 10,000 for α-aryloxy and α-alkyloxy ketones; *S/C* =1,000 for α-halo, α-cyano, α-dialkylamino ketones, α- and β-ketoesters).[8b] However, for our catalyst, there was no need to modify the catalyst ligand or to adjust the reaction conditions. Again, the catalyst loading for our catalyst was lower (*S/C* = 10,000 in most cases and *S/C* = 50,000 in special cases). However, α-dialkylamino ketones were not suitable substrates in the reductions with our catalysts. The basic dialkylamino group was not compatible, and several products were formed. [12]

Reduction feasibility of different substrates with our catalysts

The TH reduction of aldehydes with our catalysts was highly regioselective, and the C=C double bonds of α,β-unsaturated aldehydes remained intact.[9a] Contrastingly, for the reduction of α,β-unsaturated ketones, the outcomes are different (Scheme 2). The TH of cyclohex-2-en-1-one **3m** produced cyclohexanol **2v**, with full reduction of both C=C and C=O bonds (*eqn*. 1). Further studies showed that cyclohexanone **1v** could be readily reduced to **2v** (*eqn*. 2), while cyclohex-2-en-1-ol **5** could not (*eqn*. 3). The above results disclosed that the TH of **3l** should first occur at the activated C=C bond, and then at the C=O bond of the resulting intermediate **1v**. Subsequent

experiments on 4-methylpent-3-en-2-one (**3n**), 4-methylpentan-2-one (**1u**), and 4-methylpent-3-en-2-ol (**6**) demonstrated that the reduction of sterically larger α,β-unsaturated ketones gave similar results (*eqn*. 4-6).
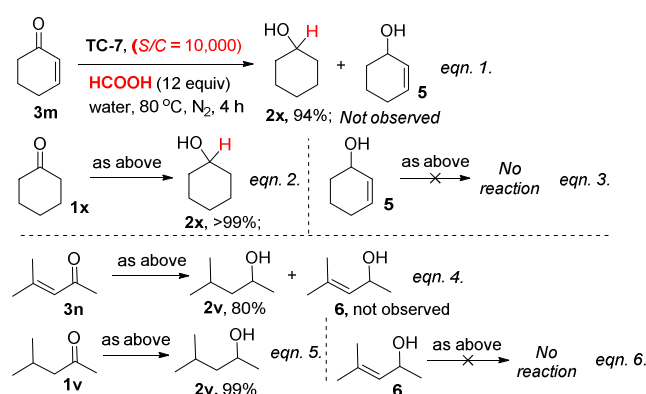
Scheme 2. Full reduction of α,β-unsaturated ketones.

Gram-scale reduction

In a gram-scale experiment, 50 mmol of ninhydrin **3o** was facilely reduced (Scheme 3). As the reaction proceeded, the white suspension finally turned to a clear yellow solution upon complete reduction. After cooling, desired product **4o** precipitated, and was conveniently collected in quantitative yield by filtration.
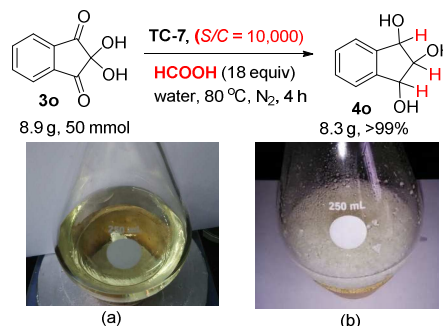
Scheme 3. Gram-scale reduction of ninhydrin. (a) Clear yellow solution upon complete reduction; (b) Precipitated product after cooling.

Mechanistic studies

A plausible mechanism was proposed in Figure 2. Key intermediate iridium hydride **B** is generated from catalyst **TC-7** through intermediate **A**.[13] On one hand, the highly reductive iridium hydride **B** is fast protonated to release hydrogen gas.[13] On the other hand, **B** slowly reacts with proton-activated ketones **1** or **3**,[8a,14] through four-membered transition state **C**, to deliver hydroiridation intermediate **D**. Hydrogen release and hydroiridation of ketones are two competitive evolutions of iridium hydrides **B**. Ligand exchange between **D** and formate anion delivers alcohols **2** or **4** and regenerates active catalyst **A**.

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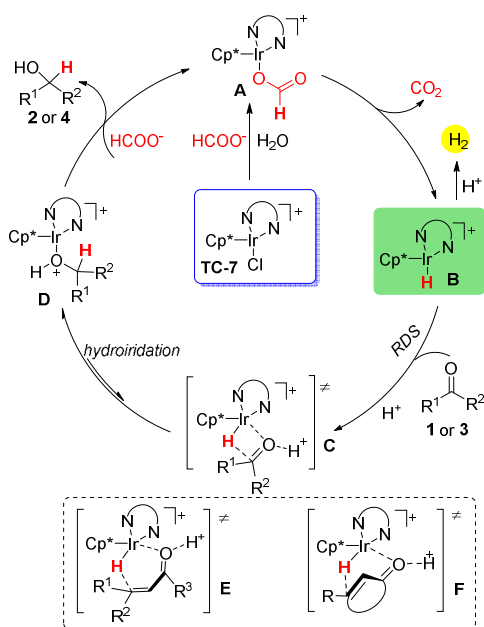
Figure 2. Proposed mechanism for the TH reduction of ketones

In the formic acid dehydrogenation and aldehyde reduction, the generation of iridium hydride was proposed as the rate-determining step (RDS).[9a,13] To determine the RDS in ketone reduction, the kinetic isotope effect (KIE) studies were conducted. At S/C = 10,000, the addition of DCOOD resulted in trace amount of alcohol products in H_2O or D_2O (see Scheme S2 in ESI). Thus, we decreased the S/C ratio to 100. The yields and H/D ratios are shown in Table 4. In H_2O, the H/D ratios with HCO_2H, DCO_2D, and $HCO_2H:DCO_2D$ (1:1) are 100:0, 49:51, and 82:18, respectively (Table 4, entries 1-3). In D_2O, the corresponding ratios with the above reducing reagents are 67:33, 0:100, and 43:57 (Table 4, entries 4-6). The results in entries 2 and 4 unexpectedly revealed H-D exchanges between [Ir]-D and H_2O, as well as between [Ir]-H and D_2O. The observed H-D exchanges make the KIE studies very complex. Therefore, in this case, simple KIE studies are not suitable for determining the rate-determining step.

However, the reaction rates are very sensitive to the electronic and steric properties of substrates, and relatively long time is always required to get a satisfactory result. Therefore, the hydroiridation of ketones is proposed to be the rate-determining step.

Table 4. The kinetic isotope study.[a]

| Entry	Solvent	Reagent (12 equiv.)	Total yield (%)[b]	H/D ratio (2a:d-2a)[b]
1	H_2O	HCO_2H	89	100:0
2	H_2O	DCO_2D	90	49:51
3	H_2O	$HCO_2H:DCO_2D$ (1:1)[c]	92	82:18
4	D_2O	HCO_2H	96	67:33
5	D_2O	DCO_2D	96	0:100
6	D_2O	$HCO_2H:DCO_2D$ (1:1)[c]	96	43:57

[a]Reactions performed on 0.25-mmol scale. [b]Determined by ^{1}H NMR spectra of the crude reaction mixtures. [c]Molar ratios.

Additionally, the congested transition state **C** explains the sensitivity to steric hindrance of ketones. For the reductions of α,β-unsaturated ketones, six-membered transition states **E** (for linear ones) and **F** (for cyclic ones) are envisioned. Since these two transition states are less congested than their corresponding four-membered transition states, the activated C=C double bonds are hydrogenated preferentially.

Ligand effect on the reduction

The data shown in Table 1 (entries 1-8) indicate some ligand effects, and non-substituted catalyst **TC-7** gives the highest TOF and conversion for the reduction of ketone. These results may be due to the competition between hydroiridation of activated ketones and protonation of iridium hydrides to form hydrogen gas. Hydrides derived from catalysts **TC-1** to **TC-5** with an electron-donating substituent are more readily protonated to give higher hydrogenation rates (see Table S3 in ESI) and lower ketone reduction rates (Table 1, entries 1-5). The hydride derived from **TC-8** with an electron-withdrawing substituent has lower overall reactivity (Table 1, entry 8). The low efficiency of **TC-6** is possibly due to the unfavourable steric interactions between the 3-methoxy substituent and the adjacent imidazoline ring (Table 1, entry 6). Overall, **TC-7** shows best activity for transfer hydrogenation of ketones (Table 1, entry 7).

Conclusions

We have achieved the highly efficient and chemoselective TH reduction of ketones in water with our iridium catalysts under inert atmosphere, using formic acid as the traceless hydride source. Not only simple ketones, but also α- or β-functionalized ketones undergo the reduction facilely. No waste is left in vessels when reductions were finished. Impressively, the iridium catalyst is very efficient, even at very low catalyst loading (S/C = 10,000). In some cases, further lower catalyst loading (S/C = 50,000 or 100,000) still gives satisfactory results. The TOF value can be as high as up to 26,000 mol mol^{-1} h^{-1}. The reduction is additionally featured by its good tolerance of a variety of functional groups, for example, hetero or fused aryls, aryloxy, alkyloxy, halogen, cyano, nitro, ester, especially acidic methylene, phenol and carboxylic acid groups. Our study presents a green and useful method for reducing ketones.

Conflicts of interests

There are no conflicts to declare.

Acknowledgements

Journal Name

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