ChemPubSoc Europe

DOI: 10.1002/chem.201403701

CHEMISTRY
A European Journal
Full Paper

Transfer Hydrogenation

Versatile Iridicycle Catalysts for Highly Efficient and Chemoselective Transfer Hydrogenation of Carbonyl Compounds in Water

Dinesh Talwar, Xiaofeng Wu, Ourida Saidi, Noemí Poyatos Salguero, and Jianliang Xiao*[a]

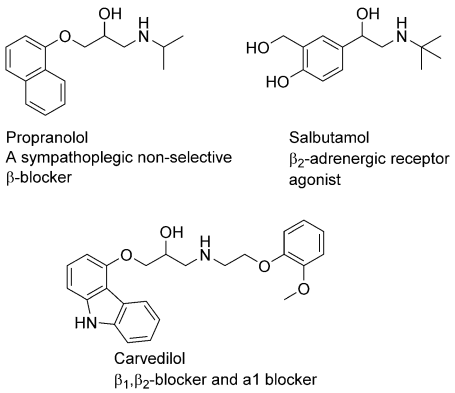
Dedicated to Professor Takao Ikariya on the occasion of his 65th birthday

Abstract: Cyclometalated iridium complexes are shown to be highly efficient and chemoselective catalysts for the transfer hydrogenation of a wide range of carbonyl groups with formic acid in water. Examples include α-substituted ketones (α-ether, α-halo, α-hydroxy, α-amino, α-nitrile or α-ester), α-keto esters, β-keto esters and α,β-unsaturated aldehydes. The reduction was carried out at substrate/catalyst ratios of up to 50000 at pH 4.5 and required no organic solvent. The protocol provides a practical, easy and efficient way for the synthesis of β-functionalised secondary alcohols, such as β-hydroxyethers, β-hydroxyamines and β-hydroxyhalo compounds, which are valuable intermediates in pharmaceutical, fine chemical, perfume and agrochemical synthesis.

Introduction

Transfer hydrogenation (TH) has emerged as a practical, powerful alternative to hydrogenation with H_2 for the reduction of C=X (X: O, N, C) bonds. The resulting products are important intermediates for fine chemical, pharmaceutical, agrochemical and advanced material synthesis. The merit of TH is significantly strengthened by its operational simplicity and the ready availability of hydrogen sources with the desired properties.[1] TH can be carried out in organic solvents or in aqueous media. From the viewpoint of environmental friendliness and easy catalyst/product separation, the latter is more appealing. Indeed, since the pioneering work of Sasson and co-workers[2] and of Benyei and Joo[3] in the 1980s, TH in water with metal catalysts has been continuously explored. However, highly efficient and chemoselective TH in water is still challenging.[1,4] For most of the catalysts reported, the turnover numbers (TONs) and turnover frequencies (TOFs) are low, with values ranging from a few to hundreds per hour in the case of the latter. Moreover, only a few catalytic systems have been reported that enable fast, selective and productive TH with inexpensive, safe reductants in water while tolerating synthetically useful functional groups.[1a,c–f,h, i,4a] A case in point is the TH of α-substituted ketones, which has been rarely studied in aqueous media.[5]

The reduction of α-substituted ketones to form β-functionalised secondary alcohols has drawn a lot of attention in the last two decades, due to the products being ubiquitous in naturally occurring and synthetic bioactive compounds.[6] For example, β-hydroxyethers have been used as biological probes and synthetic intermediates for molecular switches.[6a–c,k,m,7] β-Aminoethers can be readily derived from β-hydroxyethers and are important precursors in the preparation of a wide variety of pharmaceutical compounds.[6a–c,k,m] A further example is found in β-hydroxyamines, which have been demonstrated as building blocks in many synthetic methodologies leading to various bioactive compounds, including, for example, medicines that affect the central nervous and respiratory systems (Scheme 1).[6a–e,k–p] Of further interest are β-hydroxyhalo compounds, which have found use in the preparation of numerous compounds for pharmaceuticals, fine chemicals and functional materials.[6b,e,i,l–m]



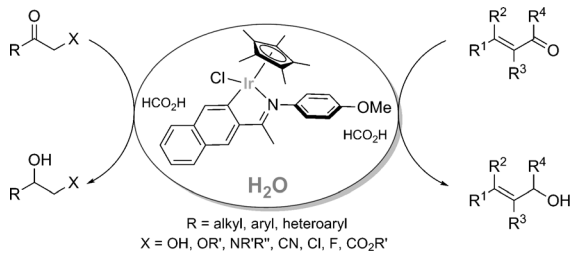
Scheme 1. Examples of drugs containing β-functionalised secondary alcohols.

[a] D. Talwar, Dr. X. Wu, Dr. O. Saidi, N. P. Salguero, Prof. J. Xiao
Department of Chemistry, University of Liverpool
Liverpool, L69 7ZD (UK)
E-mail: jxiao@liv.ac.uk
Homepage: http://pcwww.liv.ac.uk/~jxiao

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201403701.

Given the versatility of the α-substituted ketones, a number of reagents and methods have been developed for their selective reduction, especially the asymmetric version.[6a–m,8] However, few catalysts are known that are capable of selective TH of a wide range of α-substituted ketones.[6a–i,l–m,9] In addition, most of the reactions are conducted in organic solvents, which generates unwanted waste. One way of minimising the environmental impact caused by the use of organic solvents would be the use of water as the reaction medium. It is cheap, benign and readily available. However, the reduction of α-substituted ketones with TH in water is challenging, because the substrates/products are usually acid and/or base sensitive.[6c–e,l,9a,c] Thus, there is a need for a catalyst that is versatile, active and chemoselective for the TH of α-substituted ketones with diverse properties to form the corresponding secondary alcohols.

Recently we[10] and other groups[11] have reported a series of cyclometalated iridium complexes. Some of these have been successfully applied to the hydrogenation of imines with H_2, the TH of ketones and imines and the reductive amination of ketones with formate, which demonstrates the versatility of these catalysts.[10] In particular, the TH and reductive amination of ketones can be efficiently carried out in water, although only simple ketones were demonstrated.[10d,h] Herein, we report that such cyclometalated iridium complexes are also highly efficient and chemoselective for the TH of various α-substituted ketones, keto esters and α,β-unsaturated aldehydes in water (Scheme 2).

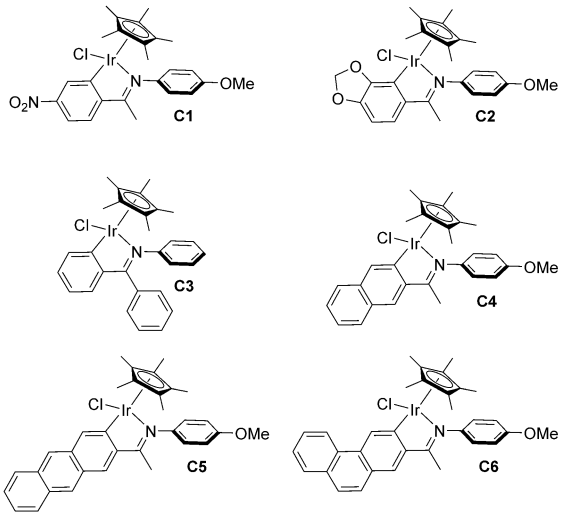


Scheme 2. Transfer hydrogenation of α-substituted ketones and α,β-unsaturated carbonyl compounds under aqueous conditions.

Results and Discussion

Our previous studies have shown that the structures of the cyclometalated iridium complexes can significantly impact on their ability to catalyse a reaction.[10a–i] Bearing this in mind, we firstly synthesised a series of cyclometalated iridium complexes, iridicycles **C1**–**C6** (Scheme 3), according to the reported procedures.[10k,11d,h] These iridicycles are diverse in both the conjugation and electronic properties of the aromatic rings coordinated to the iridium metal, with some having been exploited in the hydrogenation with H_2 and transfer hydrogenation with formate of imino bonds.[10a–c,g–h,k]

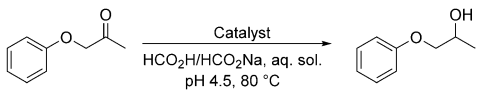
To investigate the efficacy of the iridicycles in reducing α-substituted ketones, we set out to screen the complexes synthesised, by using 1-phenoxypropan-2-one as the benchmark substrate at a substrate/catalyst (S/C) ratio of 1000. As



Scheme 3. Iridicycle catalysts examined for TH in water.

shown in Table 1, all of these six precatalysts afforded good to excellent conversions for the TH in water at pH 4.5 in a short reaction time of 0.5 h (Table 1, entries 3–8). Without the imino ligand, the iridium is inactive (Table 1, entry 2). As expected, no TH took place without a catalyst (Table 1, entry 1). It appears that the more electronic donation of the imino ligand to the iridium, the faster the reduction in water. This is seen by comparing the TH by using **C2** with those by using **C1** and **C3**. The highly conjugated **C4** and **C6** gave even higher conversions, although the anthracenyl-containing **C5** was surprisingly less active. In particular, the phenanthrenyl-ligated **C6** afforded almost full conversion in 0.5 h (Table 1, entry 8), with higher S/C ratios being feasible. Thus, at an S/C value of 10000, the TH was approximately complete in 2 h (Table 1, entry 9), and

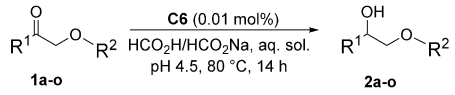
Table 1. Screening of catalysts for the TH of 1-phenoxypropan-2-one in water.[a]



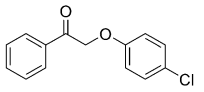
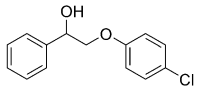
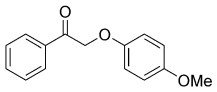
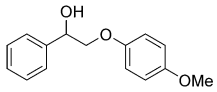
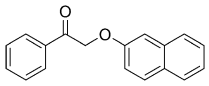
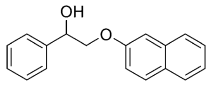
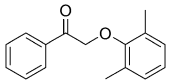
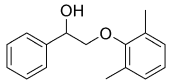
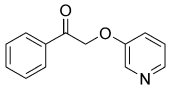
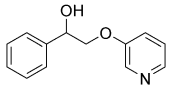
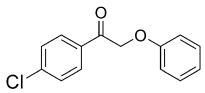
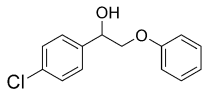
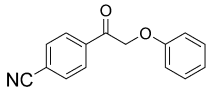
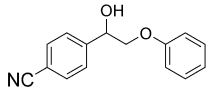
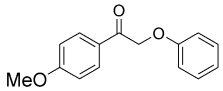
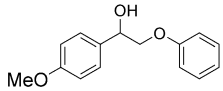
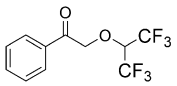
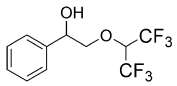
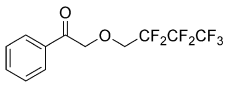
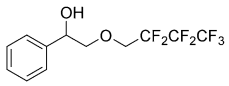
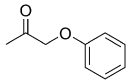
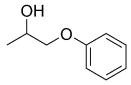
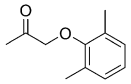
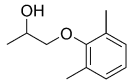
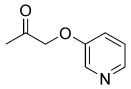
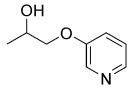
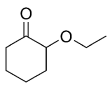
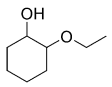
Entry	Catalyst	S/C[b]	*t* [h]	Conv. [%][c]
1	–	–	0.5	N.R.
2	$[Cp^*IrCl_2]_2$[d]	1000	0.5	<2
3	**C1**	1000	0.5	88
4	**C2**	1000	0.5	96
5	**C3**	1000	0.5	59
6	**C4**	1000	0.5	98
7	**C5**	1000	0.5	75
8	**C6**	1000	0.5	>99
9	**C6**	10000	2	99
10	**C6**	20000	6	96
11	**C6**	50000	20	82

[a] Reaction conditions: ketone (2.5 mmol), catalyst (0.01 mol%), HCO_2H/HCO_2Na aqueous solution (pH 4.5; 3 mL; 14.0 mmol of HCO_2H and 29.4 mmol of HCO_2Na in 2.8 mL of H_2O), 80 °C, stirred in a carousel tube for 0.5 h. [b] S/C: substrate/catalyst molar ratio. [c] Conversion determined by NMR spectroscopy. N.R.: no reaction. [d] Cp*: pentamethylcyclopentadienyl.

Table 2. TH of β-keto ethers with **C6** in water.[a]



1a-o **2a-o**

Entry	Substrate	Product		Yield [%][b]
1			**2a**	93
2			**2b**	91
3			**2c**	97
4			**2d**	95
5			**2e**	89
6			**2f**	97
7			**2g**	97
8			**2h**	93
9			**2i**	87
10			**2j**	86
11			**2k**	98
12			**2l**	97
13			**2m**	91
14			**2n**	90
15			**2o**	87

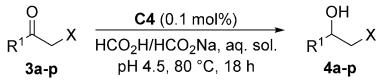
[a] Reaction conditions: ketone (2.5 mmol), **C6** (0.01 mol%), HCO_2H/HCO_2Na aqueous solution (pH 4.5; 3 mL; 14.0 mmol of HCO_2H and 29.4 mmol of HCO_2Na in 2.8 mL of H_2O), 80 °C, stirred in a carousel tube for 14 h. [b] Yield of isolated product.

the catalyst delivered a conversion of 82% in 20 h at the much higher S/C value of 50000 (Table 1, entry 11).

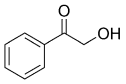
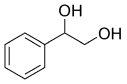
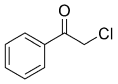
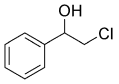
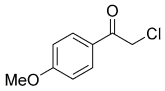
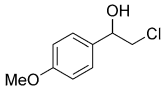
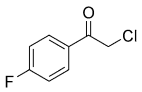
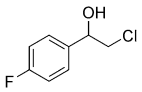
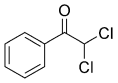
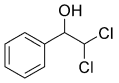
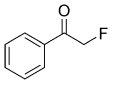
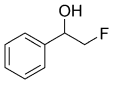
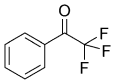
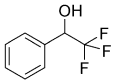
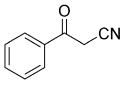
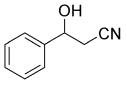
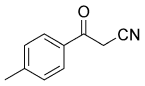
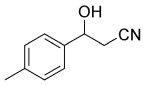
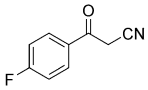
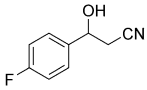
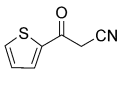
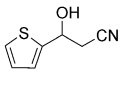
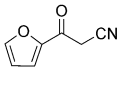
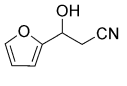
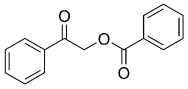
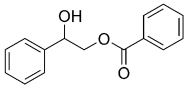
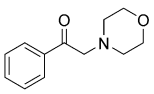
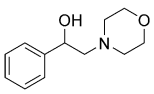
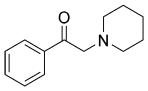
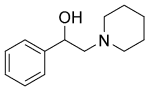
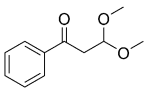
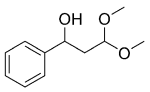
The TH reactions above were carried out at pH 4.5. Screening of the reaction conditions with **C4** revealed that the solution pH value plays a critical role in the reduction. Thus, the TH occurred only within a certain window of acidic conditions (pH 3.0–5.0 for greater than 50% conversions), with the optimal pH value being 4.5, which was adopted for subsequent studies. This value is higher than that required for the TH of acetophenone by using an analogous catalyst,[10d] which presumably reflects the more electron-rich ketone being reduced in this study. However, pH 4.5 is lower than that used with the Noyori–Ikariya catalysts, for which neutral to slightly basic reaction conditions were found to be optimal.[1f,4a,12] As explained before,[10a,d,e] the iridicycle catalyst is not capable of activating the ketone through its ligands, which renders activation through an acidic medium necessary, whereas the Noyori–Ikariya type catalysts are able to readily hydrogenate a ketone by virtue of hydrogen bonding between the NH proton of the ligand and the substrate.[13]

With the optimised reaction conditions in hand, we then expanded the substrate scope of the reduction. Firstly, a wide range of β-keto ethers were effectively and chemoselectively reduced to the desired β-hydroxyethers. As shown in Table 2, the **C6** catalyst is capable of reducing all types of β-keto ethers. Keto ethers featuring either aromatic or aliphatic units and aromatic, aliphatic, heterocyclic and fluorinated ethers were all viable and furnished excellent yields at the S/C ratio of 10000 and 2.5 mmol substrate scale without dissociation of any ether groups. Fur-

Table 3. TH of α-substituted ketones with **C4** in water.[a]



3a-p **4a-p**

Entry	Substrate	Product		Yield [%][b]
1			**4a**	93
2			**4b**	94
3			**4c**	92
4			**4d**	93
5[c]			**4e**	87
6			**4f**	95
7			**4g**	96
8			**4h**	90
9			**4i**	92
10			**4j**	91
11			**4k**	89
12			**4l**	90
13			**4m**	96
14			**4n**	88
15[d]			**4o**	86
16			**4p**	94

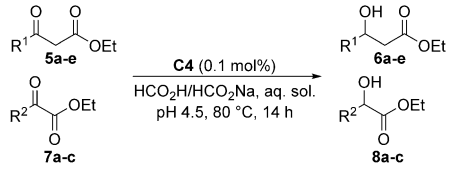
[a] Reaction conditions: ketone (2.5 mmol), **C4** (0.1 mol%), HCO_2H/HCO_2Na aqueous solution (pH 4.5; 3 mL; 14.0 mmol of HCO_2H and 29.4 mmol of HCO_2Na in 2.8 mL of H_2O), 80 °C, stirred in a carousel tube for 18 h. [b] Yield of isolated product. [c] S/C = 200. [d] Yield determined by ^1H NMR spectroscopy.

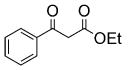
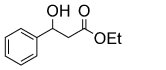
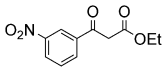
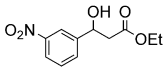
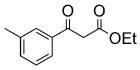
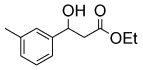
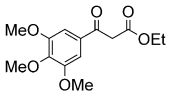
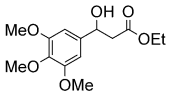
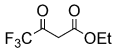
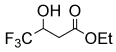
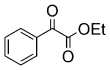
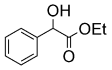
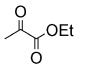
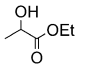
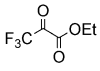
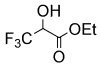
thermore, for β-aryl ketone aryl ethers, neither electron-withdrawing substituents nor electron-donating groups on the aryl ring of either ketones and ethers significantly affected the productivity and selectivity of the catalyst. Thus, TH of **1a** and **1b** afforded similar yields (Table 2, entry 1 versus 2) and the reductions of **1f**, **1g** and **1h** all provided excellent yields (Table 2, entries 6–8). The sterically bulky substituent on the aryl ether **1d** also has little effect (Table 2, entry 4). More importantly, substrates containing a hexafluoroisopropyl group (**1i**) and a heptafluorobutoxy group (**1j**) can be reduced smoothly with 87% and 86% yields to afford highly demanding intermediates for pharmaceuticals and fine chemicals.[14] Hydrogenolysis of the C–O bond was not noticed. To the best of our knowledge, there is no literature report for the TH of these substrates previously. There are still difficulties in the literature concerning the reduction of **1m**–**1o**.[15] However, with the current protocol, these substrates can be translated into the desired products smoothly with good to excellent yields (Table 2, entries 13–15).

α-Halo-, hydroxy- and nitrile-substituted ketones are more challenging to reduce due to the ease of dissociation/decomposition of these α-functional groups under acidic and/or basic conditions.[6b–i,l,8,16] However, the current reduction system overcomes these challenges. After modification of the reaction conditions, the desired products were obtained with excellent yields for almost all of these problematic ketones. As shown in Table 3, with the cyclometalated complex **C4**, which is slightly more active than **C6**, α-hydroxyacetophenone (**3a**) was converted into a 1,2-diol with 93% yield at an S/C ratio of 1000 (Table 3, entry 1). α-Chloroaceto-

phenone (**3b**) was reduced to the α-chlorophenylethanol with 94% yield (Table 3, entry 2). For substrates **3c** and **3d**, which bear an electron-donating and -withdrawing group, respectively, the reduction afforded almost identical yields (Table 3, entries 3 and 4). Moreover, α,α-dichloroacetophenone (**3e**) was successfully reduced to α,α-dichlorophenylethanol with 87% yield (Table 3, entry 5), albeit at a lower S/C ratio of 200. The reduction of α-chloroketones is often problematic because they are vulnerable to dechlorination, which gives rise to epoxide products. The α-fluoroketones were also viable for this reduction system. Thus, excellent yields were obtained for the TH of α-fluoro- and α,α,α-trifluoroacetophenone (**3f** and **3g**, respectively; Table 3, entries 6 and 7). Equally, the α-nitrile ketones (**3h**–**3l**) were converted into the corresponding secondary alcohols with excellent yields, including examples of heterocyclic ketones (Table 3, entries 8–12). Still further, the catalytic system was successfully applied to α-acyloxy, α-morpholino and α-semialdehyde ketones (**3m**–**3p**; Table 3, entries 13–16), with the α-functional groups tolerated and high yields obtained for all of the desired products. Selective reduction of analogues of **3m** by TH is difficult, because the acyl group is prone to migration by hydrolysis.[17] Indeed, there are only a few literature reports describing the TH of this class of substrates; however, the catalyst loadings are high and the yields are relatively low due to the aforementioned problem.[18] To the best of our knowledge, this is the first time that a homogeneous catalyst has been reported for the TH of α-piperidyl and α-semialdehyde ketones.

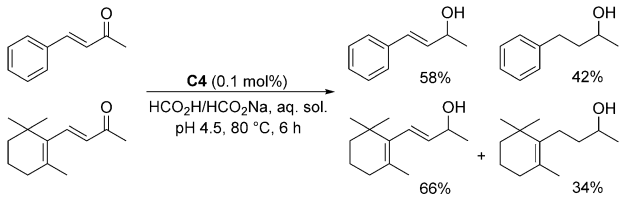
Table 4. TH of α- and β-keto esters with **C4** in water.[a]



Entry	Substrate	Product		Yield [%][b]
1			**6a**	94
2			**6b**	91
3			**6c**	94
4			**6d**	92
5			**6e**	95
6			**8a**	96
7[c]			**8b**	91
8			**8c**	92

[a] Reaction conditions: keto ester (2.5 mmol), **C4** (0.1 mol%), HCO_2H/HCO_2Na aqueous solution (pH 4.5; 3 mL; 14.0 mmol of HCO_2H and 29.4 mmol of HCO_2Na in 2.8 mL of H_2O), 80 °C, stirred in a carousel tube for 14 h. [b] Yield of isolated product. [c] Yield determined by ^1H NMR spectroscopy.

To showcase the broader utility of the catalytic system, we also applied **C4** to the reduction of keto esters.[6a,d,i,19] Both aromatic and aliphatic β-keto esters were reduced to afford the corresponding alcohols with excellent yields under the catalysis of 0.1 mol% of **C4** (Table 4). Likewise, the analogous α-keto esters were also reduced with ease, which demonstrates the versatility of the cyclometalated iridium catalyst. Products **6e** and **8c** are known to be important intermediates for medicines and fine chemicals.[14b,20] Again, there appears to be no correlation between the electron properties of the substituents on the phenyl ring and the yield obtained under the conditions employed (Table 4, entries 1–4).



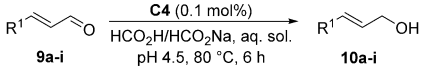
Scheme 4. Attempted chemoselective TH of α,β-unsaturated ketones in water.

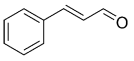
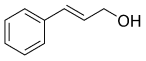
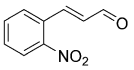
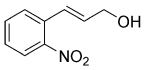
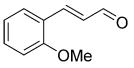
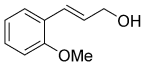
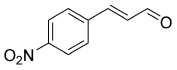
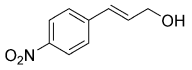
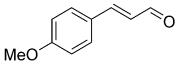
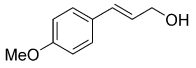
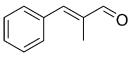
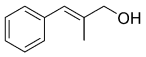
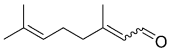
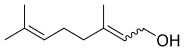
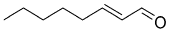
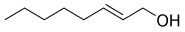
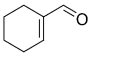
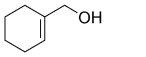
The highly efficient and chemoselective reduction of α,β-unsaturated ketones and aldehydes has been a research topic in the last several decades.[21] Mixtures of products are frequently obtained, because many catalysts reduce both the C=O and C=C bonds rather than exclusively either the C=O or C=C bond. Hence, selectivity is still an issue.[21] Therefore, we subsequently examined these substrates with the current reduction system. Disappointingly, **C4** was not chemoselective for the reduction of α,β-unsaturated ketones and catalysed the reduction of both the C=C and C=O bonds (Scheme 4).

Catalyst **C4** is, however, highly chemoselective in the reduction of α,β-unsaturated aldehydes to afford only unsaturated

alcohols (Table 5). In the case of the aromatic α,β-unsaturated aldehydes, almost identical yields of allylic alcohols were obtained for those substrates that are relatively sterically demanding (**9b**, **9c** and **9f**; Table 5, entries 2, 3 and 6) or that bear electron-withdrawing or -donating groups substituted on the phenyl ring (**9d** versus **9e**; Table 5, entry 4 versus 5). Good yields were also achieved for the TH of aliphatic α,β-unsaturated aldehydes (Table 5, entries 7–9). The chemoselectivity observed with the α,β-unsaturated aldehydes may stem from the aldehyde group being easier to reduce than a ketone. Once reduced, the C=C bond can no longer be hydrogenated by the catalyst.

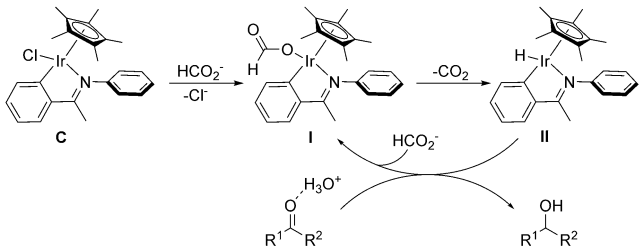
Table 5. TH of α,β-unsaturated aldehydes with **C4** in water.[a]



Entry	Substrate	Product		Yield [%][b]
1			**10a**	89
2			**10b**	88
3			**10c**	90
4			**10d**	90
5			**10e**	92
6			**10f**	92
7[c]			**10g**	90
8			**10h**	78
9			**10i**	85

[a] Reaction conditions: aldehyde (2.5 mmol), **C4** (0.1 mol%), HCO_2H/HCO_2Na aqueous solution (pH 4.5; 3 mL; 14.0 mmol of HCO_2H and 29.4 mmol of HCO_2Na in 2.8 mL of H_2O), stirred in a carousel tube for 6 h. [b] Yield of isolated product. [c] *E/Z* = 52:48.

A plausible mechanism is proposed for the TH in question in Scheme 5. Catalyst **C** is first converted into the formate complex **I** in the presence of formate.[22] Decarboxylation of **I** leads to the active, but coordinatively saturated, hydride species **II**.[10a] The ketone substrate, activated by the hydroxonium ion under the acidic conditions employed,[10d] is then reduced through direct hydride transfer from **II** without ketone coordination to the metal centre, that is, by the ionic or outer-sphere mechanism.[23] In previous studies, we have shown that hydride species can be easily generated from an iridicycle and formate and transferred to protonated imines.[10a,f,h]



Scheme 5. Proposed mechanism for the TH by an iridicycle.

Conclusion

In summary, this paper has demonstrated that cyclometalated iridium complexes, iridicycles, catalyse the highly efficient and chemoselective TH of a wide variety of carbonyl groups, including a series of α-substituted ketones, α- and β-keto esters and α,β-unsaturated aldehydes. With the reduction feasible in water at S/C ratios of 1000–50000, the current protocol provides a practical, easy and efficient synthesis of β-functionalised secondary alcohols, especially β-hydroxyethers, β-aminoethers, β-hydroxyamines and β-hydroxyhalo compounds, which are bioactive and/or of value for the synthesis of pharmaceuticals, fine chemicals, perfumes and agrochemicals.

Experimental Section

Typical procedure for the TH of β-keto ethers in water

β-Keto ether (2.5 mmol) and **C6** (0.17 mg, 2.5×10^{-4} mmol) were placed in a carousel reaction tube. The tube was degassed and charged with nitrogen. An aqueous solution of HCO_2Na/HCO_2H at pH 4.5 (3 mL) was then introduced, and the mixture was stirred at 80 °C for 14 h under nitrogen. The reaction mixture was cooled to room temperature and quenched with saturated sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate (3×25 mL), and the combined organic layers were washed with brine (25 mL). The organic layer was collected and dried over anhydrous sodium sulfate. Filtration, followed by evaporation of the solvent under reduced pressure, gave the crude mixture. Flash column chromatography of the crude mixture afforded the desired β-hydroxyether product.

Typical procedure for the TH of α-functionalised aromatic ketones in water

Ketone (2.5 mmol) and **C4** (1.6 mg, 2.5×10^{-3} mmol) were placed in a carousel reaction tube. The tube was degassed and charged with nitrogen. An aqueous solution of HCO_2Na/HCO_2H at pH 4.5 (3 mL) was then introduced, and the mixture was stirred at 80 °C for 18 h under nitrogen. The reaction mixture was cooled to room temperature, quenched with saturated NaCl solution (20 mL) and extracted with ethyl acetate (3×25 mL). The combined organic layer was dried over anhydrous sodium sulfate. Filtration, followed by evaporation of the solvent under reduced pressure, gave the crude mixture. Flash column chromatography of the crude mixture afforded the desired product.

Typical procedure for the TH of α-keto and β-keto esters in water

Keto ester (2.5 mmol) and **C4** (1.6 mg, 2.5×10^{-3} mmol) were placed in a carousel reaction tube. The tube was degassed and charged with nitrogen. An aqueous solution of HCO_2Na/HCO_2H at pH 4.5 (3 mL) was then introduced, and the mixture was stirred at 80 °C for 14 h under nitrogen. The reaction mixture was cooled to room temperature, quenched with saturated NaCl solution (20 mL) and extracted with ethyl acetate (3×25 mL). The combined organic layer was dried over anhydrous sodium sulfate. Filtration, followed by evaporation of the solvent under reduced pressure, gave the crude mixture. Flash column chromatography of the crude mixture afforded the desired hydroxyester product.

Typical procedure for the TH of α,β-unsaturated aldehydes in water

α,β-Unsaturated aldehyde (2.5 mmol) and **C4** (1.6 mg, 2.5×10^{-3} mmol) were placed in a carousel reaction tube. The tube was degassed and charged with nitrogen. An aqueous solution of HCO_2Na/HCO_2H at pH 4.5 (3 mL) was then introduced, and the mixture was stirred at 80 °C for 6 h under nitrogen. The reaction mixture was cooled to room temperature, quenched with saturated NaCl solution (20 mL) and extracted with ethyl acetate (3×25 mL). The combined organic layer was dried over anhydrous sodium sulfate. Filtration, followed by evaporation of the solvent under reduced pressure, gave the crude mixture. Flash column chromatography of the crude mixture afforded the desired alcohol product.

Acknowledgements

We thank the University of Liverpool for support (D.T. and X.W.). We are also grateful to Angela Gonzalez De Castro, Antonio David Conde and Ho Yin Li for technical assistance and useful discussions. Mass spectrometry data were acquired at the EPSRC UK National Mass Spectrometry Facility at Swansea University.

Keywords: carbonyl groups · cyclometalated complexes · iridium · transfer hydrogenation · water

[1] a) X. F Wu, J. L. Xiao, in *Metal Catalyzed Reactions in Water* (Eds.: P. H. Dixneuf, V. Cadierno), Wiley-VCH, Weiheim, **2013**, p. 173; b) X. F. Wu, J. L. Xiao, in *Water in Organic Synthesis* (Ed.: S. Kobayashi), Thieme, New York, **2012**, p. 257; c) M. O. Simon, C. J. Li, *Chem. Soc. Rev.* **2012**, *41*, 1415 – 1427; d) A. Robertson, T. Matsumoto, S. Ogo, *Dalton Trans.* **2011**, *40*, 10304 – 10310; e) R. N. Butler, A. G. Coyne, *Chem. Rev.* **2010**, *110*, 6302 – 6337; f) X. F. Wu, J. L. Xiao, *Chem. Commun.* **2007**, 2449 – 2466; g) A. Rossin, G. Kovacs, G. Ujaque, A. Lledos, F. Joo, *Organometallics* **2006**, *25*, 5010 – 5023; h) N. Pinault, D. W. Bruce, *Coord. Chem. Rev.* **2003**, *241*, 1 – 25; i) K. Nomura, *J. Mol. Catal. A* **1998**, *130*, 1 – 28.

[2] a) R. Bar, L. K. Bar, Y. Sasson, J. Blum, *J. Mol. Cat.* **1985**, *33*, 161 – 177; b) R. Bar, Y. Sasson, J. Blum, *J. Mol. Cat.* **1984**, *26*, 327 – 332.

[3] A. Bényei, F. Joo, *J. Mol. Cat.* **1990**, *58*, 151 – 163.

[4] a) X. F. Wu, C. Wang, J. L. Xiao, *Platinum Met. Rev.* **2010**, *54*, 3 – 19; b) X. F. Wu, J. K. Liu, X. H. Li, A. Zanotti-Gerosa, F. Hancock, D. Vinci, J. W. Ruan, J. L. Xiao, *Angew. Chem.* **2006**, *118*, 6870 – 6874; *Angew. Chem. Int. Ed.* **2006**, *45*, 6718 – 6722.

[5] a) E. Fuglseth, E. Sundby, B. H. Hoff, *J. Fluorine Chem.* **2009**, *130*, 600 – 603; b) O. Soltani, M. A. Ariger, H. Vazquez-Villa, E. M. Carreira, *Org. Lett.* **2010**, *12*, 2893 – 2895.

[6] a) R. Bhuniya, T. Mahapatra, S. Nanda, *Eur. J. Org. Chem.* **2012**, 1597 – 1602; b) S. Eagon, N. Ball-Jones, D. Haddenham, J. Saavedra, C. DeLieto, M. Buckman, B. Singaram, *Tetrahedron Lett.* **2010**, *51*, 6418 – 6421; c) Y. Suzuki, D. Kaneno, M. Miura, S. Tomoda, *Tetrahedron Lett.* **2008**, *49*, 4223 – 4226; d) P. Peach, D. J. Cross, J. A. Kenny, I. Mann, I. Houson, L. Campbell, T. Walsgrove, M. Wills, *Tetrahedron* **2006**, *62*, 1864 – 1876; e) D. J. Cross, J. A. Kenny, I. Houson, L. Campbell, T. Walsgrove, M. Wills, *Tetrahedron: Asymmetry* **2001**, *12*, 1801 – 1806; f) H. Yamashita, K. Narasaka, *Chem. Lett.* **1996**, 539 – 540; g) X. F. Li, J. J. Chen, D. D. Tanner, *J. Org. Chem.* **1996**, *61*, 4314 – 4318; h) K. Krishnan, J. Chandrasekaran, *Indian J. Chem. Sect. B* **1982**, *21*, 595 – 597; i) C. Kowalski, X. Creary, A. J. Rollin, M. C. Burke, *J. Org. Chem.* **1978**, *43*, 2601 – 2608; j) J. Armand, L. Boulares, *B. Soc. Chim. Fr. Ii-Ch.* **1975**, 711 – 718; k) K. Huang, M. Ortiz-Marciales, W. Correa, E. Pomales, X. Y. Lopez, *J. Org. Chem.* **2009**, *74*, 4195 – 4202; l) J. E. D. Martins, D. J. Morris, B. Tripathi, M. Wills, *J. Organomet. Chem.* **2008**, *693*, 3527 – 3532; m) D. S. Matharu, D. J. Morris, A. M. Kawamoto, G. J. Clarkson, M. Wills, *Org. Lett.* **2005**, *7*, 5489 – 5491; n) R. T. Brittain, J. B. Farmer, D. Jack, L. E. Martin, W. T. Simpson, *Nature* **1968**, *219*, 862 – 863; o) J. W. Black, A. F. Crowther, R. G. Shanks, L. H. Smith, A. C. Dornhorst, *Lancet* **1964**, *283*, 1080 – 1081; p) P. C. Stafylas, P. A. Sarafidis, *Vasc. Health Risk Manag.* **2008**, *4*, 23 – 30.

[7] a) R. T. Luibrand, I. R. Taigounov, A. A. Taigounov, *J. Org. Chem.* **2001**, *66*, 7254 – 7262; b) S. Tomoda, T. Senju, M. Kawamura, T. Ikeda, *J. Org. Chem.* **1999**, *64*, 5396 – 5400; c) G. Mehta, J. Chandrasekhar, *Chem. Rev.* **1999**, *99*, 1437 – 1467.

[8] J. M. Saveant, H. Veillard, *Bull. Soc. Chim. Fr.* **1967**, 2415.

[9] a) J. M. Saveant, *Bull. Soc. Chim. Fr.* **1967**, 471; b) J. M. Saveant, *Bull. Soc. Chim. Fr.* **1967**, 493; c) M. Watanabe, K. Murata, T. Ikariya, *J. Org. Chem.* **2002**, *67*, 1712 – 1715.

[10] a) D. Talwar, N. P. Salguero, C. M. Robertson, J. L. Xiao, *Chem. Eur. J.* **2014**, *20*, 245 – 252; b) W. J. Tang, C. H. Lau, X. F. Wu, J. L. Xiao, *Synlett* **2014**, *25*, 81 – 84; c) J. Wu, J. H. Barnard, Y. Zhang, D. Talwar, C. M. Robertson, J. L. Xiao, *Chem. Commun.* **2013**, *49*, 7052 – 7054; d) Y. W. Wei, D. Xue, Q. Lei, C. Wang, J. L. Xiao, *Green Chem.* **2013**, *15*, 629 – 634; e) Y. W. Wei, C. Wang, X. Jiang, D. Xue, J. Li, J. L. Xiao, *Chem. Commun.* **2013**, *49*, 5408 – 5410; f) C. Wang, H. Y. T. Chen, J. Bacsa, C. R. A. Catlow, J. L. Xiao, *Dalton Trans.* **2013**, *42*, 935 – 940; g) B. Villa-Marcos, W. J. Tang, X. F. Wu, J. L. Xiao, *Org. Biomol. Chem.* **2013**, *11*, 6934 – 6939; h) Q. Lei, Y. W. Wei, D. Talwar, C. Wang, D. Xue, J. L. Xiao, *Chem. Eur. J.* **2013**, *19*, 4021 – 4029; i) J. H. Barnard, C. Wang, N. G. Berry, J. L. Xiao, *Chem. Sci.* **2013**, *4*, 1234 – 1244; j) J. X. Jiang, C. Wang, A. Laybourn, T. Hasell, R. Clowes, Y. Z. Khimyak, J. L. Xiao, S. J. Higgins, D. J. Adams, A. I. Cooper, *Angew. Chem.* **2011**, *123*, 1104 – 1107; *Angew. Chem. Int. Ed.* **2011**, *50*, 1072 – 1075; k) C. Wang, A. Pettman, J. Basca, J. L. Xiao, *Angew. Chem.* **2010**, *122*, 7710 – 7714; *Angew. Chem. Int. Ed.* **2010**, *49*, 7548 – 7552; l) J. Wu, D. Talwar, S. Johnston, M. Yan, J. Xiao, *Angew. Chem.* **2013**, *125*, 7121 – 7125; *Angew. Chem. Int. Ed.* **2013**, *52*, 6983 – 6987.

[11] a) B. Li, T. Roisnel, C. Darcel, P. H. Dixneuf, *Dalton Trans.* **2012**, *41*, 10934 – 10937; b) E. Kumaran, W. K. Leong, *Organometallics* **2012**, *31*, 4849 – 4853; c) A. J. Howarth, D. L. Davies, F. Lelj, M. O. Wolf, B. O. Patrick, *Dalton Trans.* **2012**, *41*, 10150 – 10152; d) N. Pannetier, J. B. Sortais, J. T. Issenhuth, L. Barloy, C. Sirlin, A. Holuigue, L. Lefort, L. Panella, J. G. de Vries, M. Pfeffer, *Adv. Synth. Catal.* **2011**, *353*, 2844 – 2852; e) D. L. Davies, M. P. Lowe, K. S. Ryder, K. Singh, S. Singh, *Dalton Trans.* **2011**, *40*, 1028 – 1030; f) Y. Boutadla, D. L. Davies, R. C. Jones, K. Singh, *Chem. Eur. J.* **2011**, *17*, 3438 – 3448; g) Y. Boutadla, D. L. Davies, O. Al-Duaij, J. Faw-

cett, R. C. Jones, K. Singh, *Dalton Trans.* **2010**, *39*, 10447 – 10457; h) D. L. Davies, O. Al-Duaij, J. Fawcett, M. Giardiello, S. T. Hilton, D. R. Russell, *Dalton Trans.* **2003**, 4132 – 4138. For a recent review, see: i) Y. F. Han, G. X. Gin, *Chem. Soc. Rev.* **2014**, *43*, 2799 – 2823.

[12] a) X. F. Wu, X. G. Li, W. Hems, F. King, J. L. Xiao, *Org. Biomol. Chem.* **2004**, *2*, 1818 – 1821; b) X. F. Wu, X. G. Li, F. King, J. L. Xiao, *Angew. Chem.* **2005**, *117*, 3473 – 3477; *Angew. Chem. Int. Ed.* **2005**, *44*, 3407 – 3411; c) X. F. Wu, X. H. Li, M. McConville, O. Saidi, J. L. Xiao, *J. Mol. Catal. A* **2006**, *247*, 153 – 158; d) X. W. Zhou, X. F. Wu, B. L. Yang, J. L. Xiao, *J. Mol. Catal. A* **2012**, *357*, 133 – 140.

[13] a) M. Yamakawa, H. Ito, R. Noyori, *J. Am. Chem. Soc.* **2000**, *122*, 1466 – 1478; b) T. Ikariya, K. Murata, R. Noyori, *Org. Biomol. Chem.* **2006**, *4*, 393 – 406.

[14] a) J.-F. Cheng, Y. Huang, R. Penuliar, M. Nishimoto, L. Liu, T. Arrhenius, G. Yang, E. O'Leary, M. Barbosa, R. Barr, J. R. B. Dyck, G. D. Lopaschuk, A. M. Nadzan, *J. Med. Chem.* **2006**, *49*, 4055 – 4058; b) P. S. Hynes, D. Stranges, P. A. Stupple, A. Guarna, D. J. Dixon, *Org. Lett.* **2007**, *9*, 2107 – 2110; c) S. V. Kovalenko, J. Swinson, US2010/0312019A1, **2010**; d) L. S. Croix, US3883665, **1975**; e) I. Masao, O. Kazuya, T. Hirokazu, O. Hidekazu, EP1679298A1, **2006**.

[15] a) M. Boukachabia, S. Zeror, J. Collin, J.-C. Fiaud, L. A. Zouioueche, *Tetrahedron Lett.* **2011**, *52*, 1485 – 1489; b) J. Li, Y. Tang, Q. Wang, X. Li, L. Cun, X. Zhang, J. Zhu, L. Li, J. Deng, *J. Am. Chem. Soc.* **2012**, *134*, 18522 – 18525; c) K. Ahlford, J. Lind, L. Mäler, H. Adolfsson, *Green Chem.* **2008**, *10*, 832 – 835; d) A. Schlatter, M. K. Kundu, W.-D. Woggon, *Angew. Chem.* **2004**, *116*, 6899 – 6902; *Angew. Chem. Int. Ed.* **2004**, *43*, 6731 – 6734.

[16] a) F. Wang, H. Liu, L. Cun, J. Zhu, J. Deng, Y. Jiang, *J. Org. Chem.* **2005**, *70*, 9424 – 9429; b) Y. Ma, H. Liu, L. Chen, X. Cui, J. Zhu, J. Deng, *Org. Lett.* **2003**, *5*, 2103 – 2106.

[17] J. Chen, D. Liu, N. Butt, C. Li, D. Fan, Y. Liu, W. Zhang, *Angew. Chem.* **2013**, *125*, 11846 – 11850; *Angew. Chem. Int. Ed.* **2013**, *52*, 11632 – 11636.

[18] a) J. A. Kenny, M. J. Palmer, A. R. C. Smith, T. Walsgrove, M. Wills, *Synlett* **1999**, *10*, 1615 – 1617; b) M. Wills, M. Palmer, A. Smith, J. Kenny, T. Walsgrove, *Molecules* **2001**, *5*, 4 – 18.

[19] a) X. F. Wu, X. H. Li, A. Zanotti-Gerosa, A. Pettman, J. K. Liu, A. J. Mills, J. L. Xiao, *Chem. Eur. J.* **2008**, *14*, 2209 – 2222; b) L. Yin, X. Jia, X. S. Li, A. S. C. Chan, *Tetrahedron: Asymmetry* **2009**, *20*, 2033 – 2037; c) S. Zeror, J. Collin, J. C. Fiaud, L. A. Zouioueche, *Tetrahedron: Asymmetry* **2010**, *21*, 1211 – 1215.

[20] a) Y. Kuroki, D. Asada, K. Iseki, *Tetrahedron Lett.* **2000**, *41*, 9853 – 9858; b) L. Antolini, A. Forni, P. Davoli, I. Moretti, F. Prati, *Tetrahedron: Asymmetry* **1998**, *9*, 285 – 292; c) C. V. D. Bussche-Hünnefeld, C. Cescato, D. Seebach, *Chem. Ber.* **1992**, *125*, 2795 – 2802.

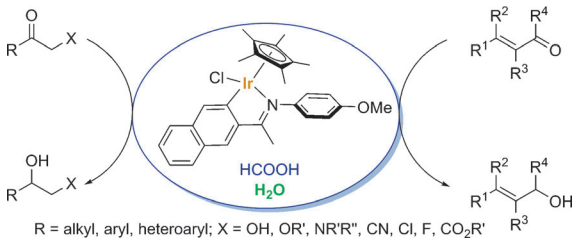
[21] a) B. R. James, R. H. Morris, *J. Chem. Soc. Chem. Commun.* **1978**, 929 – 930; b) S. Bhaduri, K. Sharma, *J. Chem. Soc. Chem. Commun.* **1988**, 173 – 174; c) S. Bhaduri, K. Sharma, D. Mukesh, *J. Chem. Soc. Dalton Trans.* **1992**, 77 – 81; d) T. Mizugaki, Y. Kanayama, K. Ebitani, K. Kaneda, *J. Org. Chem.* **1998**, *63*, 2378 – 2381; e) E. Mizushima, M. Yamaguchi, T. Yamagishi, *J. Mol. Catal. A* **1999**, *148*, 69 – 75; f) S. Sakaguchi, T. Yamaga, Y. Ishii, *J. Org. Chem.* **2001**, *66*, 4710 – 4712; g) S. U. Sonavane, R. V. Jayaram, *Synlett* **2004**, 146 – 148; h) J. W. Yang, M. T. H. Fonseca, N. Vignola, B. List, *Angew. Chem.* **2005**, *117*, 110 – 112; *Angew. Chem. Int. Ed.* **2005**, *44*, 108 – 110; i) M. Hall, B. Hauer, R. Stuermer, W. Kroutil, K. Faber, *Tetrahedron: Asymmetry* **2006**, *17*, 3058 – 3062; j) N. J. A. Martin, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 13368 – 13369; k) Y. Z. Zhu, G. K. Chuah, S. Jaenicke, *J. Catal.* **2006**, *241*, 25 – 33; l) C. A. Mebi, R. P. Nair, B. J. Frost, *Organometallics* **2007**, *26*, 429 – 438; m) S. Naskar, M. Bhattacharjee, *Tetrahedron Lett.* **2007**, *48*, 465 – 467; n) P. G. N. Mertens, P. Vandezande, X. P. Ye, H. Poelman, I. F. J. Vankelecom, D. E. De Vos, *Appl. Catal. A* **2009**, *355*, 176 – 183; o) C. Ebner, A. Pfaltz, *Tetrahedron* **2011**, *67*, 10287 – 10290; p) W. L. Xu, Y. G. Zhou, R. M. Wang, G. T. Wu, P. Chen, *Org. Biomol. Chem.* **2012**, *10*, 367 – 371; q) R. X. Liu, Y. Wang, H. Y. Cheng, Y. C. Yu, F. Y. Zhao, M. Arai, *J. Mol. Catal. A* **2013**, *366*, 315 – 320.

[22] a) S. Ogo, H. Nishida, H. Hayashi, Y. Murata, S. Fukuzumi, *Organometallics* **2005**, *24*, 4816 – 4823; b) M. Ito, A. Watanabe, Y. Shibata, T. Ikariya, *Organometallics* **2010**, *29*, 4584 – 4592; c) T. Touge, T. Hakamata, H. Nara, T. Kobayashi, N. Sayo, T. Saito, Y. Kayaki, T. Ikariya, *J. Am. Chem. Soc.* **2011**, *133*, 14960 – 14963.

[23] a) T. Abura, S. Ogo, Y. Watanabe, S. Fukuzumi, *J. Am. Chem. Soc.* **2003**, *125*, 4149 – 4154; b) S. Ogo, T. Abura, Y. Watanabe, *Organometallics* **2002**, *21*, 2964 – 2969.

Received: June 1, 2014
Published online on ■■ ■■, 0000

FULL PAPER



Water wonder: Iridicycle catalysts are versatile and allow the highly efficient and chemoselective transfer hydrogenation of a variety of carbonyl compounds, including problematic and challenging ones, with formate in neat water (see scheme).

Transfer Hydrogenation

*D. Talwar, X. Wu, O. Saidi, N. P. Salguero, J. Xiao**

■■ – ■■

Versatile Iridicycle Catalysts for Highly Efficient and Chemoselective Transfer Hydrogenation of Carbonyl Compounds in Water