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Homogeneous Catalysis | *Hot Paper*

A Simple Iridicycle Catalyst for Efficient Transfer Hydrogenation of N-Heterocycles in Water

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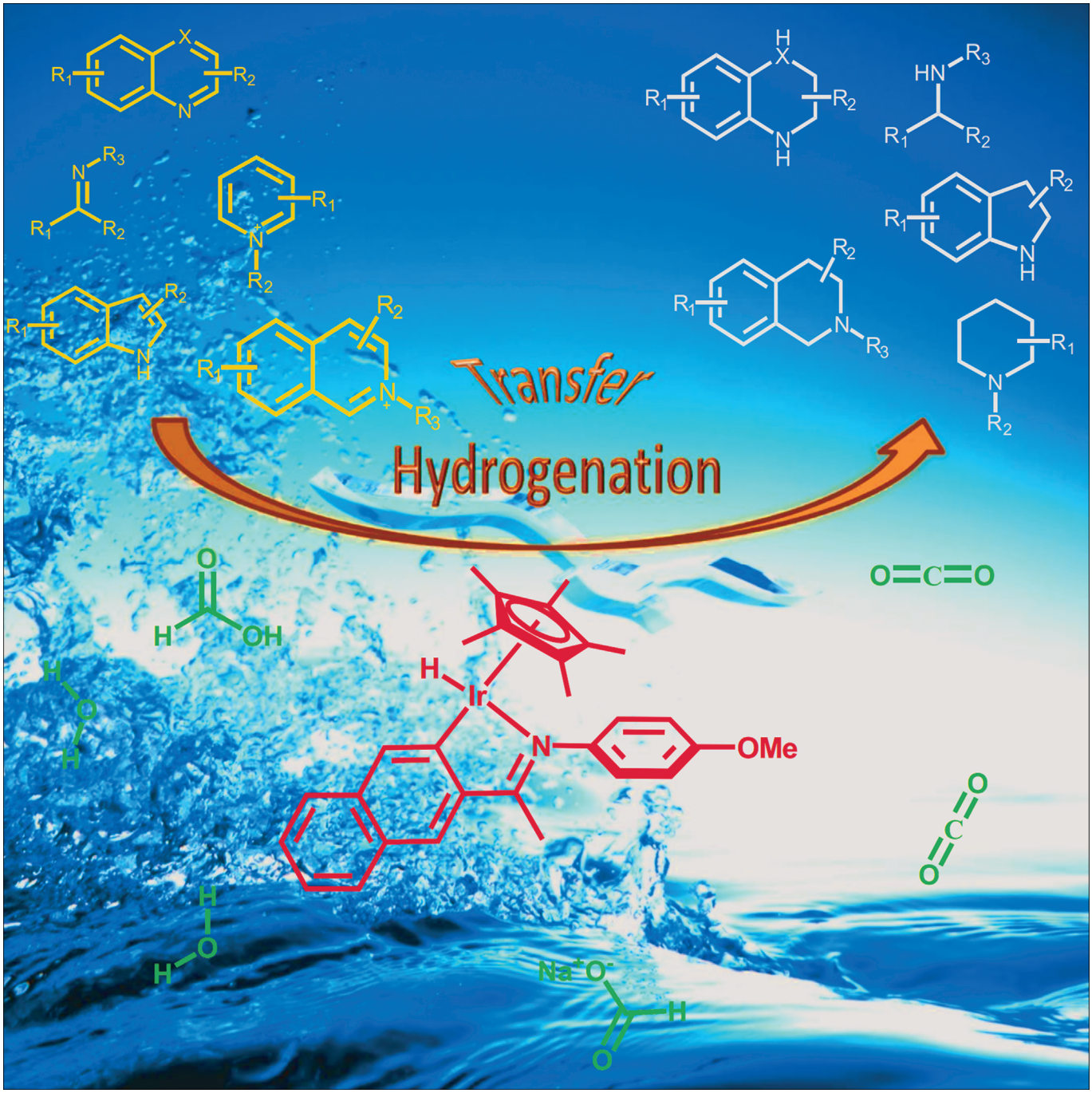
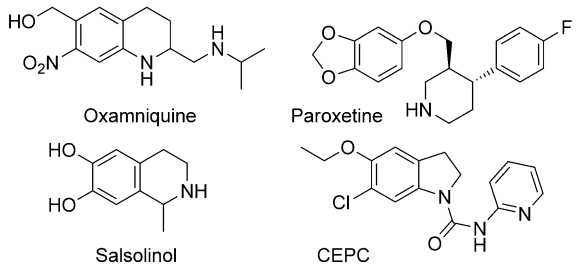


Abstract: A cyclometalated iridium complex is shown to catalyse the transfer hydrogenation of various nitrogen heterocycles, including but not limited to quinolines, isoquinolines, indoles and pyridinium salts, in an aqueous solution of HCO_2H/HCO_2Na under mild conditions. The catalyst shows excellent functional-group compatibility and high turnover number (up to 7500), with catalyst loadings as low as 0.01 mol% being feasible. Mechanistic investigation of the quinoline reduction suggests that the transfer hydrogenation proceeds via both 1,2- and 1,4-addition pathways, with the catalytic turnover being limited by the step of hydride transfer.

Introduction

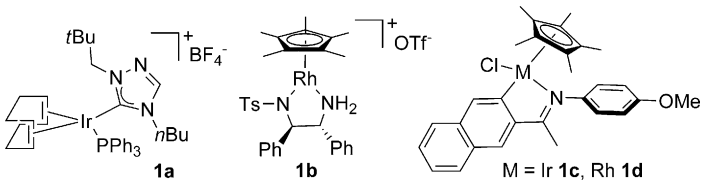
Saturated nitrogen heterocycles are frequently found in drug and biologically active molecules (Scheme 1), such as oxamniquine (a schistosomicide),[1] paroxetine (a CCRI-type antidepressant),[2] salsolinol (an endogenous monoamine oxidase inhibitor)[3] and CEPC (a serotonin 5-HT_{2C} antagonist).[4] The most obvious route to access these types of molecules is via the reduction of the corresponding unsaturated parent heterocycles, which can be efficiently synthesised by cross-coupling and classic heterocyclic chemistry. Nonetheless, this method only has 0.8% occurrence rate among the medical chemist's toolbox, despite the fact that approximately 43% of the total pharmaceutical compounds contain aliphatic amines.[5] This must be a reflection of either limited supply of the building blocks from commercial sources or significant challenges at the late-stage reduction step.[5]



Scheme 1. Bioactive molecules that contain a saturated nitrogen heterocycle.

Reduction of nitrogen heterocycles has traditionally been carried out by using heterogeneous hydrogenation catalysis (e.g., Pd/C, Rh/C, Adams's catalyst, Raney nickel),[6,7] Birch reduction,[8] and more recently with homogenous hydrogenation catalysis.[9,10] Although there are many examples in the literature, one or more significant limitations are always found under those reaction conditions. For example, Birch and metal hydride reduction require stoichiometric amounts of metallic reductants and have very limited functional-group compatibilities. Whereas heterogeneous catalysts containing Pd, Pt, Ni or Rh on supported materials can reduce a range of heterocycles even under atmospheric pressure of hydrogen, they often have limited selectivity and the potential of over reduction. Homogeneous catalysis has attracted much attention, due to the easily controllable selectivities and reactivities through ligand modification. Nevertheless, there are still significant challenges in this area, including the improvement in turnover number (TON) and turnover frequency (TOF), reduction in cost, and the expansion of the reaction scope.

Transfer hydrogenation (TH) is a reaction of great interest due to its operational simplicity. However, in contrast to that of ketones, the TH of heterocycles has been much less explored. Yamaguchi demonstrated that by using $[\{Cp^*IrCl_2\}_2]$ in a mixture of *i*PrOH and H_2O under refluxing conditions, a series of quinolines could be fully reduced to tetrahydroquinolines.[11] The presence of an acid considerably enhanced the reduction rate, presumably by activating the quinoline through protonation to form a quinolinium salt, which is easier to reduce.[10] Frediani and co-workers reported a Rh–bipyridine catalyst that could reduce quinoline and pyridines with a moderate conversion by using *i*PrOH as the hydride source.[12] Crabtree identified a cationic Ir^I–N-heterocyclic carbene (NHC) catalyst (**1a**) that could reduce quinolines to tetrahydroquinolines in *i*PrOH with moderate yields (Scheme 2). Pyrazine showed complete conversion to piperazine under the reported reaction conditions.[13] Other N-heterocycles, such as isoquinoline, indole and *N*-methylated pyridinium iodide, were found to be inactive in this system. A versatile, simple and yet highly active system was recently reported by our group. By using $[\{Cp^*RhCl_2\}_2]$ with KI as an additive, a range of N-heterocycles, including quinolines, isoquinolines, quinoxalines and pyridinium salts, were reduced in the HCO_2H/Et_3N (F/T) azeotrope with high yields using just 0.01–0.2 mol% catalyst.[14,15] TH of indoles did not proceed under the protocol, however, and the reduction of 4-substituted quinoline was rather sluggish. For example, at



Scheme 2. Examples of catalysts studied for TH of quinolines.

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a higher catalyst loading of 2 mol% and 50% KI, only 23% conversion of 4-methyl quinoline was obtained after 24 h.

Asymmetric transfer hydrogenation (ATH) of N-heterocycles has also been investigated, with organocatalysts[16] and, to a lesser degree, homogeneous catalysts.[17] However, Hantzsch esters (HEH) are predominantly used in organocatalysis, which are expensive hydrogen donors compared with others that are commercially available (e.g., *t*Bu–HEH = £70.5 per gram versus HCO_2H = £30 per litre).

The reaction conditions for both TH and ATH of N-heterocycles are not yet ideal, as high catalyst loadings, high reaction temperatures and/or a limited substrate scope are limitations often encountered. Moreover, organic solvents are normally used, which imposes an environmental impact. In addition, an active, versatile catalyst capable of either hydrogenation or TH of various N-heterocycles, such as quinolines, isoquinolines, quinoxalines, indoles and pyridines, remains to be developed.

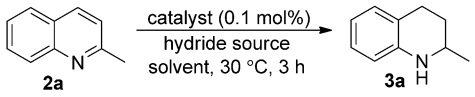
Recently, we[18] and other groups[19] have reported a series of cyclometalated iridium complexes (iridicycles), some of which have been successfully applied to the reduction of carbonyls and imines and reductive amination of ketones with various hydrogen sources.[18a–d,g,h,j,l,19d,i] Of particular relevance is that an iridicycle complex also catalyses the hydrogenation with H_2 (1 bar) of various quinolines, quinoxalines and indoles.[18c] The hydrogenation appears to work well only in 2,2,2-trifluoroethanol (TFE), albeit with a catalyst loading of $\geq$1 mol%. The catalyst was not capable of hydrogenating more inert N-heterocycles such as isoquinolines or pyridines. We recently developed the cyclometalated iridium complex **1c** (Scheme 2), which was found to be robust for the TH of a range of α-substituted ketones and for the reductive amination of ketones in water.[18h,l] Herein, we report a TH protocol with this catalyst, which enables the efficient reduction of an ample variety of N-heterocycles, including isoquinolines and pyridinium salts, at a low catalyst loading in water without the addition of any organic solvent.

Results and Discussion

In our previous study on the TH of α-substituted ketones in water, the catalyst **1c** (Scheme 2) exhibited the highest activity at pH 4.5;[18l] therefore, the same condition was adopted for the optimisation study here. 2-Methylquinoline (**2a**) was chosen as a model substrate. TH of **2a** gave full conversion within 3 h with only 0.1 mol% loading of **1c** at 80 °C or 60 °C, in an aqueous formate solution of pH 4.5 (Table 1, entries 1 and 2). Gratifyingly, lowering the temperature to 30 °C also led to a 70% conversion within 3 h (Table 1, entry 3). Screening of the solution pH with **1c** revealed that the reaction occurs only within a certain window of acidic conditions (Table 1, entries 4 and 5). Thus, pH 4.5 was adopted for subsequent studies. In contrast, the analogous Rh complex **1d** only gave a 12% conversion (Table 1, entry 6). Other catalysts that are known to be active for the TH of quinolines (Scheme 2) showed much lower activities under the reaction conditions employed (Table 1, entries 7–11). Although the dimeric [{Cp*$IrCl_2$}$_2$] also led to moderate conversion (38% in 3 h, Table 1, entry 11), further testing showed that it exhibited very limited substrate scope (see the Supporting Information). For instance, TH of 3-methylquinoline led to its tetrahydro variant only in 4% conversion after 20 h. To establish whether aqueous conditions were optimum, other hydride sources and solvents were also tested using **1c** for the TH of 2-methylquinoline. Apart from water, TH also worked in MeOH and TFE with F/T as the hydrogen source, with slightly lower or comparable conversions (64% and 68%, respectively; Table 1, entries 12 and 13). Much lower conversions were recorded in nonprotic solvents, such as THF or DMF (<5% conversion in 3 h; Table 1, entries 14 and 17). Other commonly used hydride sources such as *i*PrOH and Et_3SiH gave sluggish rates under the reaction conditions (Table 1, entries 18 and 19).

Once the optimal TH condition for 2-methylquinoline had been established, an array of 26 diversely substituted quinolines (**2a–z**) was hydrogenated in the aqueous formate solution of pH 4.5 (Table 2). The Ir-based catalyst **1c** exhibited high reactivity for all of the quinoline substrates examined. Thus, unsubstituted quinoline **2d**, 2-substituted quinoline **2a** and 3-substitued quinoline **2b** were all effectively reduced at 30 °C with excellent yields (Table 2, entries 1, 2 and 4). Increasing the steric bulkiness at the 2-postion led to a decrease in conversion, which could be compensated by increasing the reaction temperature to reflux (e.g., **3e**; Table 2, entry 5). Challenging 4-substitued quinolines **2c** and **2z** were also reduced in high yields, albeit requiring high temperatures (Table 2, entries 3 and 26).

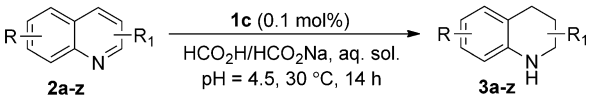
Table 1. Optimisation of conditions for the TH of 2-methylquinoline.[a]

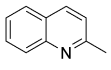
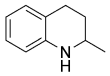
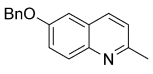
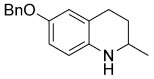
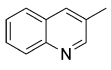
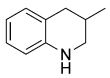
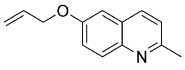
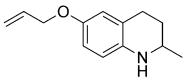
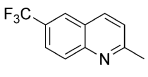
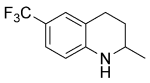
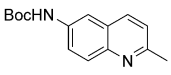
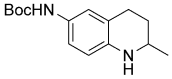
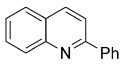
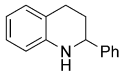
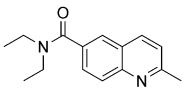
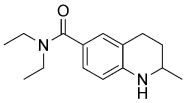
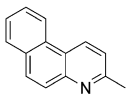
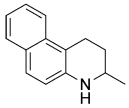
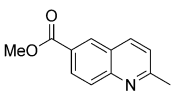
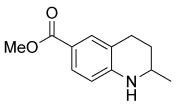
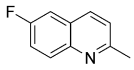
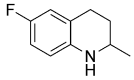
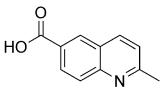
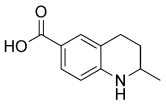
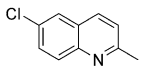
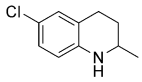
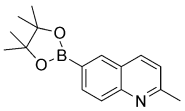
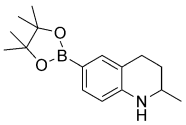
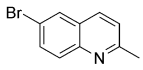
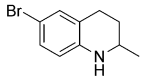
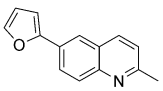
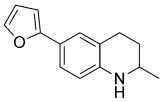
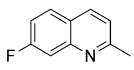
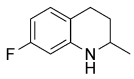
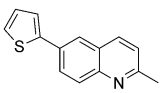


Entry	Catalyst	Hydride source	Solvent	Conv. [%][b]
1[c]	**1c**	HCO_2H/HCO_2Na (pH 4.5)	H_2O	>99
2[d]	**1c**	HCO_2H/HCO_2Na (pH 4.5)	H_2O	>99
3	**1c**	HCO_2H/HCO_2Na (pH 4.5)	H_2O	70
4	**1c**	HCO_2H/HCO_2Na (pH 2.5)	H_2O	20
5	**1c**	HCO_2H/HCO_2Na (pH 6.5)	H_2O	<5
6	**1d**	HCO_2H/HCO_2Na (pH 4.5)	H_2O	12
7	**1a**	HCO_2H/HCO_2Na (pH 4.5)	H_2O	<1
8	**1b**	HCO_2H/HCO_2Na (pH 4.5)	H_2O	8
9	[{Cp*$RhCl_2$}$_2$]	HCO_2H/HCO_2Na (pH 4.5)	H_2O	5
10[e,f]	[{Cp*$RhCl_2$}$_2$]	HCO_2H/HCO_2Na (pH 4.5)	H_2O	4
11	[{Cp*$IrCl_2$}$_2$]	HCO_2H/HCO_2Na (pH 4.5)	H_2O	38
12[g]	**1c**	HCO_2H/Et_3N (5:2)	MeOH	64
13[g]	**1c**	HCO_2H/Et_3N (5:2)	TFE	68
14[g]	**1c**	HCO_2H/Et_3N (5:2)	THF	1
15[g]	**1c**	HCO_2H/Et_3N (5:2)	Toluene	3
16[g]	**1c**	HCO_2H/Et_3N (5:2)	DCM	13
17[g]	**1c**	HCO_2H/Et_3N (5:2)	DMF	4
18	**1c**	0.1 M KOH/*i*PrOH	*i*PrOH	15
19[h]	**1c**	Et_3SiH	H_2O	n.r.

[a] See the experimental section for reaction conditions. [b] Conversion determined by ^1H NMR spectroscopy. [c] Reaction conducted at 80 °C. [d] Reaction conducted at 60 °C. [e] With 10 mol% KI. [f] This reaction proceeds well when run in HCO_2H/Et_3N (5:2) azeotrope in the absence of water and in presence of KI as an additive (see ref. [14]). [g] 0.5 mL of HCO_2H/Et_3N (5:2). [h] Et_3SiH (20 equiv); n.r. = no reaction observed.

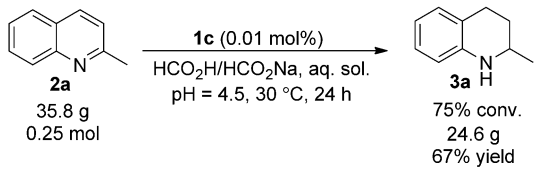
Table 2. TH of quinolines with **1c** in water.[a]



Entry	Substrate	Product		Yield [%][b]	Entry	Substrate	Product		Yield [%][b]
1			**3a**	96	14			**3n**	94
2			**3b**	93	15			**3o**	93
3[c]			**3c**	90	16			**3p**	98
4			**3d**	90	17[c,d]			**3q**	90
5[c]			**3e**	84	18[c]			**3r**	91
6			**3f**	94	19			**3s**	92
7			**3g**	97	20			**3t**	82
8			**3h**	97	21[c]			**3u**	62
9			**3i**	95	22			**3v**	95
10			**3j**	98	23			**3w**	96
11			**3k**	92	24[c]			**3x**	82
12			**3l**	95	25			**3y**	95
13			**3m**	96	26[c,e]			**3z**	84

[a] Reaction conditions (unless otherwise stated): **2** (2.5 mmol), **1c** (0.1 mol%), HCO_2H/HCO_2Na aqueous solution (pH 4.5; 3 mL; prepared using 14.0 mmol of HCO_2H and 29.4 mmol of HCO_2Na in 2.8 mL of H_2O), 30 °C, stirred in a carousel tube for 14 h; [b] Yield of isolated product. [c] Reaction was carried out at reflux. [d] Yield determined by ^1H NMR spectroscopy. [e] 0.5 mol% **1c** used.

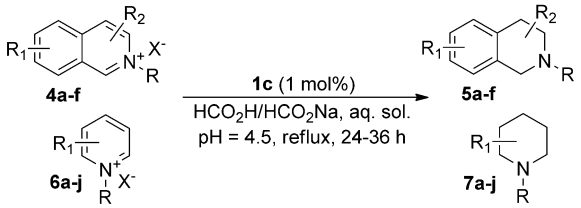
Functional groups including halogen (**2g–k**), ether (**2m–o**), amine (**2q**), amide (**2r**), ester (**2s**), carboxylic acid (**2t**), heterocycles (**2v–x**) and a trifluoromethyl group (**2p**) were all tolerated under the reaction conditions. They appear to have exhibited insignificant effect on the yields, with products isolated in average yields of >90% (Table 2, entries 7–20 and 22–24). Even a product bearing a highly sensitive functional group, that is, boronic acid pinacol ester **3u**, was isolated in 62% (Table 2, entry 21), together with 30% of the deboronated product **3a**.

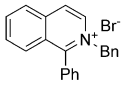
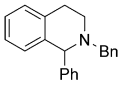
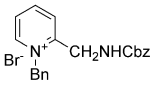
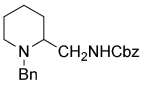
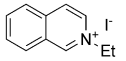
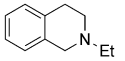
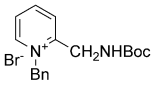
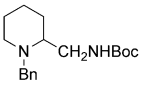
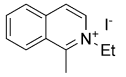
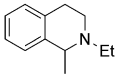
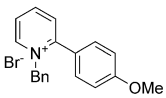
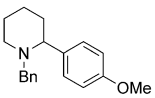
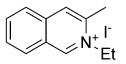
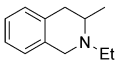
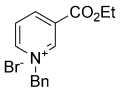
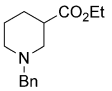
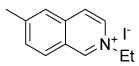
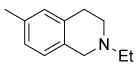
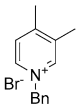
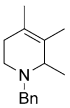
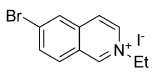
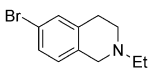
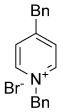
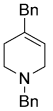
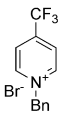
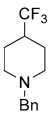
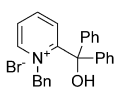
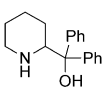
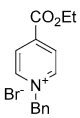
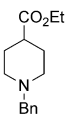


Scheme 3. Large-scale TH of 2-methylquinoline in water.

To demonstrate the potential usefulness of this method in process chemistry, **2a** was used as the model substrate for a larger scale reduction. As shown in Scheme 3, 35.8 g (0.25 mol) of **2a** was effectively reduced with just 0.01 mol% **1c** at 30 °C (75% conversion in 24 h; TON = 7500). The product was separated from the reaction mixture by a simple phase separation and purified by fractional distillation. No special equipment was required for this reaction, nor was an inert atmosphere necessary. In addition, no organic solvent was re-

Table 3. TH of isoquinolinium and pyridinium salts in water.[a]



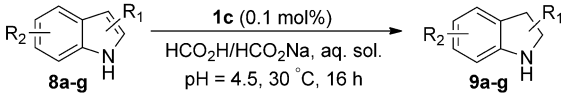
Entry	Substrate	Product		Yield [%][b]	Entry	Substrate	Product		Yield [%][b]
1			**5a**	90	9			**7c**	90
2			**5b**	95	10			**7d**	94
3[c]			**5c**	98	11			**7e**	81
4[c]			**5d**	97	12[c]			**7f**	82
5			**5e**	99	13[c]			**7g**	95
6			**5f**	91	14			**7h**	92
7			**7a**	90	15			**7i**	82
8[d]			**7b**	72	16			**7j**	80

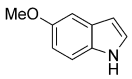
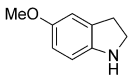
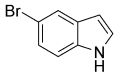
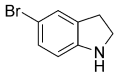
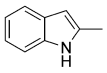
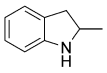
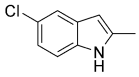
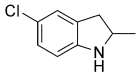
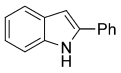
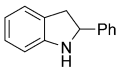
[a] Reaction conditions: isoquinolinium or pyridinium salt (2.5 mmol), **1c** (1 mol%), HCO_2H/HCO_2Na aqueous solution (pH 4.5; 3 mL; prepared using 14.0 mmol of HCO_2H and 29.4 mmol of HCO_2Na in 2.8 mL of H_2O), reflux, stirred in a carousel tube for 24 h (isoquinolinium) or 36 h (pyridinium). [b] Yield of isolated product. [c] Yield determined by ^1H NMR spectroscopy. [d] Isolated as debenzylated product after the column.

quired for the entire operation, and only minimal waste was generated, showing the protocol to be greener than traditional methods that use $NaBH_3CN$ in acetic acid or Raney nickel or Pd/Al_2O_3 under high pressure of H_2.[20,21]

Based on the successful results obtained for the TH of quinolines with **1c**, the substrate scope was expanded to more challenging isoquinolines and pyridines. However, reduction of isoquinoline and 2-phenylpyridine led to the recovery of the starting material under the reaction conditions used in Table 2 (see the Supporting Information). It was thought that activating the substrate by quaternising the nitrogen atom would lead to a higher activity.[10] This was indeed the case, and the results obtained for isoquinoline and pyridine reduction are shown in Table 3. Using optimised conditions, an array of six isoquinolinium (**4a–f**) and ten pyridinium (**6a–j**) salts were reduced. Unsubstituted isoquinolinium, 1-methyl, 3-methyl and 6-methyl isoquinolinium salts gave the highest yields (>95%; Table 3, entries 2–5). Increasing the steric bulk at the 1-position by replacing the hydrogen or methyl group with a phenyl did not affect the yield significantly (Table 3, entries 1–3). A functional group, for example, bromide, was well tolerated under the reaction conditions (Table 3, entry 6). Likewise, 2-substituted pyridinium salts (**6a–e**) were all reduced with good yields, regardless of the nature of the functional groups (Table 3, entries 7–11). Interestingly, substrates bearing an electron-withdrawing group at the 4-position gave exclusively the fully reduced piperidines, whereas those having an electron-donating group led to the partially reduced 3,4-unsaturated piperidines (Table 3, entries 13 and 14 versus 15 and 16). This phenomenon could be explained by a competitive 1,2-hydride addition versus 1,4-hydride addition (see below). Having an electron-withdrawing substituent probably renders the 4-position more electrophilic, favouring the 1,4-addition.

Table 4. TH of indoles in water.[a]



Entry	Substrate	Product		Yield [%][b]
1			**9a**	96
2			**9b**	94
3[c,d]			**9c**	30
4			**9d**	92
5[c]			**9e**	78
6[c,d]			**9f**	33
7			**9g**	n.r.

[a] Reaction conditions (unless otherwise stated): Indole (2.5 mmol), **1c** (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), 30 °C, stirred in a carousel tube for 16 h. [b] Yield of isolated product; n.r. = no reaction observed. [c] Using 0.5 mol% **1c**, at reflux and with the addition of MeOH (1 mL). [d] Yield determined by ^1H NMR spectroscopy.

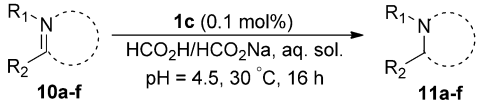
The substrate scope of indoles was examined next with **1c** under the conditions of Table 2. A range of indoles with both electron-donating and electron-withdrawing groups were reduced to the corresponding indolines in good yields (Table 4). However, TH of 5-bromoindole **8c** gave a lower yield (Table 4, entry 3). For this substrate, a thick layer of coating was always observed on the reaction vessel above the solvent level, even at reflux and with the addition of MeOH as a co-solvent. This reflects that the solubility of **8c** was an issue under the reaction conditions employed, which might have led to the lower conversion. Disappointingly, TH of the sterically hindered 2-phenylindole failed to proceed under the present reaction conditions, and 3-methylindole gave a low yield (Table 4, entries 6 and 7). One of the explanations could be the unfavourable tautomerisation of **8f** or difficulty in its protonation at the 3-position due to steric effects, following which 1,2-hydride addition could occur.

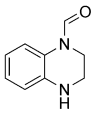
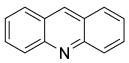
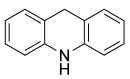
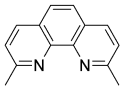
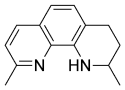
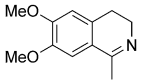
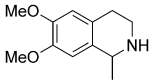
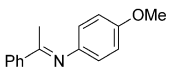
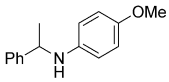
To further demonstrate the potential of **1c** as a versatile catalyst for the TH of a range of heterocycles, rather than a specialised one for a particular class of substrates, a range of diverse substrates, including cyclic and acyclic imines and other fused heterocycles, were examined (Table 5). Quinoxaline (**10a**), acridine (**10b**) and neocuproine (**10c**) were all reduced to their corresponding products in excellent yields, although the former was isolated exclusively as its mono *N*-formyl derivative (Table 5, entries 1–3). Interestingly, 1*H*-cyclopenta[*b*]pyridine **10d** was reduced at the carbocycle ring to give the pyridine **11d** (Table 5, entry 4). Both the cyclic and acyclic imines were fully reduced to give the corresponding amines **11e** and **11f**, respectively, with good yields (Table 5, entries 5 and 6). Salsolidine (**11e**) is isolated from the plants of the genus *salsola* and is a stereoselective competitive inhibitor of the enzyme monoamine oxidase.[22]

The reduction of quinolines in an acidic medium has been suggested to proceed by an ionic or outer-sphere pathway.[23] The initial hydride delivery to the protonated quinoline may occur in a 1,4-addition fashion; subsequent isomerisation and further reduction via 1,2-addition would afford the product (Scheme 4). If the reaction is initiated by 1,2-hydride addition, the resulting 1,2-dihydroquinoline may not be further reduced; but it may undergo dehydrogenation to go back to the starting material or disproportionate.[24] To gain more insight into the reaction mechanism, a combination of reactions of intermediates, isotope labelling and stoichiometric reactions was explored.

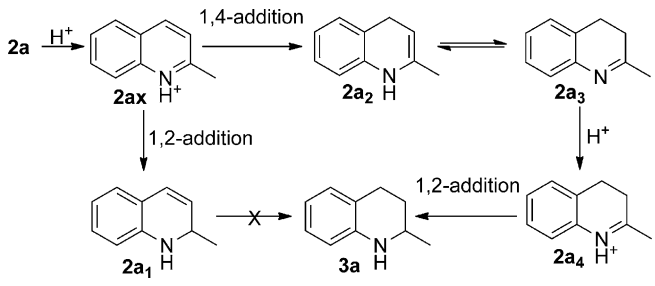
Deuterium labelling reactions were carried out on the model substrate **2a** with **1c** at 30 °C in water. By using fully deuterated reagents and solvent, 87%, 94% and 100% deuterium in-

Table 5. TH of other N-heterocycles and imines in water.[a]



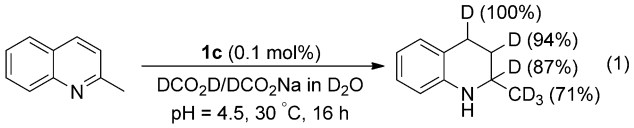
Entry	Substrate	Product		Yield [%][b]
1[c]			**11 a**	90
2			**11 b**	82
3			**11 c**	96
4[c]			**11 d**	99
5			**11 e**	98
6[d]			**11 f**	90

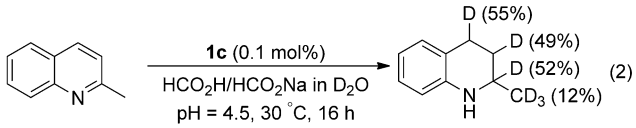
[a] Reaction conditions (unless otherwise stated): **10** (2.5 mmol), **1 c** (0.1 mol %), HCO_2H/HCO_2Na aqueous solution (pH 4.5; 3 mL; 14.0 mmol of HCO_2H and 29.4 mmol of HCO_2Na in 2.8 mL of H_2O), reflux, stirred in a carousel tube for 16 h. [b] Yield of isolated product. [c] Reaction conducted at reflux. [d] Reaction conducted at 80 °C and yield determined by ^1H NMR spectroscopy.

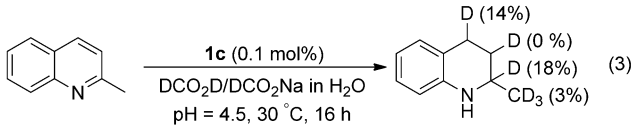


Scheme 4. Possible reaction pathways for the TH of quinolines.

corporation was observed at the 2-, 3- and 4-positions of the product, respectively [Eq. (1)]. When HCO_2Na and HCO_2H were used together with D_2O, 52%, 49%, and 55% deuterium incorporation took place at the 2-, 3- and 4-position of the product, respectively [Eq. (2)]. However, when DCO_2D and DCO_2Na were used in H_2O, only 18%, 0%, and 14% deuterium incorporation occurred at these positions, respectively [Eq. (3)].







One possible explanation for deuterium [Eq. (2)] and hydrogen [Eq. (3)] incorporation at the 2- and 3-positions is that following the formation of the iridium hydride/deuteride, the transfer of the hydride/deuteride to the substrate is the rate-limiting step. This would allow the iridium hydride/deuteride to be scrambled with the solvent [Eqs. (4) and (5)], producing a mixture of iridium hydride and deuteride and leading to the partial incorporation of deuterium into the product.[25] The reaction shown in Eq. (3) also reveals that when H_2O was used as the solvent, no deuterium was incorporated at the 3-position. This is consistent with the assumption that there is an acid-mediated enamine–imine isomerisation reaction between the hydride addition steps (Scheme 4).

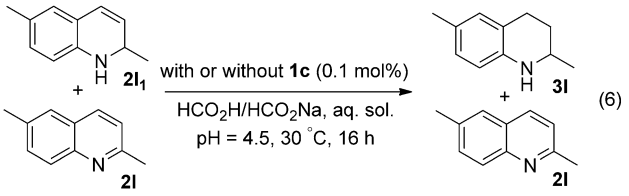
$$[Ir]{-}H + D_2O \rightleftharpoons [Ir]{-}D + HDO \quad (4)$$

$$[Ir]{-}D + H_2O \rightleftharpoons [Ir]{-}H + HDO \quad (5)$$

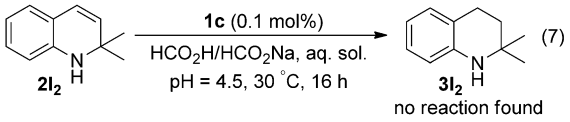
Further support to the hydride transfer being rate limiting was gained by monitoring the reduction of the protonated **2 a** (p*K*a 5.4) with **1 c** using in situ ^1H NMR spectroscopy (see the Supporting Information). As noted before, neutral **2 a** could not be reduced with an isolated, closely-related iridium hydride.[18c] The reaction was carried out in an NMR tube equipped with a Young's tap, containing 1 equivalent of **1 c** and 5 equivalents of **2 a**·HBF_4 in [D_3]MeCN. After the addition of 5 equivalents of F/T, a hydride signal was immediately detected at $\delta = -15.8$ ppm.[26] Whereas the signal of the product tetrahydroquinoline gradually increased in intensity over time, signals corresponding to the potential intermediates **2 a**$_1$, **2 a**$_2$ and **2 a**$_3$ were not observed. However, the hydride signal remained, which, together with its rapid formation, is consistent with the assumption that the transfer hydrogenation in question is turnover-limited by the hydride-transfer step.

The TH of **2 a** may yield two distinct intermediates, namely 1,2-dihydroquinoline (via 1,2-addition) and 3,4-dihydroquinoline (via 1,4-addition; Scheme 4). To gain evidence into their possible involvement in the reduction, a 1:1 mixture of dihydroquinoline **2 l**$_1$ and quinoline **2 l** was subjected to the standard reduction conditions [Eq. (6)]. In the presence of **1 c**, only the fully reduced tetrahydroquinoline **3 l** (100%) was obtained after the reaction. However, in the absence of **1 c**, 23% of **3 l** and 77% of **2 l** were obtained. In both cases, no starting dihy-

droquinoline **2l**$_1$ remained after the reaction. These results supports the hypothesis that the 1,2-addition product (e.g., **2l**$_1$) is consumed via a disproportionation pathway instead of being reduced by the catalysis of **1c**. Further evidence supporting this hypothesis comes from the observation that when **2l**$_2$ was used as a substrate, no reaction occurred [Eq. (7)].

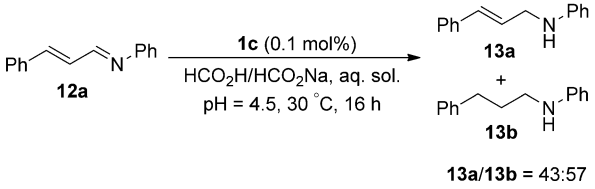


(6)



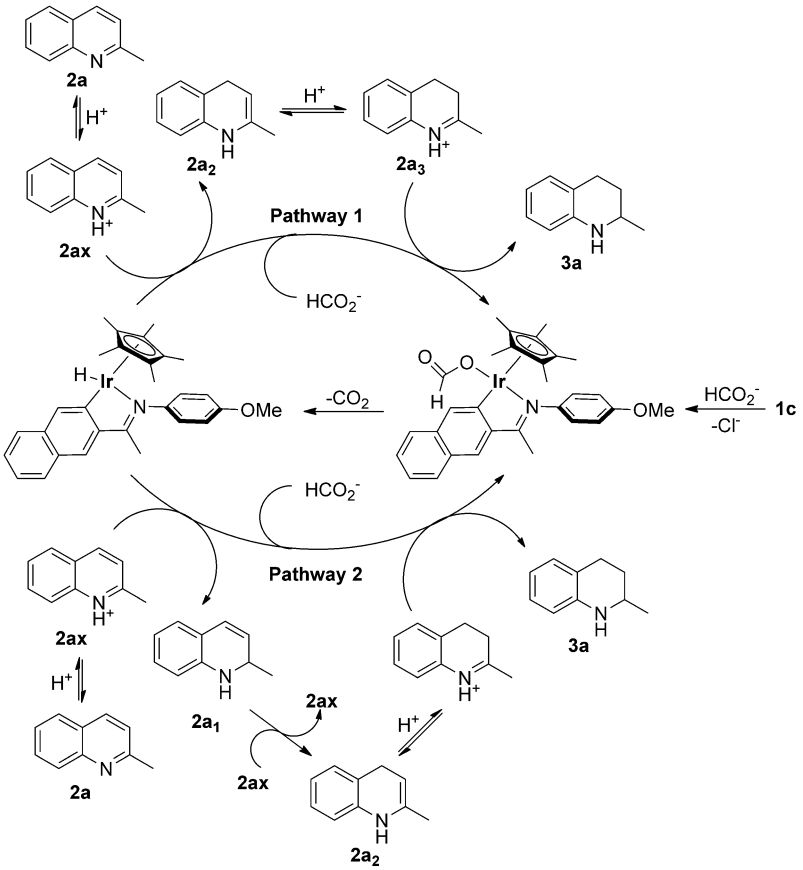
(7)

To probe whether the 1,4-addition precedes the 1,2-addition in the TH or vice versa, a model substrate, *N*-cinnamylidene aniline **12a**, was subjected to the **1c**-catalysed reduction. Under the standard reaction conditions, a mixture of **13a** and **13b** (43:57) was obtained (Scheme 5), indicating that both 1,2- and 1,4-hydride additions are likely to happen for quinoline-type substrates.



Scheme 5. TH of *N*-cinnamylidene aniline with **1c** in water.

On the basis of the experimental results presented above, a simplified mechanism is proposed for the TH of quinolines (Scheme 6). Catalyst **1c** reacts with formate to generate the active Ir-H species that can react with the **2ax** in two different pathways. In Pathway 1, **2ax** undergoes 1,4-addition to give the 1,4-dihydroquinoline **2a**$_2$, which equilibrates with **2a**$_3$ under the acidic conditions. Further reduction by a new hydride via 1,2-addition then yields **3a**. Pathway 2 involves the 1,2-hydride addition as the first step to give 1,2-dihydroquinoline **2a**$_1$, which acts as a hydrogen donor, reducing **2ax** to **2a**$_2$ with itself turning into **2ax**. The intermediate **2a**$_2$ is reduced to **3a** in the same way as in Pathway 1. While the pathways 1 and 2 are competitive, the rate of each is likely to be affected by both steric and electronic effects arising from the catalyst as well as substrate.



Scheme 6. Proposed mechanism for the TH of quinolines catalysed by **1c**.

Conclusions

In summary, a wide variety of N-heterocycles, including, but not limited to, quinolines, isoquinolines, indoles, quinoxalines and pyridinium salts, have been effectively reduced using an iridicycle catalyst in water. This reaction is applicable to large-scale synthesis with no need for specialised equipment. The use of environmentally benign solvent, renewable hydride donor and easy workup and purification provides a significant advantage for practical applications. To our knowledge, this work constitutes the first example of a versatile homogeneous

catalyst that can reduce a range of N-heterocycles in water under the TH conditions. In addition, the iridicycle has been shown to be highly effective in TH of various carbonyl compounds in water and in reductive amination to afford primary amines.[18a,l] Further work including preparation of a chiral version of this and related iridicycles is ongoing in our laboratory.

Experimental Section

Typical procedure for the TH of quinolines

Quinoline (2.5 mmol) and **1c** (1.6 mg, 2.5×10^{-3} mmol) were placed in a carousel reaction tube. HCO_2H/HCO_2Na aqueous solution of pH 4.5 (3 mL; prepared using 14.0 mmol of HCO_2H and 29.4 mmol of HCO_2Na in 2.8 mL of H_2O) was then introduced and the mixture was stirred at 30 °C for 14 h. The reaction mixture was quenched with saturated sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate (3×10 mL) and the combined organic layers were washed with brine (20 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 that was purified with flash column chromatography to afford the desired 1,2,3,4-tetrahydroquinoline.

Typical procedure for the TH of isoquinolinium and pyridinium salts

Isoquinolinium or pyridinium (2.5 mmol) and **1c** (16 mg, 2.5×10^{-2} mmol) were placed in a carousel reaction tube. HCO_2H/HCO_2Na aqueous solution of 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) was then introduced and the mixture was stirred at reflux temperature for 24 h (36 h for pyridinium). The reaction mixture was quenched with saturated sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate (3×10 mL) and the combined organic layers were washed with brine (20 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 that was purified with flash column chromatography to afford the desired 1,2,3,4-tetrahydroisoquinoline or piperidine.

Typical procedure for the TH of indoles, imines and other N-heterocycles

Imine or N-heterocycle (2.5 mmol) and **1c** (1.6 mg, 2.5×10^{-3} mmol) were placed in a carousel reaction tube. HCO_2H/HCO_2Na aqueous solution of 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) was then introduced (for substrate **8c, 8e** and **8f**, 1 mL of MeOH was added) and the mixture was stirred at 30 °C (or at reflux; refer to Tables 4 and 5 for the reaction temperature) for 16 h. The reaction mixture was quenched with saturated sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate (3×10 mL) and the combined organic layers were washed with brine (20 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 that was purified with flash column chromatography to afford the desired product.

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Keywords: green chemistry · iridium · N-heterocycles · transfer hydrogenation · water

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[26] The active hydride catalyst derived from **1 c** has been isolated and characterised: see reference [18 a] for details.

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