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Transfer hydrogenation in aqueous media

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ABSTRACT

Transfer hydrogenation has become a versatile and practical method for reduction in organic synthesis. The development of aqueous transfer hydrogenation reactions is not only fundamentally interesting in terms of understanding enzymatic catalysis, but also offers economic and environmental benefits, as water is cheap and nontoxic. In this review paper, an account of the work on transfer hydrogenation in aqueous media done by the Xiao group is given. Aqueous transfer hydrogenation of ketones, aldehydes and heterocycles as well as reductive amination reactions, including extension into biomass-derived platform molecules, has been successfully developed employing the classical Noyori-type catalysts or the newly invented iridacycles, with most of the reactions taking place "on water". Water is shown to be an enabling medium for transfer hydrogenation reactions of various features. Not only can it accelerate a reduction, it also provides a simple tool, the solution pH, to control a reaction.

1. Introduction

Transfer hydrogenation (TH), where a non-H_2 hydrogen source is used, has drawn a great deal of attention in the reduction of various polar bonds, finding numerous applications in synthetic chemistry [1–9]. Although enzyme catalysed TH using formate as hydrogen source has been taking place in aqueous media for billions of years [10], most man-made TH catalysts use organic media. The development of aqueous TH reactions is not only fundamentally interesting in terms of understanding enzymatic catalysis, but also offers economic and environmental benefits, as water is cheap and nontoxic. The research for aqueous TH reactions started in ca the 1980s [11,12], and great progress has been made since the 1990s [7,13–15]. In this review, we would like to give an account of our own work on TH in aqueous media.

2. TH in aqueous media with Noyori-Ikariya type catalysts

2.1. ATH of ketones with HCOONa in water

Due to the importance of chiral compounds, a lot of attention has been paid to developing asymmetric transfer hydrogenation (ATH) systems. One milestone in the history of ATH is the discovery of the Ru-TsDPEN (TsDPEN = *N*-(p-toluenesulfonyl)-1,2-diphenylethylenediamine) catalyst by Noyori, Ikariya, Hashiguchi and co-workers in 1995, which afforded enantiomeric excess (ee) up to 99% for the asymmetric reduction of aromatic ketones [16]. This and the related Noyori-Ikariya type catalysts, which have found broad applications and operate via a novel metal–ligand bifunctional mechanism, have since inspired intense research into ATH [17–25]. One direction is the development of aqueous ATH system based on these catalysts.

Our group has an enduring interest in asymmetric catalysis. In one of the projects, we developed a method for the immobilisation of chiral diamine ligands [26], which could be used as a platform to build supported chiral catalysts. We started our journey on TH reactions by using a poly(ethylene glycol) (PEG)-supported complex Ru-**1** for ATH in HCOOH-Et_3N mixture [26,27]. Ru-**1** catalysed the ATH of ketones effectively; but unexpectedly the catalyst recycle via solvent extraction of the chiral alcohol product was possible only when water was present as cosolvent. In its absence, much reduced conversions and ees were observed, indicating catalyst decomposition. This finding prompted us to examine the behaviour of sulfonamide ligands **2** and **3** (Scheme 1) in acetophenone reduction by HCOONa in neat water. Rather pleasingly, we found that, without any modification, the Noyori-Ikariya catalyst Ru-**2**, derived in situ from $[RuCl_2(p\text{-cymene})]_2$ and **2**, enables efficient ATH in neat water. The reaction was significantly faster than in organic media and afforded excellent enantioselectivities [28]. Thus, following the addition of 5 equivalents of HCOONa and acetophenone (acp) with

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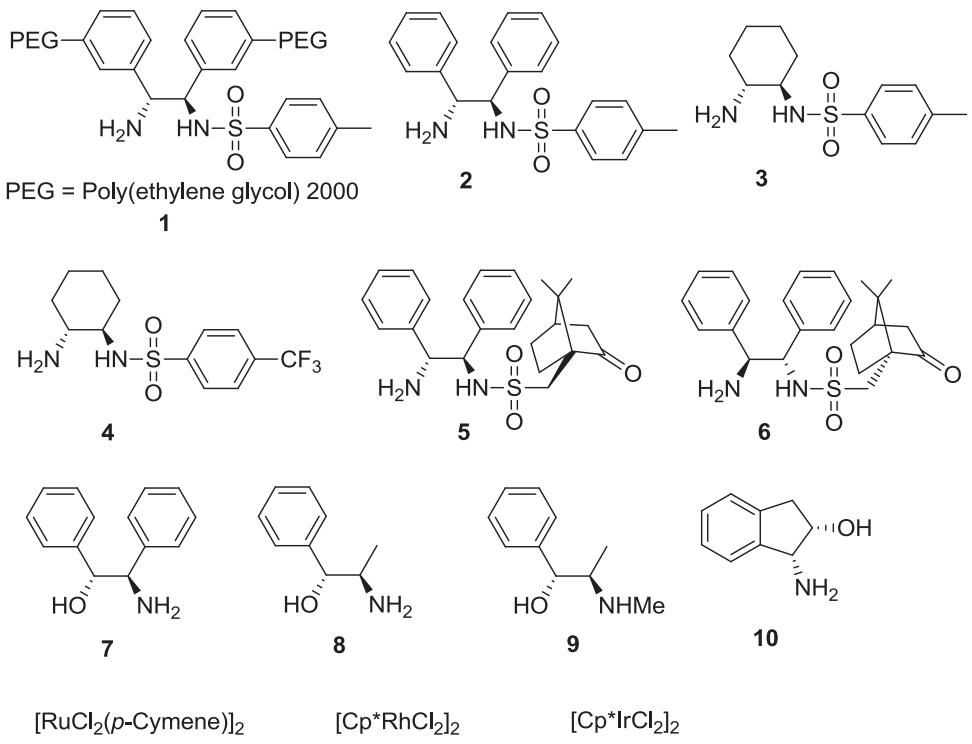


Scheme 1. Ligands and metal precursors used for ATH in water.

a molar substrate-to-catalyst ratio (S/C) of 100, the ketone was fully converted into (*R*)-1-phenylethanol in 95% ee after 1 h reaction time at 40 °C. In comparison, the reaction run in the HCOOH-NEt_3 (F/T) azeotrope afforded a conversion of less than 2% in 1 h, with full conversion requiring more than 10 h (97% ee) at 40 °C. This initial finding has since proven to be quite general, in that other ligands (shown in Scheme 1) which were designed for organic solvents are also effective for ATH in water with no need for modification or organic solvents [29–35]. In Table 1, we summarise the results obtained with various metal catalysts based on Ru, Rh and Ir, in the ATH of the benchmark substrate acp. The catalysts were usually generated from the ligand and a metal precursor at the reaction temperature in water without adding a base, for example Ru-**2** from $[RuCl_2(p\text{-cymene})]_2$ and ligand **2**. The structure of Ru-**2** prepared under such conditions has been confirmed by X-ray diffraction to be the same as the one obtained in 2-propanol [20]. These precatalysts show varying solubilities in water. Presumably their water solubility stems from chloride-water exchange, resulting in the formation of monoaqua cations. However, they show much higher solubility in ketones and alcohols, most of which are insoluble in water. Hence, we conclude that the reaction is biphasic and takes place "on water" (or in aqueous suspension). As shown in Table 1, the monotosylated diamines **1**–**6** all served as efficient ligands for the ATH of ketones in water, with almost full conversion and up to 99% ee reached in short reaction times (Entries 2–25, Table 1). Under the given conditions, the ligands **2** and **5/6** afforded the best enantioselectivity. The reaction was frequently carried out at an S/C ratio of 100; however, a high S/C ratio of 10,000 has been demonstrated to be feasible (Entry 7, Table 1).

In comparison with ATH in the azeotropic HCOOH-NEt_3 with or without water, ATH in aqueous HCOONa is much faster (Entries 1 and 2 vs 3 and 4, Table 1). This finding prompted us to explore factors that might lead to these contrasting results [30,34]. The clearest difference between the two systems was found to be the solution pH. Subsequently, the pH value was indeed found to be critical to the reaction rate and enantioselectivity [30]. As a matter of fact, efficient ATH can be performed with HCOOH-Et_3N in water, provided the ratio of HCOOH/Et_3N is controlled such that the solution is close to neutral pH (Entries 4–7, Table 1). Interestingly, while β-aminoalcohol ligands were believed to be incompatible with formic acid as a reductant for ATH of ketones [36], the commercially available simple β-aminoalcohol ligands **7**–**10** do catalyse the ATH of acetophenone by HCOONa or HCOOH/NEt_3 in water, albeit with slower rates and lower enantioselectivities than those obtained with the diamine ligands (Entries 26–38, Table 1) [32].

We also reported examples of aqueous ATH with catalysts derived from $[Cp^*RhCl_2]_2$ and $[Cp^*IrCl_2]_2$ [29,31,33,35]. Detailed studies showed that these Rh and Ir catalysts have advantageous features compared with Ru catalysts, e.g. faster reaction rates or higher ees in some cases. Moreover, the reaction with Rh-diamine catalysts can be carried out effectively in the open air without degassing and/or inert gas protection throughout, rendering the reduction much more practical.

The metal-catalysed (M = Ru, Rh, Ir) ATH has since been applied to a wide range of aromatic ketones (Table 2). The reduction is easy to perform, affording the chiral alcohols with high ee's in a short reaction time for most of the substrates at S/C ratios from 100:1 to 1000:1. While the substrate ketones are generally water-insoluble, this does not appear to have a negative effect on the reaction rates. The reduction of most ketones proceeded significantly faster in water than in azeotropic HCOOH/Et_3N. For example, the reduction of *p*-methoxyacetophenone, which is difficult under normal conditions, gave a conversion of >99% and an ee of 95% with Ru-**2** in 1 h at an S/C ratio of 100 and a temperature of 40 °C [28]. With the azeotropic HCOOH/Et_3N mixture as the reductant, the same catalyst required about 60 h to complete the reduction (97% ee) at 28 °C and an S/C ratio of 200 [17]. In the aqueous phase ATH, there appears to be no clear correlation between the electronic properties of substituents and the enantioselectivity, as shown by the reduction of *para*-OMe- and *para*-CF_3-acetophenone with Ru-**2**, with both giving ~95% ee in 2 h.

The Rh-diamine catalysts are of particular note. Apart from the normal unfunctionalised aromatic ketones which have been successfully reduced with the Ru catalysts, heterocyclic, functionalised

Table 1
Summary of ATH of acp in water.[a]

Entry	Catalyst	[H][b]	S/C	Time (h)	Conv. (%)	ee (%)	Ref
1	Ru-**1**	HCOONa	100	1	99	92	[27]
2	Ru-**2**	HCOONa	100	1	>99	95	[28]
3	Ru-**2**	F/T[c]	100	12	98	97	[28]
4	Ru-**2**	F/T-H_2O	100	1.5	>99	97	[30]
5	Ru-**2**	F/T-H_2O	1000	9	>99	96	[30]
6	Ru-**2**	F/T-H_2O	5000	57	98	96	[30]
7	Ru-**2**	F/T-H_2O	10,000	110	98	94	[30]
8	Rh-**2**	HCOONa	100	0.5	99	97	[33]
9	Rh-**2**	HCOONa[d]	100	0.5	99	97	[33]
10	Rh-**2**	HCOONa	1000	3	93	97	[33]
11	Ir-**2**	HCOONa	100	3	99	93	[33]
12	Ru-**3**	HCOONa	100	2	99	85	[31]
13	Rh-**3**	HCOONa[d]	100	0.25	>99	95	[31]
14	Ir-**3**	HCOONa[d]	100	1	99	93	[31]
15	Ru-**4**	HCOONa	100	2.5	>99	81	[37]
16	Rh-**4**	HCOONa[d]	100	0.25	>99	94	[37]
17	Ir-**4**	HCOONa	100	1.5	>99	92	[37]
18	Ru-**5**	HCOONa	100	2	99	97	[29]
19	Ru-**5**	HCOONa	1000	20	95	96	[29]
20	Rh-**5**	HCOONa	100	0.7	99	99	[29]
21	Rh-**5**	HCOONa	1000	20	89	99	[29]
22	Ir-**5**	HCOONa	100	0.7	98	97	[29]
23	Ir-**5**	HCOONa	1000	2.5	97	98	[29]
24	Ir-**6**	HCOONa	100	0.7	98	98[e]	[29]
25	Ir-**6**	HCOONa	1000	2.5	99	98[e]	[29]
26	Ru-**7**	HCOONa	100	10	95	50	[32]
27	Rh-**7**	HCOONa	100	20	85	41	[32]
28	Ir-**7**	HCOONa	100	1.5	100	27	[32]
29	Ir-**7**	F/T-H_2O	100	1.5	100	55	[32]
30	Ru-**8**	HCOONa	100	5	97	60	[32]
31	Rh-**8**	HCOONa	100	5	63	31	[32]
32	Ir-**8**	HCOONa	100	5	61	7	[32]
33	Ru-**9**	HCOONa	100	3.5	>99	73	[32]
34	Rh-**9**	HCOONa	100	22	77	68	[32]
35	Ir-**9**	HCOONa	100	2.5	100	54	[32]
36	Ru-**10**	HCOONa	100	12	84	71	[32]
37	Rh-**10**	HCOONa	100	20	92	54	[32]
38	Ir-**10**	HCOONa	100	5	>99	27	[32]

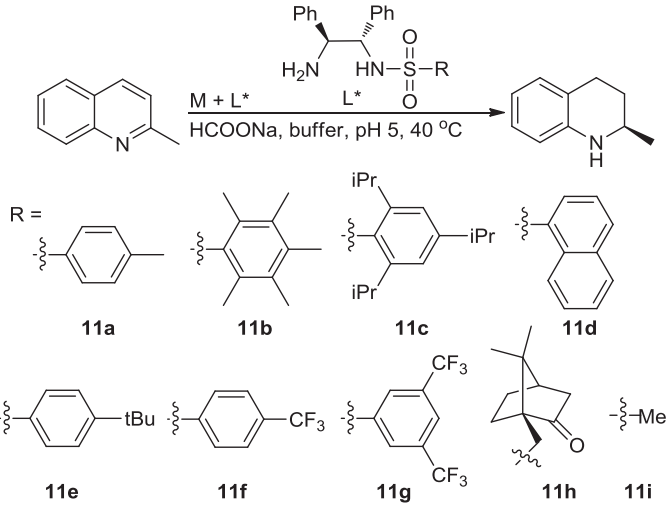
[a] Reaction conditions: the reaction was carried out in water (2 mL) or a mixture of water and azeotropic F/T under inert gas protection unless otherwise specified.
[b] 5 equiv. of hydrogen donor were used unless otherwise specified.
[c] Without water, F/T refers to the azeotropic HCOOH/Et_3N mixture.
[d] Without inert gas protection.
[e] (*S*)-Alcohol was obtained.

and multi-substituted ketones are all viable substrates with the Rh-catalysed reduction (Table 2). The Ir catalysts can also be applied to the reduction of other ketones. Most of the ketones were reduced in several hours with Ir-**5** by formate in water at an S/C ratio of 1000, affording excellent enantioselectivities. The electronic properties of the substituent on the ketones impact significantly on the reaction rate, as does the steric effect. Thus, faster reduction was observed for ketones with electron withdrawing groups, such as halides, CN or NO_2; in contrast, electron donating groups, such as Me or OMe, necessitated longer reaction times (Table 2).

2.2. ATH of quinolines with HCOONa in water

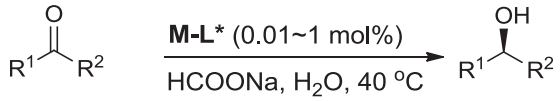
1,2,3,4-Tetrahydroquinolines exist as key structural elements in many natural products and have found broad commercial applications. In particular, optically pure tetrahydroquinolines are commonly present in alkaloids and are required in pharmaceutical and agrochemical synthesis. The most convenient route to chiral tetrahydroquinolines is the asymmetric reduction of quinolines. In continuing our research in ATH, we found that the protocol for highly efficient and enantioselective asymmetric reduction of ketones can also been applied to ATH of cyclic C=N bonds upon a slight modification of the tosylated diamine ligand and adjusting the solution pH [38].

The optimal reaction conditions were initially searched with Rh-**2** in the ATH of quinoline in aqueous media by using HCOONa as reductant. The most important finding was that the solution needs to be more acidic than that for the ATH of ketones, with the best pH



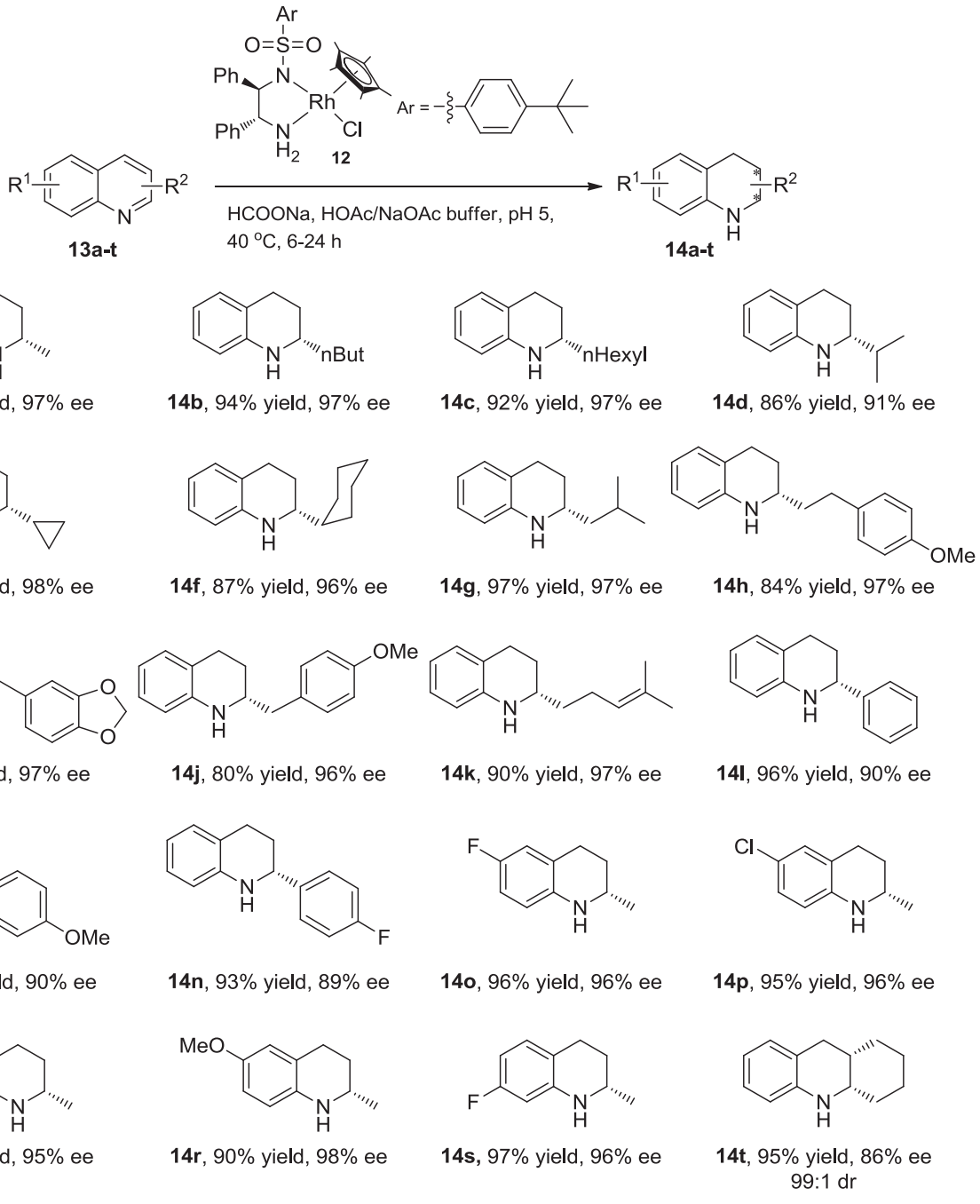
Scheme 2. Diamine ligands studied for the ATH of quinolines in water.

Table 2
ATH of ketones with formate in water.[a]



Entry	R^1	R^2	Catalyst/[H]/S/C	Time (h)	ee (%)[b]	Ref
1	4-Me-C_6H_5	Me	Ru-**2**/HCOONa/100	2	90	[28]
2	4-Me-C_6H_5	Me	Rh-**2**/HCOONa/100	6	93	[33]
3	4-Me-C_6H_5	Me	Rh-**3**/HCOONa/100	0.5	92	[31]
4	4-Me-C_6H_5	Me	Rh-**4**/HCOONa/100	0.5	91	[37]
5	4-Me-C_6H_5	Me	Ir-**5**/HCOONa/1000	8.5	92	[29]
6	4-OMe-C_6H_5	Me	Ru-**2**/HCOONa/100	2	95	[28]
7	4-OMe-C_6H_5	Me	Ru-**2**/HCOOH-Et_3N/100	5	97	[30]
8	4-OMe-C_6H_5	Me	Rh-**2**/HCOONa/100	20	97	[33]
9	4-OMe-C_6H_5	Me	Rh-**3**/HCOONa/100	0.5	93	[31]
10	4-OMe-C_6H_5	Me	Ir-**5**/HCOONa/1000	22	97	[29]
11	4-Cl-C_6H_5	Me	Ru-**1**/HCOONa/100	1.2	89	[27]
12	4-Cl-C_6H_5	Me	Ru-**2**/HCOONa/100	2	91	[28]
13	4-Cl-C_6H_5	Me	Ru-**2**/HCOOH-Et_3N/1000	11	93	[30]
14	4-Cl-C_6H_5	Me	Rh-**2**/HCOONa/100	0.4	94	[33]
15	4-Cl-C_6H_5	Me	Rh-**2**/HCOONa/1000	3	94	[33]
16	4-Cl-C_6H_5	Me	Rh-**3**/HCOONa/100	0.17	94	[31]
17	4-Cl-C_6H_5	Me	Rh-**4**/HCOONa/100	0.17	92	[37]
18	4-Cl-C_6H_5	Me	Ir-**5**/HCOONa/1000	2	96	[29]
19	4-CF_3-C_6H_5	Me	Ru-**2**/HCOONa/100	2	94	[28]
20	4-CF_3-C_6H_5	Me	Ru-**2**/HCOOH-Et_3N/100	1.3	95	[30]
21	4-CF_3-C_6H_5	Me	Rh-**2**/HCOONa/1000	1.8	94	[33]
22	4-CF_3-C_6H_5	Me	Rh-**3**/HCOONa/100	0.17	91	[31]
23	4-Br-C_6H_5	Me	Ru-**2**/HCOONa/1000	18	93	[28]
24	4-Br-C_6H_5	Me	Rh-**2**/HCOONa/1000	4	95	[30]
25	4-Br-C_6H_5	Me	Rh-**3**/HCOONa/100	0.25	94	[31]
26	4-Br-C_6H_5	Me	Ir-**5**/HCOONa/1000	1.8	95	[29]
27	4-CN-C_6H_5	Me	Ru-**2**/HCOOH-Et_3N/100	1.5	93	[30]
28	4-CN-C_6H_5	Me	Rh-**2**/HCOONa/1000	4.5	92	[33]
29	4-CN-C_6H_5	Me	Rh-**3**/HCOONa/100	0.4	90	[31]
30	4-NO_2-C_6H_5	Me	Ru-**2**/HCOOH-Et_3N/100	2	85	[30]
31	4-NO_2-C_6H_5	Me	Rh-**2**/HCOONa/100	0.5	88	[33]
32	4-NO_2-C_6H_5	Me	Rh-**3**/HCOONa/100	0.75	87	[31]
33	4-NO_2-C_6H_5	Me	Ir-**5**/HCOONa/1000	2	93	[29]
34	3-OMe-C_6H_5	Me	Ru-**2**/HCOONa/100	2	94	[28]
35	3-OMe-C_6H_5	Me	Ru-**2**/HCOOH-Et_3N/100	2.5	95	[30]
36	3-OMe-C_6H_5	Me	Rh-**2**/HCOONa/100	0.5	98	[33]
37	3-OMe-C_6H_5	Me	Rh-**3**/HCOONa/100	0.5	93	[31]
38	3-OMe-C_6H_5	Me	Ir-**5**/HCOONa/1000	3	98	[29]
39	2-OMe-C_6H_5	Me	Ru-**2**/HCOONa/100	2	72	[28]
40	2-OMe-C_6H_5	Me	Rh-**2**/HCOONa/100	24	81	[33]
41	2-OMe-C_6H_5	Me	Rh-**3**/HCOONa/100	1	79	[31]
42	2-OMe-C_6H_5	Me	Ir-**5**/HCOONa/1000	21	85	[29]
43	2-Me-C_6H_5	Me	Ru-**2**/HCOONa/100	6	80	[28]
44	2-Me-C_6H_5	Me	Rh-**3**/HCOONa/100	1	80	[31]
45	2-Me-C_6H_5	Me	Ir-**5**/HCOONa/1000	29	93	[29]
46	2-Cl-C_6H_5	Me	Ru-**1**/HCOONa/100	1.5	85	[27]
47	2-Cl-C_6H_5	Me	Ru-**2**/HCOONa/100	2	89	[28]
48	2-Cl-C_6H_5	Me	Rh-**2**/HCOONa/100	1	71	[33]
49	2-Cl-C_6H_5	Me	Rh-**3**/HCOONa/100	0.3	77	[31]
50	2-Cl-C_6H_5	Me	Ir-**5**/HCOONa/1000	3	88	[29]
51	C_6H_5	Et	Ru-**2**/HCOONa/100	2	86	[28]
52	C_6H_5	Et	Rh-**3**/HCOONa/100	1	92	[31]
53	C_6H_5	Et	Ir-**5**/HCOONa/1000	9.5	97	[29]
54	2-Furanyl	Me	Rh-**2**/HCOONa/100	0.08	99	[30]
55	2-Furanyl	Me	Rh-**3**/HCOONa/100	0.08	99	[31]
56	2-Thiophenyl	Me	Rh-**2**/HCOONa/100	1.5	99	[30]
57	2-Thiophenyl	Me	Rh-**3**/HCOONa/100	0.25	94	[31]
58	3-Thiophenyl	Me	Rh-**3**/HCOONa/100	0.75	99	[31]
59	4-Pyridyl	Me	Rh-**2**/HCOONa/100	0.5	98	[30]
60	3-Pyridyl	Me	Rh-**2**/HCOONa/100	16	78	[30]
61	2-Pyridyl	Me	Rh-**2**/HCOONa/100	24	98	[30]
62	2-Naphthyl	Me	Ru-**1**/HCOONa/100	8	92	[27]
63	2-Naphthyl	Me	Ru-**2**/HCOONa/100	3	95	[28]
64	2-Naphthyl	Me	Rh-**2**/HCOONa/100	0.75	96	[30]
65	2-Naphthyl	Me	Rh-**3**/HCOONa/100	0.75	95	[31]
66	2-Naphthyl	Me	Rh-**4**/HCOONa/100	0.75	96	[37]
67	2-Naphthyl	Me	Ir-**5**/HCOONa/1000	4	97	[29]
68	1-Indanone		Ru-**1**/HCOONa/100	3	92	[27]
69	1-Indanone		Ru-**2**/HCOONa/100	2	95	[28]
70	1-Indanone		Rh-**2**/HCOONa/100	9	97	[30]
71	1-Indanone		Rh-**3**/HCOONa/100	0.5	95	[31]
72	1-Tetralone		Ru-**1**/HCOONa/100	3	92	[27]
73	1-Tetralone		Ru-**2**/HCOONa/100	3	94	[28]
74	1-Tetralone		Rh-**2**/HCOONa/100	3	99	[30]
75	1-Tetralone		Rh-**3**/HCOONa/100	0.5	97	[31]

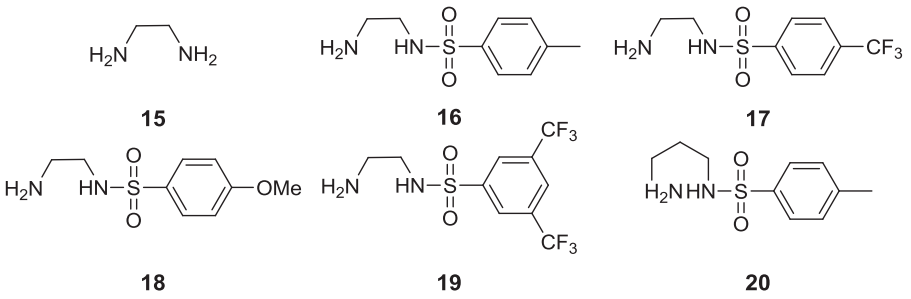
[a] For reaction conditions see Table 1. Full conversion and good to excellent isolated yields were obtained in all cases.
[b] Determined by GC or HPLC with chiral column.



Scheme 3. Examples of ATH of quinolines with the rhodium catalyst **12** in water.

being 5, which should be kept approximately constant throughout the ATH. A buffer solution of HOAc/NaOAc was chosen to minimise the pH fluctuation, ensuring complete reduction. A series of modified diamine ligands were subsequently screened on this basis and the 4-*tert*-butylphenyl-substituted ligand **11e** afforded the best reactivity and enantioselectivity (Scheme 2).

Various quinoline derivatives were subjected to the ATH catalysed by **12** under the conditions optimised. Excellent enantioselectivities and yields were observed for a range of substrates (Scheme 3). Thus, the ATH of quinoline **13a** afforded the 1,2,3,4-tetrahydroquinoline in 96% yield with 97% ee in 6 h. Notably, the ATH was carried out in air, without degassing. When the reaction was performed under nitrogen, no significant difference in either the reduction rate or the enantioselectivity was observed. The chain length of the alkyl substituents at the 2-position had little effect on the enantioselectivity (**14a**–**14d**); the same was true for various substituents at 6- or 7-position (**14o**–**14r**). Of particular note are the excellent ee values observed for quinolines with sterically more demanding substituents at the 2-position (**14d**–**14k**), although lower yields were encountered in some cases. The hydrogenation of some of these substrates, for example, hydrogenation of 2-(4-methoxybenzyl)-quinoline (**13j**) to **14j**, with H_2 was challenging. Furthermore, isolated C=C bonds were tolerated under these conditions (**14k**); overreduction only happened after a prolonged reaction time of about 9 h. A problem arose with the less basic, 2-phenyl-substituted substrate **13l**. When the precatalyst was used at pH 5, only 30% conversion was observed in 24 h. However, when the buffered solution was adjusted to a lower pH value of 4, and the ligand **11g** was combined with $[(Cp^*RhCl_2)_2]$ to form the catalyst, **13l** was reduced to **14l** in 96% yield with 90% ee. Similar results



Scheme 4. Selected diamine ligands used for TH of aldehydes in water.

were obtained with **13m** and **13n**. Asymmetric hydrogenation reactions of substrates of this type with H_2 and organometallic catalysts tend to proceed with lower enantioselectivities. Also interesting is that 2,3-di-substituted quinoline **13t** was reduced to **14t** with high enantioselectivity. It was proposed that a possible dynamic kinetic resolution in the ATH may occur since it is difficult for Noyori-type catalyst to reduce the enamine intermediate after 1,4-hydrogenation of quinoline substrate, which is the reduction of a C=C double bond.

2.3. TH of aldehydes in water

In a related study, Ir complexes containing tosylated ethylenediamines (**15**–**20**, Scheme 4) were found to be excellent catalysts for the reduction of aldehydes by HCOONa in neat water, providing fast rate and excellent chemoselectivity towards the formyl group [39]. Whilst the reduction of benzaldehyde with $[Cp^*IrCl_2]_2$ afforded a turnover frequency of only 20 h^{-1}, introduction of a diamine ligand led to a dramatic increase in the reaction rate. In particular, Ir-**17**, formed in situ from $[Cp^*IrCl_2]_2$ and **17**, afforded turnover frequencies of up to 1.3×10^5 h^{-1} in the transfer hydrogenation of benzaldehyde. Under these conditions, 5.30 g of benzaldehyde was reduced to give phenylmethanol in 98% isolated yield (5.28 g) in 1 h with 0.4 mg of $[Cp^*IrCl_2]_2$, demonstrating the superior activity, robustness and scalability of the aqueous Ir(III) catalytic system.

The aqueous TH system works for aromatic, α,β-unsaturated and aliphatic aldehydes and for those bearing functional groups, such as halo, acetyl, alkenyl and nitro groups, and is highly chemoselective towards the formyl group (Scheme 5). For example, 4-acetylbenzaldehyde was reduced only to 4-acetylphenylethanol, and the reduction of 4-acetylcinnamaldehyde took place without affecting the ketone and olefin double bonds. Furthermore, the reduction is highly efficient and can be carried out in air, without inert gas protection throughout. Thus, S/C ratios of 2000–10,000 were feasible for both Ir-**16** and Ir-**17**, although the electron-deficient Ir-**17** generally displayed a higher catalytic activity than Ir-**16**. The same aldehyde substrates have also been reduced with H_2 in water with Ir-**17** as the catalyst [40]. Again, a wide range of aldehydes, including aromatic, aliphatic, heterocyclic and α,β-unsaturated aldehydes, were readily reduced. And as with the TH, the hydrogenation is efficient and chemoselective and runs in neat water with no need for an organic cosolvent. In comparison with TH, however, the hydrogenation was less efficient in terms of catalyst loading.

2.4. TH of quinoxalines in water

The same iridium catalyst, Ir-**17**, has also been explored for the TH of quinoxalines in a project in collaboration with Professors Xu and Fan [41]. As shown in Table 3, a variety of quinoxaline derivatives were successfully reduced, in a buffered aqueous formate solution, to the corresponding tetrahydroquinoxalines in good to excellent yields under mild conditions, with or without inert gas protection. Again the pH value of the solution was crucial for the reduction. There was a pH window for optimum rate, and the use of HOAc/NaOAc buffer solution was essential for maintaining a stable pH during the reaction.

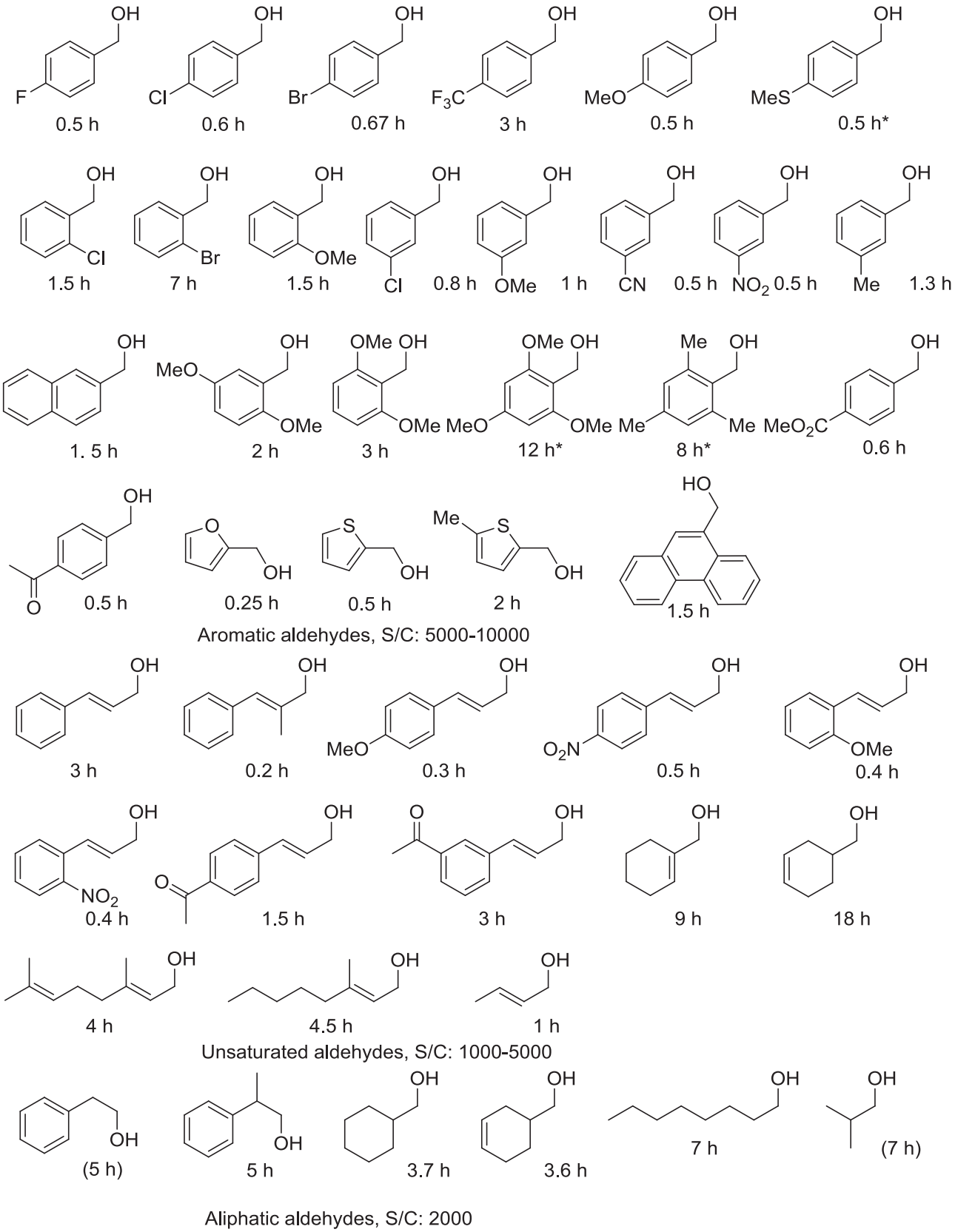
3. TH in aqueous media with iridacycles

The Noyori-Ikariya type catalysts can be applied to the ATH/TH of cyclic imine bonds (C=N) in aqueous media [42,43]. This prompted us to try to introduce this protocol to ATH/TH of acyclic imines. Disappointingly, the reduction was not successful under many reaction conditions screened. However, a very interesting cyclometalated iridium complex was observed in the TH of 4-methoxy-*N*-(1-phenylethylidene)aniline, resulting from the in situ reaction of $[Cp^*IrCl_2]_2$ with the imine substrate [44]. A variety of cyclometalated iridium complexes, iridacycles, have since been synthesised (Scheme 6) and proven to be highly efficient catalyst in a range of reactions, such as transfer hydrogenative reductive amination [45–47], hydrogenation of acyclic imines [48,49] and heterocycles [50], aqueous TH of carbonyl groups [51] and dehydrogenation of formic acid [52] and heterocycles [53]. The key intermediates for transfer hydrogenation, the iridium hydrides, have been isolated and characterised [54]. A significant advantage of these iridacycles is that they are easy to synthesise and stable in air.

3.1. TH of ketones and aldehydes in water

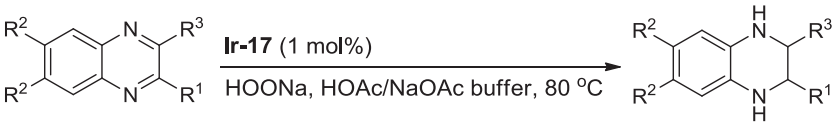
Our previous work on aqueous-phase ketone reduction revealed that water can accelerate ketone reduction, and the solution pH has a dramatic effect on both the catalytic activity and enantioselectivity, when using the Noyori-Ikariya type catalysts [30,34]. We envisioned that transfer hydrogenation of ketones with the cyclometalated iridium complexes may also be feasible in water; but the reduction rate may vary with the solution pH as well.

Using formate as a reductant, we first investigated the reduction of acp with precatalysts **24** and **25** in water [51]. The transfer hydrogenation did take place, even at a high S/C ratio of 2000, but only under certain acidic conditions. The highest reaction rate was observed at pH 3.5 for **24** and pH 2.5 for **25**. These optimal values are quite different from those observed with the previous Noyori-Ikariya catalysts, which show best performance at neutral pH [30,34]. This difference is most likely due to that the reduction with the iridacycles necessitate activation of the ketone by an acidic medium which provides hydrogen-bonding hydroxonium ion, whereas the Noyori-Ikariya catalyst needs basic conditions to generate the active $16e^-$ catalytic intermediate and is bifunctional, in which the ligand NH proton activates the substrate [55]. However, when the pH becomes too low, the active catalytic species, iridium hydride, will be protonated. Hence, there should be an optimal pH value to balance the two competing reactions. Interestingly,



Scheme 5. Examples of TH of aldehydes to alcohols with Ir-**16** by HCOONa in water at 80 °C, with full conversion and >85% isolated yields obtained in all cases. *S/C = 1000.

Table 3
TH of quinoxalines with formate in buffered water.[a]



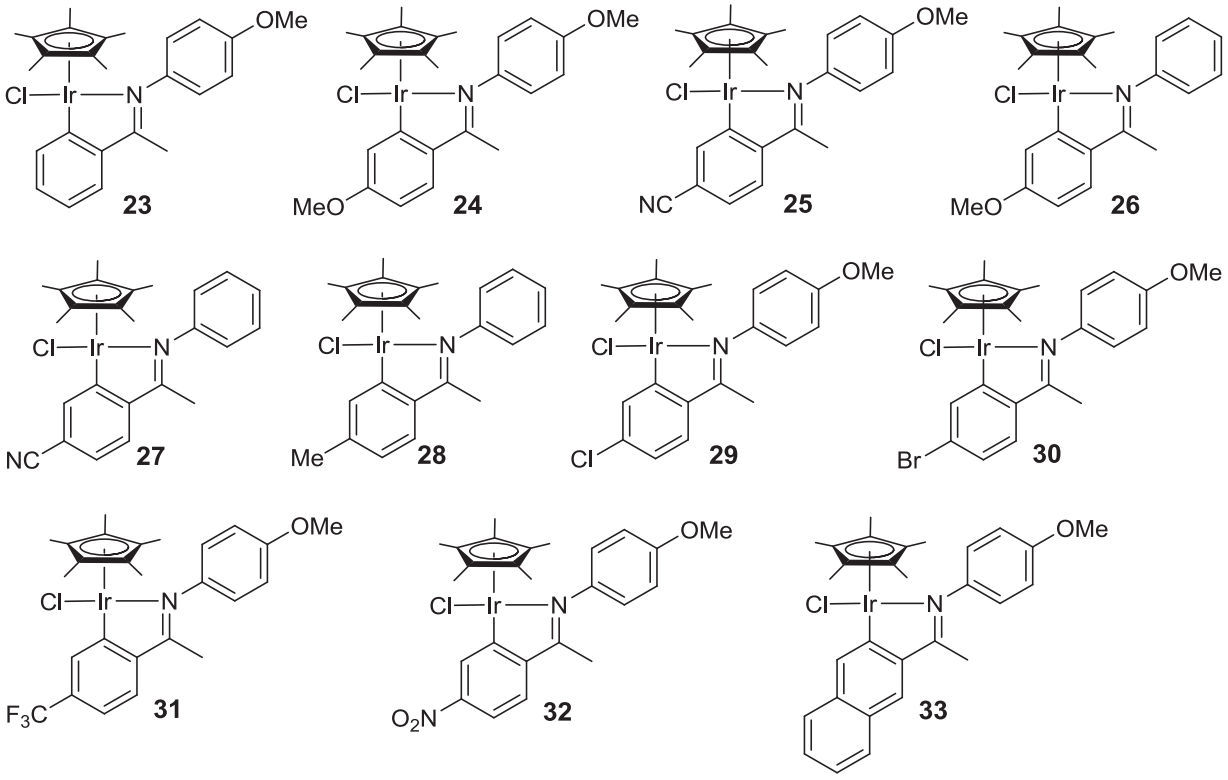
21a-r 22a-r

Entry	$R^1/R^2/R^3$	Time (h)	Yield (%)[b]	Ref
1	Me/H/H	0.25	96	[41]
2	Et/H/H	1	97	[41]
3	*i*But/H/H	2	96	[41]
4	Hexyl/H/H	2	97	[41]
5	Cyclohexyl/H/H	6	92	[41]
6	Me/Me/H	1	97	[41]
7	Et/Me/H	1	96	[41]
8	H/H/H	0.25	97	[41]
9	Me/H/Me	4	94	[41]
10[c]	C_6H_5/H/H	10	97	[41]
11[c]	4-F-C_6H_4/H/H	10	97	[41]
12[c]	4-Cl-C_6H_4/H/H	10	95	[41]
13[c]	4-Br-C_6H_4/H/H	10	95	[41]
14[c]	4-MeO-C_6H_4/H/H	10	97	[41]
15[c]	4-C_6H_4-C_6H_4/H/H	10	91	[41]
16[d]	C_6H_5CHCH/H/H	12	95	[41]
17[d]	2-Cl-C_6H_4CHCH/H/H	12	96	[41]
18[d]	3-NO_2-C_6H_4CHCH/H/H	12	95	[41]

[a] Reaction conditions: quinoxalines 21 (0.5 mmol), $[Cp^*IrCl_2]_2$ (2.5 μmol), **17** (6 μmol), HCOONa (5 mmol), 5 M HOAc/NaOAc buffer (5 mL), pH = 5.5, 80 °C.
[b] Isolated yield.
[c] The reaction was carried out at pH 4.3 in 5 M HOAc/NaOAc (5 mL) and EtOAc (0.3 mL).
[d] The reaction was carried out at pH 4.5 in 5 M HOAc/NaOAc buffer solution.

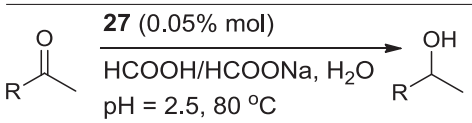
the precatalyst **24** bearing an electron donating methoxy group and precatalyst **25** with an electron withdrawing cyano group require different pH values for achieving their best activities. The higher optimal pH value for **24** is likely to result from its higher hydricity conferred by the methoxy group. Subsequent screening established **27** to be more active.

A range of aromatic ketones were reduced with the Iridacycle **27** at pH 2.5, affording good to excellent isolated yields in 4–12 h (Table 4). Substrates with *para*-electron donating substituents showed lower activities (Entry 2 and 3, Table 4) than *para*-electron withdrawing substituents (Entries 4 and 5, Table 4). However, the ketone with a *para*-cyano group showed relatively



Scheme 6. Selected examples of cyclometalated iridium catalysts.

Table 4
TH of ketones with the cyclometalated iridium **27** in water.[a]



Entry	R	Time (h)	Conv. (%)[b]	Ref
1	C_6H_5	4	96	[51]
2[c]	4-Me-C_6H_5	12	87	[51]
3[d]	4-OMe-C_6H_5	12	79	[51]
4	4-NO_2-C_6H_5	4	97	[51]
5	4-CF_3-C_6H_5	4	95	[51]
6	4-CN-C_6H_5	12	91	[51]
7[c]	4-F-C_6H_5	12	89	[51]
8[e]	4-Cl-C_6H_5	12	89	[51]
9[e]	4-Br-C_6H_5	12	94	[51]
10	3-NO_2-C_6H_5	4	96	[51]
11[c]	3-Br-C_6H_5	12	93	[51]
12[c]	3-CF_3-C_6H_5	12	91	[51]
13[e]	3,5-$(CF_3)_2$-C_6H_5	12	90	[51]
14[e]	2-F-C_6H_5	12	91	[51]
15	2-Naphthyl	4	89	[51]
16[e]	$C_6H_5(CH_2)_2$	12	97	[51]
17[c,f]	$CH_3(CH_2)_5$	12	100	[51]
18[c,f]	-$(CH_2)_5$-	12	100	[51]
19[g]	C_6H_5	24	97	[51]

[a] Reaction conditions: ketone (5 mmol), catalyst (0.0025 mmol), pH 2.5 aqueous HCOOH–HCOONa solution (4 mL), 80 °C.
[b] Isolated yield.
[c] S/C = 1000.
[d] S/C = 200.
[e] S/C = 500.
[f] Determined by GC.
[g] 6.00 g of acp was used.

low activity, probably due to the coordination ability of the cyano group (Entry 6, Table 4). Similarly, *para*-halogen atoms on the phenyl ring render the substrates less reactive than acetophenone (Entries 7–9, Table 4). *meta*- and *ortho*-Substituents afforded similar or slightly worse activity than *para*-substituents (Entries 10–14, Table 4), while ketones with a naphthyl group showed good activity (Entry 15, Table 4). Aliphatic ketones are also viable substrates (Entries 16–18, Table 4). To demonstrate the practical applicability of the catalyst, a larger scale reduction of acp was carried out under the conditions shown in Table 4. Thus, TH of acp at a 6.00 g scale was achieved under the standard reaction conditions, where phenethyl alcohol was obtained in 97% isolated yield in 24 h at a S/C ratio of 2000.

The reduction of aldehydes was also explored under the optimal conditions for ketones [51]. Aldehydes are less reactive than ketones under these conditions, generally requiring a lower S/C and 12 h reaction time. This may be due to the aldehyde existing mainly in its hydrate form. Nonetheless, a series of aromatic aldehydes were reduced to afford aromatic alcohols in moderate to excellent yields at S/C = 1000 Table 5. However, the influence of electron-withdrawing and electron-donating substituents on the catalytic activity is not obvious under the conditions used. These results, together with those shown in Table 4, demonstrate the wide substrate scope of the protocol and hence the potential of the iridacycles in aqueous-phase organic synthesis.

3.2. Reductive amination of ketones and aldehydes in water

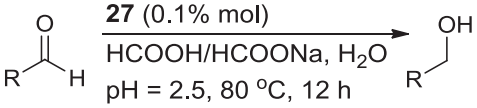
Aqueous-phase reductive amination (RA) reactions are scarce in the literature. This is not surprising, as water is generally thought to be adverse for the formation of imines, key intermediates in the RA reactions. In fact, drying agents are sometimes used to remove water generated from the imine formation step [56,57]. Due to the high activity observed with our iridacycle catalysts for RA in organic solvent [44], we were interested in developing a greener version of the reaction by replacing the organic solvent with water.

In our initial study of the aqueous RA, we chose **24** as catalyst and sodium formate as hydrogen source for the RA of acp with *p*-anisidine [45]. Imine formation from the ketone and amine and the subsequent imine reduction are known to benefit from acidic conditions. With this in mind, we first examined the effect of the pH value of the solution on the model reaction, by using HCOOH and HCOONa to adjust the pH values. It was found that both the catalytic activity and selectivity were influenced dramatically by the pH of the solution. At pH 4.8, the best selectivity was observed without sacrificing too much of the activity. Thus, pH 4.8 was chosen for further optimisation. A series of iridacycles (**25**–**33**) were examined and the complex **33**, the structure of which was confirmed by X-ray diffraction, provided the best activity. Under the optimal conditions, 95% isolated yield was obtained for the reaction of acp with *p*-anisidine.

Aromatic ketones with various amines were firstly examined for the RA with catalyst **33** in the aqueous HCOOH/HCOONa system. The results are shown in Table 6. Excellent yields were obtained for aromatic ketones with both electron-withdrawing and electron-donating substituents in 2 h with S/C of 1000 (Entries 1–10, Table 6). A lower pH of 4.2 was required for the reaction of β-ketoester to afford amino ester (Entry 11, Table 6). The RA is more significantly affected by the amine partners, however. For aromatic amines, relatively lower yields were obtained for substituents other than *para*-OMe (Entries 12–16, Table 6). This appears to suggest that the RA is rate limited by the step of the imine formation. Aliphatic amines were viable substrates; for instance, 87% yield was obtained for benzyl amine with acp at S/C of 2000 in 4 h. A chiral amino acid ester could also act as the amine source, providing excellent diastereoselectivity, albeit with low yield.

Subsequently, the reactions of aliphatic ketones with various amines were investigated (Table 7). Higher activities were generally observed for aliphatic ketones. An S/C of 2000 can be employed

Table 5
TH of aldehydes with **27** in water.[a]



Entry	R	Yield (%)[b]	Ref
1[c]	C_6H_5	96	[51]
2	3-Me-C_6H_5	79	[51]
3	4-OMe-C_6H_5	73	[51]
4	4-NO_2-C_6H_5	75	[51]
5	4-CF_3-C_6H_5	93	[51]
6[c]	4-F-C_6H_5	94	[51]
7	4-Cl-C_6H_5	80	[51]
8	2,4-$(Cl)_2$-C_6H_5	62	[51]

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

for most of the substrates. Again, aromatic amines with electron-withdrawing substituents showed lower activities. Although good yield was obtained for benzylamine under the standard conditions, other aliphatic amines showed poorer activities.

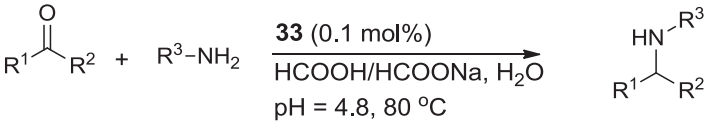
Aldehydes were more reactive than ketones in general (Table 8). Over 90% yield was obtained for most of the aromatic aldehydes reacting with *para*-anisidine at S/C of 2000 in 2 h. The only exception was found for *para*-chlorobenzaldehyde, which gave a lower yield of 79%. Aliphatic amines generally showed better activity in reactions with aldehydes than with ketones. For example, 97% yield was achieved for *n*-octylamine at S/C of 2000 in 2 h (Entry 16, Table 8). The lower steric hindrance of the aldehydes compared with the ketones renders their reaction with secondary amines much easier. 98% yield was obtained for the reaction of *N*-methylbenzylamine with benzylaldehyde (Entry 20, Table 8). The methyl ester of phenylalanine is also a good amine donor. Higher catalyst to substrate ratio (S/C) was tested for the reaction of benzyaldehyde with *para*-anisidine to explore the potential application of the catalytic system in practical synthesis of amines. At pH 4.6, the reaction with a S/C of 1×10^5 (250 mmol scale) afforded 95% yield in 48 h. This is the highest S/C ratio ever reported for RA reactions (Entry 2, Table 8).

3.3. Reductive amination of levulinic acids in water

More challenging applications of these iridacycle catalysts have been demonstrated in the RA of levulinic acid (LA) into pyrrolidinones via TH in water very recently [47]. As is well-known, renewable biomass could be an ideal replacement for fossil resources, which are limited and non-renewable, to provide fuels and particularly, chemicals. LA, which can be obtained by simple acidic dehydration of carbohydrates, has been identified as a platform chemical from biomass-derived products. The RA of LA with formic acid as hydrogen source would be ideal, as formic acid is a by-product during the production of LA. By using our iridacycle catalysts, we discovered the first true TH system for RA of LA to produce pyrrolidinones using formic acid as the hydrogen source.

Our initial studies revealed that this reaction was also affected strongly by solution pH, with pH 3.5 identified as the best pH value for the **24**-catalysed RA of LA with *para*-anisidine. After screening of different iridacycle catalysts and optimisation of reaction conditions, we examined the substrates scope for the RA of LA. The reaction was carried out at S/C ratio of 2000 and pH 3.5 with a 3.2 mmol scale of LA. As can be seen from Table 9, the RA afforded good yields for a range of aromatic amines. In particular, those

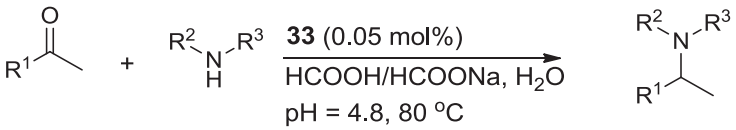
Table 6
RA of aromatic ketones with amines in water.[a]



Entry	R^1	R^2	R^3	Time (h)	Yield (%)[b]	Ref
1	C_6H_5	Me	4-MeO-C_6H_5	2	95	[45]
2	4-Me-C_6H_5	Me	4-MeO-C_6H_5	2	98	[45]
3	4-MeO-C_6H_5	Me	4-MeO-C_6H_5	2	95	[45]
4	4-F-C_6H_5	Me	4-MeO-C_6H_5	2	94	[45]
5	4-Cl-C_6H_5	Me	4-MeO-C_6H_5	2	98	[45]
6	4-Br-C_6H_5	Me	4-MeO-C_6H_5	2	98	[45]
7	4-CN-C_6H_5	Me	4-MeO-C_6H_5	2	98	[45]
8	4-CF_3-C_6H_5	Me	4-MeO-C_6H_5	2	96	[45]
9	4-NO_2-C_6H_5	Me	4-MeO-C_6H_5	2	93	[45]
10	2-Naphthyl	Me	4-MeO-C_6H_5	2	92	[45]
11[c]	C_6H_5	CH_2CO_2Me	4-MeO-C_6H_5	12	71	[45]
12	C_6H_5	Me	C_6H_5	2	82	[45]
13	C_6H_5	Me	4-Me-C_6H_5	2	91	[45]
14	C_6H_5	Me	4-F-C_6H_5	2	93	[45]
15	C_6H_5	Me	4-Cl-C_6H_5	10	77	[45]
16[c]	C_6H_5	Me	4-Br-C_6H_5	24	59	[45]
17	C_6H_5	Me	$C_6H_5CH_2$	4	87	[45]

[a] Reaction conditions: ketone (2.5 mmol), amine (5 mmol), HCOOH/HCOONa solution (pH 4.8, 4 mL), 80 °C.
[b] Isolated yield.
[c] S/C = 200.

Table 7
RA of aliphatic ketones with amines in water.[a]



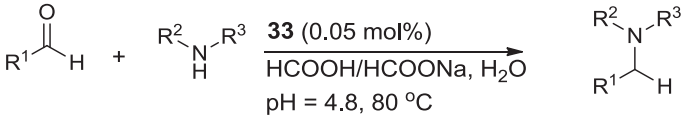
Entry	R^1	R^2/R^3	Time (h)	Yield (%)[b]	Ref
1	$C_6H_5CH_2CH_2$	4-MeO-C_6H_5/H	2	98	[45]
2	$C_6H_5CH_2CH_2$	C_6H_5/H	2	99	[45]
3	$C_6H_5CH_2CH_2$	4-Me-C_6H_5/H	2	98	[45]
4	$C_6H_5CH_2CH_2$	4-F-C_6H_5/H	2	98	[45]
5	$C_6H_5CH_2CH_2$	4-Cl-C_6H_5/H	2	99	[45]
6[c]	$C_6H_5CH_2CH_2$	4-Br-C_6H_5/H	2	96	[45]
7	$C_6H_5CH_2CH_2$	4-CF_3-C_6H_5/H	2	79	[45]
8	$C_6H_5CH_2CH_2$	$C_6H_5CH_2$/H	2	97	[45]
9	$C_6H_5CH_2CH_2$	$CH_3(CH_2)_{10}CH_2$/H	2	54	[45]
10[c]	$C_6H_5CH_2CH_2$	$CH_3(CH_2)_6CH_2$/H	6	85	[45]
11	$C_6H_5CH_2CH_2$	-$(CH_2)_6$-/H	48	52	[45]
12[d]	$C_6H_5CH_2CH_2$	C_6H_5/Me	24	64	[45]
13[c]	C_6H_5CHCH	4-MeO-C_6H_5/H	4	93	[45]
14	Me	4-MeO-C_6H_5/H	2	98	[45]
15	$CH_3CH_2CH_2$	4-MeO-C_6H_5/H	2	88	[45]
16	$CH_3(CH_2)_4CH_2$	4-MeO-C_6H_5/H	2	98	[45]

[a] Reaction conditions: ketone (5 mmol), amine (10 mmol), HCOOH/HCOONa solution (pH 4.8, 8 mL), 80 °C.
[b] Isolated yield.
[c] S/C = 1000.
[d] pH = 5.0.

with relatively electron-donating substituents gave higher yields than those with electron-withdrawing substituents. Thus, over 90% of isolated yields were obtained in 2 h for 4-OMe, 4-Me and 4-H substituted substrates (Entries 1–3, Table 9). The catalytic system also worked for aliphatic amines. Thus, 86% yield was achieved for benzylamine in 4 h at an S/C of 2000. Varying the position of the methoxy substituent on the phenyl ring of the benzyl group affects the reaction rate, with increasing steric hindrance requiring longer reaction time or a lower S/C ratio (Entries 11–13, Table 9). However, long chain aliphatic amines required some special conditions to achieve acceptable yields (Entries 16, 17, Table 9).

The robustness of this catalytic system was further demonstrated by the reaction of 5-oxohexanoic acid with various amines to produce six membered heterocycles, another class of important heterocycle compounds [47]. The results are summarised in Table 10.

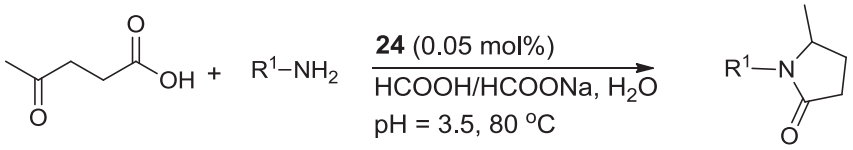
Table 8
RA of aldehydes with amines in water.[a]



Entry	R^1	R^2/R^3	Time (h)	Yield (%)[b]	Ref
1	C_6H_5	4-MeO-C_6H_5/H	2	98	[45]
2[c]	C_6H_5	4-MeO-C_6H_5/H	48	95	[45]
3	4-Me-C_6H_5	4-MeO-C_6H_5/H	2	98	[45]
4	4-MeO-C_6H_5	4-MeO-C_6H_5/H	2	95	[45]
5	4-F-C_6H_5	4-MeO-C_6H_5/H	2	97	[45]
6	4-Cl-C_6H_5	4-MeO-C_6H_5/H	2	79	[45]
7	4-Br-C_6H_5	4-MeO-C_6H_5/H	2	92	[45]
8	4-CF_3-C_6H_5	4-MeO-C_6H_5/H	2	96	[45]
9	4-NO_2-C_6H_5	4-MeO-C_6H_5/H	4	97	[45]
10	3-Br-C_6H_5	4-MeO-C_6H_5/H	2	97	[45]
11	C_6H_5	C_6H_5/H	5	97	[45]
12	C_6H_5	4-Me-C_6H_5/H	2	94	[45]
13	C_6H_5	4-F-C_6H_5/H	2	98	[45]
14[d]	C_6H_5	4-Br-C_6H_5/H	2	95	[45]
15	C_6H_5	$C_6H_5CH_2$/H	2	95	[45]
16	C_6H_5	$CH_3(CH_2)_6CH_2$/H	2	97	[45]
17[d]	C_6H_5	$CH_3(CH_2)_{10}CH_2$/H	2	83	[45]
18[d]	C_6H_5	-$(CH_2)_6$-/H	4	93	[45]
19[d]	C_6H_5	C_6H_5/Me	4	72	[45]
20[d]	C_6H_5	$C_6H_5CH_2$/Me	5	98	[45]

[a] Reaction conditions: aldehyde (5 mmol), amine (10 mmol), HCOOH/HCOONa solution (pH 4.8, 8 mL), 80 °C.
[b] Isolated yield.
[c] pH 4.6, S/C = 100,000, 48 h, ^{1}H NMR yield.
[d] S/C = 1000.

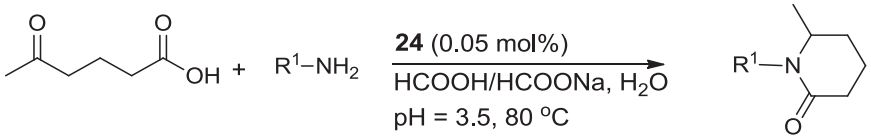
Table 9
RA of LA in water with cyclometalated iridium catalyst.[a]



Entry	R^1	Time (h)	Yield (%)[b]	Ref
1	4-MeO-C_6H_5	2	94	[47]
2	4-Me-C_6H_5	2	93	[47]
3	C_6H_5	2	91	[47]
4	4-F-C_6H_5	4	88	[47]
5	4-Cl-C_6H_5	4	73	[47]
6	4-Br-C_6H_5	4	86	[47]
7	4-OCF_3-C_6H_5	4	72	[47]
8[c]	3-MeO-C_6H_5	12	76	[47]
9	3,4-$(Me)_2$-C_6H_5	12	82	[47]
10	$C_6H_5CH_2$	4	86	[47]
11	4-MeO-$C_6H_5CH_2$	4	94	[47]
12	3-MeO-$C_6H_5CH_2$	12	94	[47]
13[d]	2-MeO-$C_6H_5CH_2$	24	96	[47]
14	3,4-$(MeO)_2$-$C_6H_5CH_2$	24	94	[47]
15	4-F-$C_6H_5CH_2$	12	91	[47]
16[e]	$CH_3(CH_2)_6CH_2$	12	88	[47]
17[f]	$CH_3(CH_2)_9CH_2$	12	73	[47]

[a] Reaction conditions: LA (3.2 mmol), amine (8.6 mmol), HCOOH/HCOONa solution (pH 3.5, 3 mL), 80 °C.
[b] Isolated yield.
[c] S/C = 1000.
[d] S/C = 200.
[e] pH = 4.5 and S/C = 500.
[f] MeOH was used as solvent, azeotropic HCOOH/Et_3N was used as hydrogen source, S/C = 500.

Table 10
RA of 5-oxohexanoic acid in water with **24**.[a]



Entry	R^1	Time (h)	Yield (%)[b]	Ref
1	4-MeO-C_6H_5	12	84	[47]
2	4-F-C_6H_5	12	97	[47]
3	4-MeO-$C_6H_5CH_2$	24	82	[47]
4	4-F-$C_6H_5CH_2$	12	81	[47]
5[c]	$CH_3(CH_2)_6CH_2$	12	86	[47]

[a] For reaction conditions see Table 9.
[b] Isolated yield.
[c] S/C = 500.

4. Concluding remarks

In the past ten years or so, we have developed several catalytic systems for the aqueous-phase TH and ATH of carbonyl compounds, starting with the Noyori-Ikariya type catalysts. Nitrogen heterocycles were also found reducible. During the course of our studies, a new class of catalysts, iridacycles, were found. These iridacycles have since found broad applications in catalysis, and they are also capable of catalysing aqueous-phase TH of carbonyls as well as RA reactions, including extension into biomass-derived platform molecules. Throughout our endeavour, water is shown to be an enabling medium for TH reactions of various features. Not only can it accelerate a reduction, it also provides a simple tool, the solution pH, to control a reaction. Necessitating different pH windows for efficient TH of carbonyl compounds, the Noyori-Ikariya type catalysts and the iridacycles provide illustrative examples.

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