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THE CHEMICAL RECORD

Transfer Hydrogenation in Water

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ABSTRACT: This article provides an account of our group's efforts in developing aqueous-phase transfer hydrogenation reactions. It is comprised of mainly two parts. The first part concentrates on asymmetric transfer hydrogenation in water, enabled by Noyori–Ikariya catalysts, while the second part is concerned with the achiral version of the reaction catalysed by a new class of catalysts, iridacycles. A range of substrates are featured, including various carbonyl compounds and N-heterocycles.

Keywords: aldehydes, ketones, nitrogen heterocycles, transfer hydrogenation, water chemistry

1. Introduction

Transfer hydrogenation (TH) has attracted a great deal of attention in recent years, finding numerous applications in synthetic chemistry.[1–9] As with other catalytic reactions, TH is usually conducted in organic solvents. This is in contrast with enzyme-catalysed TH, which uses formate as a hydrogen source and takes place in an aqueous environment.[10] The development of aqueous TH reactions is not only fundamentally interesting in terms of understanding enzymatic catalysis, but also offers economic and environmental benefits because water is cheap and non-toxic. Research into aqueous TH reactions started around the 1980s,[11,12] and great progress has been made since the 1990s.[7,13–17] Herein, we provide a summary of our own work on TH in aqueous media.

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2. TH with Noyori–Ikariya-Type Catalysts in Water

2.1. ATH of Ketones

Due to the importance of chiral compounds, extensive attention has been paid to developing asymmetric transfer hydrogenation (ATH) systems. A milestone in the history of ATH was the discovery of the Ru-TsDPEN (TsDPEN=*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine) catalyst for the asymmetric reduction of aromatic ketones by Noyori, Ikariya, Hashiguchi, and co-workers in 1995.[18] This and related Noyori–Ikariya-type catalysts have found broad applications. Giving enantiomeric excesses (*ee*) up to 99% and operating through a novel metal–ligand bifunctional mechanism, they have since inspired intense research into ATH.[19–27] One direction is the development of aqueous ATH systems based on these catalysts.

Our group has had a long interest in asymmetric catalysis. In one projects, we developed a method for the immobilisation of chiral diamine ligands,[28] which could be used as a platform to build supported chiral catalysts. We started our journey with TH reactions by using a poly(ethylene glycol) (PEG)-supported complex, Ru-**1**, for ATH in a HCOOH–Et_3N

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mixture.[28,29] Complex Ru-**1** catalysed the ATH of ketones effectively, but unexpectedly catalyst recycling by solvent extraction of the chiral alcohol product was possible only when water was present as a co-solvent. In its absence, much reduced conversions and *ee* values were observed, indicating catalyst decomposition. This finding prompted us to examine the behaviour of sulfonamide ligands **2** and **3** (Scheme 1) in acetophenone (acp) reduction by HCOONa in neat water. Pleasingly, we found that, without any modification, Noyori–Ikariya catalyst Ru-**2**, derived in situ from $[RuCl_2(p\text{-cymene})]_2$ and **2**, enabled efficient ATH in neat water. The reaction was significantly faster than that in organic media and afforded excellent enantioselectivities.[30] Thus, following the addition of 5 equivalents of HCOONa and acp with a molar substrate-to-catalyst (S/C) ratio of 100, the ketone was fully converted into (*R*)−1-phenylethanol in 95% *ee* after 1 h of 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 (Scheme 1) designed for organic solvents are also effective for ATH in water with no need for modification or organic solvents.[31–37] 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.

In comparison with ATH in the azeotropic mixture of HCOOH–NEt_3 with or without water, ATH in aqueous HCOONa is much faster (Table 1, entries 1 and 2 vs 3). This finding prompted us to explore factors that might lead to these contrasting results.[32,36] The clearest difference between the two systems was the solution pH. Subsequently, the pH value was indeed found to be critical to the reaction rate and enantioselectivity.[32] Efficient ATH can be performed with HCOOH–Et_3N in water, providing the ratio of HCOOH/Et_3N is controlled such that the solution is close to neutral pH (Table 1, entries 4–7).

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

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* values in a short reaction time for most of 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.

Xiaofeng Wu graduated from the East China University of Science and Technology in 1995, and did his MSc study at the Shanghai Institute of Organic Chemistry. Prior to obtaining his PhD with Professor Xiao at the University of Liverpool, he took up a FujiOtsuka Research Fellowship in Japan. Since 2007, he has been a Research Associate in catalysis and materials science. His interests include organic synthesis, organometallics, green chemistry, catalytic materials and catalysis.

Chao Wang received his B. S. degree from Hunan Normal University in 2004 and M.S. degree from Chengdu Institute of Organic Chemistry (Graduate School of Chinese Academy of Sciences) in 2007 in P.R. China. He then moved to the UK to pursue his Ph.D. degree at the University of Liverpool with Prof. Jianliang Xiao. After finishing his Ph.D. studies in 2011, he returned to Shaanxi Normal University as an Associate Professor. His research interests lie in the field of organometallic chemistry, catalysis and green chemistry. Current research interests include dehydrogenation reactions and related organic transformations, and selective transformation of biomass platform molecules with molecular catalysis.

Jianliang Xiao received his B.Eng. in chemical engineering at Northwest University in Xian in 1982. This was followed by an M.Eng. in catalytic engineering under the direction of Profs. Wu Chi and Wang Junyu at the Research Institute of Petroleum Processing, and a Ph.D. in chemistry at the University of Alberta mentored by Prof. Martin Cowie. After a postdoctoral appointment with Prof. Richard Puddephatt, he joined the ERATO Molecular Catalysis Project directed by Prof. Noyori. In 1996, he took up a Principal Scientist position at the University of Liverpool, becoming a Lecturer in 1999 and Professor of Catalysis in 2005 in the chemistry department. His research is mainly concerned with the design, development and understanding of molecular catalysts for sustainable chemical synthesis.

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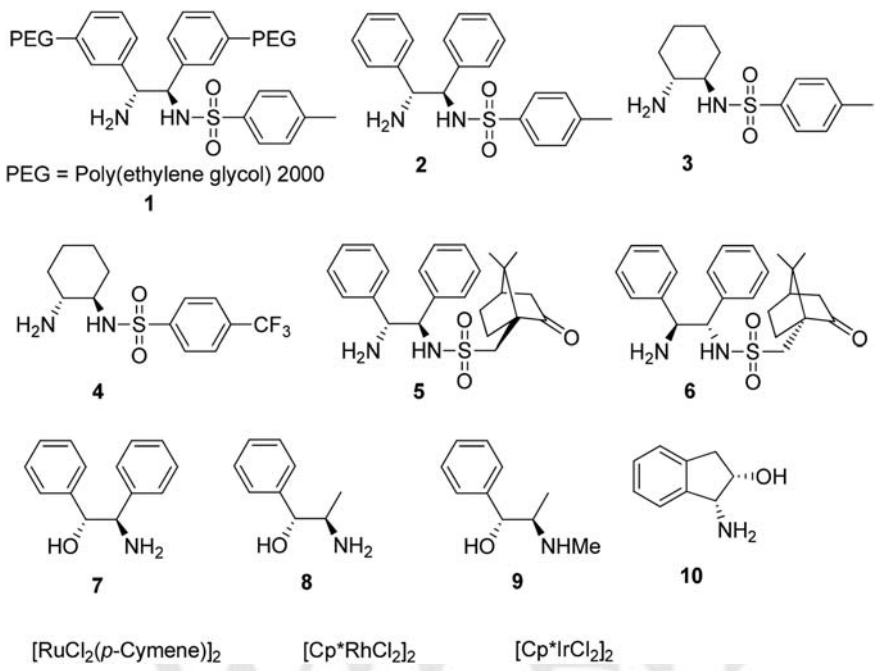

Scheme 1. Ligands and metal precursors used for ATH in water.

2.2. ATH of Quinolines

Optically pure tetrahydroquinolines are commonly present in alkaloids and are key structural units for pharmaceutical and agrochemical synthesis. The most convenient route to chiral tetrahydroquinolines is the asymmetric reduction of quinolines. In continuing our research into ATH, we found that the protocol developed for highly efficient reduction of ketones could also been applied to ATH of cyclic C=N bonds with a slight modification of the tosylated diamine ligand and adjusting the solution pH.[39,40]

The optimal reaction conditions were initially scanned with Rh-**2** in the ATH of 2-methylquinoline in aqueous media by using HCOONa as a reductant. The most important finding was that the solution needed to be more acidic than that for the ATH of ketones, pH 5 was best, and should be kept approximately constant throughout the ATH. A buffer solution of HOAc/NaOAc was chosen to minimise pH fluctuation, ensuring complete reduction. A series of modified diamine ligands were subsequently screened on this basis; ligand **11e** afforded the best reactivity and enantioselectivity (Scheme 2).

Various quinoline derivatives were then subjected to the ATH catalysed by **12** (Scheme 3). Excellent enantioselectivities and yields were observed for a range of substrates. For example, the ATH of 2-methylquinoline afforded the corresponding tetrahydroquinoline in 96% yield with 97% *ee* in 6 h. Notably, 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. Also interesting is that 2,3-di-substituted quinoline **13t** was reduced to **14t** with high enantioselectivity. A possible dynamic kinetic resolution may have occurred following the formation of an enamine intermediate.

2.3. TH of Aldehydes

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.[41] Whilst the reduction of benzaldehyde with $[Cp^*IrCl_2]_2$ afforded a turnover frequency of only 20 h^{-1}, the 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 TH of benzaldehyde. Under these conditions, benzaldehyde (5.30 g) was reduced to give phenylmethanol in 98% yield (5.28 g) in 1 h with $[Cp^*IrCl_2]_2$ (0.4 mg); this demonstrated 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). Furthermore, the reduction is highly efficient and can be carried out in air, without inert gas protection throughout. Thus, S/C ratios of 2000 to 10000 were feasible for both Ir-**16** and

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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	[29]
2	Ru-**2**	HCOONa	100	1	>99	95	[30]
3	Ru-**2**	azetrope	100	12	98	97	[32]
4	Ru-**2**	F/T–H_2O	100	1.5	>99	97	[32]
5	Ru-**2**	F/T–H_2O	1000	9	>99	96	[32]
6	Ru-**2**	F/T–H_2O	5000	57	98	96	[32]
7	Ru-**2**	F/T–H_2O	10000	110	98	94	[32]
8	Rh-**2**	HCOONa	1000	3	93	97	[35]
9	Ir-**2**	HCOONa	100	3	99	93	[35]
10	Ru-**3**	HCOONa	100	2	99	85	[33]
11	Ir-**3**	HCOONa[c]	100	1	99	93	[33]
12	Ru-**4**	HCOONa	100	2.5	>99	81	[38]
13	Rh-**4**	HCOONa[c]	100	0.25	>99	94	[38]
14	Ir-**4**	HCOONa	100	1.5	>99	92	[38]
15	Ru-**5**	HCOONa	100	2	99	97	[31]
16	Rh-**5**	HCOONa	100	0.7	99	99	[31]
17	Rh-**5**	HCOONa	1000	20	89	99	[31]
18	Ir-**5**	HCOONa	100	0.7	98	97	[31]
19	Ir-**5**	HCOONa	1000	2.5	97	98	[31]
20	Ir-**6**	HCOONa	100	0.7	98	98[d]	[31]
21	Ir-**6**	HCOONa	1000	2.5	99	98[d]	[31]
22	Ru-**7**	HCOONa	100	10	95	50	[34]
23	Rh-**7**	HCOONa	100	20	85	41	[34]
24	Ir-**7**	HCOONa	100	1.5	100	27	[34]
25	Ru-**8**	HCOONa	100	5	97	60	[34]
26	Rh-**8**	HCOONa	100	5	63	31	[34]
27	Ir-**8**	HCOONa	100	5	61	7	[34]
28	Ru-**9**	HCOONa	100	3.5	>99	73	[34]
29	Rh-**9**	HCOONa	100	22	77	68	[34]
30	Ir-**9**	HCOONa	100	2.5	100	54	[34]
31	Ru-**10**	HCOONa	100	12	84	71	[34]
32	Rh-**10**	HCOONa	100	20	92	54	[34]
33	Ir-**10**	HCOONa	100	5	>99	27	[34]

[a] Reaction conditions: The reaction was carried out in water (2 mL) or a mixture of water and F/T mixture (F/T=formic acid/triethylamine with a molar ratio of 1.2/1; azeotropic F/T with a ratio of 2.5/1) under inert gas protection, unless otherwise specified. [b] Five equivalents of hydrogen donor were used, unless otherwise specified. [c] Without inert gas protection. [d] (*S*)-Alcohol was obtained.

Ir-**17**, although electron-deficient Ir-**17** generally displayed a higher catalytic activity than that of Ir-**16**. The same aldehyde substrates have also been reduced with H_2 in water with Ir-**17** as the catalyst.[42]

2.4. TH of Quinoxalines

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.[43] 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 of the solution was crucial for the reduction (see Table 3 for details).

3. TH with Iridacycles in Water

The Noyori–Ikariya-type catalysts can be applied to the ATH/TH of cyclic imine bonds (C=N) in aqueous media.[44,45] This prompted us to try to apply this protocol to ATH/TH of acyclic imines. Disappointingly, the reduction was not successful under many reaction conditions screened. However, a very interesting cyclometallated 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.[46] A variety of cyclometallated 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 (RA),[47–49] hydrogenation of acyclic imines[50,51] and heterocycles,[52] aqueous TH of carbonyl groups[53,54] and heterocycles,[55] dehydrogenation of formic acid[56] and heterocycles,[57] and alkylation of amines with alcohols and amines.[58] The key intermediates for TH, the iridium hydrides, have been isolated and characterised.[59] More recently, the mechanistic details of the hydrogenation of imines with these iridacycles have been revealed by a kinetic study and computational modelling.[60] A significant advantage of these catalysts is that they are easy to synthesise and stable in air.

3.1. TH of Ketones and Aldehydes

Our previous work on aqueous-phase ketone reduction showed that water could accelerate ketone reduction, and the solution pH had a dramatic effect on both the catalytic activity and enantioselectivity, when using Noyori–Ikariya-type catalysts.[32,36] We envisioned that TH of ketones with the cyclometallated iridium complexes might also be feasible in water, and 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.[53] TH 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 perform best at neutral pH.[32,36] This difference is most likely to be because reduction with the iridacycles necessitate activation of the ketone by an acidic medium, which provides hydrogen-bonding hydroxonium ions, 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

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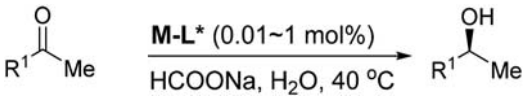
Table 2. ATH of ketones with formate in water.[a]



Entry	R^1	Catalyst/[H]/S/C	Time [h]	*ee* [%][b]	Ref.
1	4-Me-C_6H_5	Ru-**2**/HCOONa/100	2	90	[30]
2	4-Me-C_6H_5	Rh-**2**/HCOONa/100	6	93	[35]
3	4-Me-C_6H_5	Rh-**3**/HCOONa/100	0.5	92	[33]
4	4-Me-C_6H_5	Rh-**4**/HCOONa/100	0.5	91	[38]
5	4-Me-C_6H_5	Ir-**5**/HCOONa/1000	8.5	92	[31]
6	4-OMe-C_6H_5	Ru-**2**/HCOONa/100	2	95	[30]
7	4-OMe-C_6H_5	Ru-**2**/HCOOH–Et_3N/100	5	97	[32]
8	4-OMe-C_6H_5	Rh-**2**/HCOONa/100	20	97	[35]
9	4-OMe-C_6H_5	Rh-**3**/HCOONa/100	0.5	93	[33]
10	4-OMe-C_6H_5	Ir-**5**/HCOONa/1000	22	97	[31]
11	4-Cl-C_6H_5	Ru-**1**/HCOONa/100	1.2	89	[29]
12	4-Cl-C_6H_5	Ru-**2**/HCOONa/100	2	91	[30]
13	4-Cl-C_6H_5	Ru-**2**/HCOOH–Et_3N/1000	11	93	[32]
14	4-Cl-C_6H_5	Rh-**2**/HCOONa/100	0.4	94	[35]
15	4-Cl-C_6H_5	Rh-**2**/HCOONa/1000	3	94	[35]
16	4-Cl-C_6H_5	Rh-**3**/HCOONa/100	0.17	94	[33]
17	4-Cl-C_6H_5	Rh-**4**/HCOONa/100	0.17	92	[38]
18	4-Cl-C_6H_5	Ir-**5**/HCOONa/1000	2	96	[31]
19	4-CF_3-C_6H_5	Ru-**2**/HCOONa/100	2	94	[30]
20	4-CF_3-C_6H_5	Ru-**2**/HCOOH–Et_3N/100	1.3	95	[32]
21	4-CF_3-C_6H_5	Rh-**2**/HCOONa/1000	1.8	94	[35]
22	4-CF_3-C_6H_5	Rh-**3**/HCOONa/100	0.17	91	[33]
23	4-Br-C_6H_5	Ru-**2**/HCOONa/1000	18	93	[30]
24	4-Br-C_6H_5	Rh-**2**/HCOONa/1000	4	95	[32]
25	4-Br-C_6H_5	Rh-**3**/HCOONa/100	0.25	94	[33]
26	4-Br-C_6H_5	Ir-**5**/HCOONa/1000	1.8	95	[31]
27	4-CN-C_6H_5	Ru-**2**/HCOOH–Et_3N/100	1.5	93	[32]
28	4-CN-C_6H_5	Rh-**2**/HCOONa/1000	4.5	92	[35]
29	4-CN-C_6H_5	Rh-**3**/HCOONa/100	0.4	90	[33]
30	4-NO_2-C_6H_5	Ru-**2**/HCOOH–Et_3N/100	2	85	[32]
31	4-NO_2-C_6H_5	Rh-**2**/HCOONa/100	0.5	88	[35]
32	4-NO_2-C_6H_5	Rh-**3**/HCOONa/100	0.75	87	[33]
33	4-NO_2-C_6H_5	Ir-**5**/HCOONa/1000	2	93	[31]
34	3-OMe-C_6H_5	Ru-**2**/HCOONa/100	2	94	[30]
35	3-OMe-C_6H_5	Ru-**2**/HCOOH–Et_3N/100	2.5	95	[32]
36	3-OMe-C_6H_5	Rh-**2**/HCOONa/100	0.5	98	[35]
37	3-OMe-C_6H_5	Rh-**3**/HCOONa/100	0.5	93	[33]
38	3-OMe-C_6H_5	Ir-**5**/HCOONa/1000	3	98	[31]
39	2-OMe-C_6H_5	Ru-**2**/HCOONa/100	2	72	[30]
40	2-OMe-C_6H_5	Rh-**2**/HCOONa/100	24	81	[35]
41	2-OMe-C_6H_5	Rh-**3**/HCOONa/100	1	79	[33]
42	2-OMe-C_6H_5	Ir-**5**/HCOONa/1000	21	85	[31]
43	2-Me-C_6H_5	Ru-**2**/HCOONa/100	6	80	[30]
44	2-Me-C_6H_5	Rh-**3**/HCOONa/100	1	80	[33]
45	2-Me-C_6H_5	Ir-**5**/HCOONa/1000	29	93	[31]
46	2-Cl-C_6H_5	Ru-**1**/HCOONa/100	1.5	85	[29]
47	2-Cl-C_6H_5	Ru-**2**/HCOONa/100	2	89	[30]

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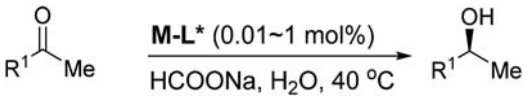
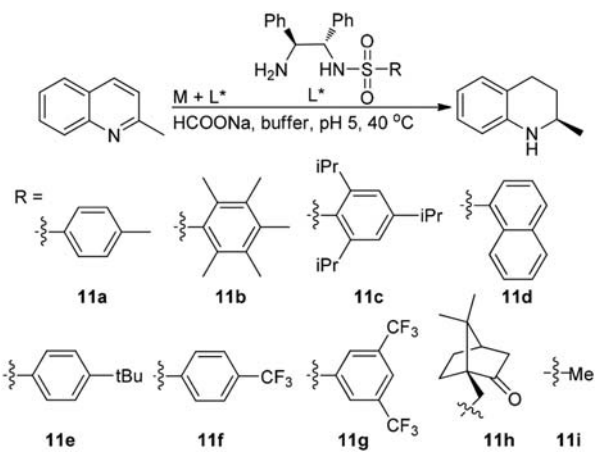
Table 2. (*Continued*)



Entry	R^1	Catalyst/[H]/S/C	Time [h]	*ee* [%][b]	Ref.
48	2-Cl-C_6H_5	Rh-**2**/HCOONa/100	1	71	[35]
49	2-Cl-C_6H_5	Rh-**3**/HCOONa/100	0.3	77	[33]
50	2-Cl-C_6H_5	Ir-**5**/HCOONa/1000	3	88	[31]
51[c]	C_6H_5	Ru-**2**/HCOONa/100	2	86	[30]
52[c]	C_6H_5	Rh-**3**/HCOONa/100	1	92	[33]
53[c]	C_6H_5	Ir-**5**/HCOONa/1000	9.5	97	[31]
54	2-furanyl	Rh-**2**/HCOONa/100	0.08	99	[32]
55	2-furanyl	Rh-**3**/HCOONa/100	0.08	99	[33]
56	2-thiophenyl	Rh-**2**/HCOONa/100	1.5	99	[32]
57	2-thiophenyl	Rh-**3**/HCOONa/100	0.25	94	[33]
58	3-thiophenyl	Rh-**3**/HCOONa/100	0.75	99	[33]
59	4-pyridyl	Rh-**2**/HCOONa/100	0.5	98	[32]
60	3-pyridyl	Rh-**2**/HCOONa/100	16	78	[32]
61	2-pyridyl	Rh-**2**/HCOONa/100	24	98	[32]
62	2-naphthyl	Ru-**1**/HCOONa/100	8	92	[29]
63	2-naphthyl	Ru-**2**/HCOONa/100	3	95	[30]
64	2-naphthyl	Rh-**2**/HCOONa/100	0.75	96	[32]
65	2-naphthyl	Rh-**3**/HCOONa/100	0.75	95	[33]
66	2-naphthyl	Rh-**4**/HCOONa/100	0.75	96	[38]
67	2-naphthyl	Ir-**5**/HCOONa/1000	4	97	[31]
68	1-indanone	Ru-**1**/HCOONa/100	3	92	[29]
69	1-indanone	Ru-**2**/HCOONa/100	2	95	[30]
70	1-indanone	Rh-**2**/HCOONa/100	9	97	[32]
71	1-indanone	Rh-**3**/HCOONa/100	0.5	95	[33]
72	1-tetralone	Ru-**1**/HCOONa/100	3	92	[29]
73	1-tetralone	Ru-**2**/HCOONa/100	3	94	[30]
74	1-tetralone	Rh-**2**/HCOONa/100	3	99	[32]
75	1-tetralone	Rh-**3**/HCOONa/100	0.5	97	[33]

[a] For reaction conditions, see the references cited. Full conversion and good to excellent yields were obtained in all cases. [b] Determined by GC or HPLC with a chiral column. [c] Me was replaced by Et in the α position.



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

the substrate.[61] 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.

A range of aromatic ketones were reduced with iridacycle **27** at pH 2.5, affording good to excellent isolated yields in 4–12 h (Table 4). Aliphatic ketones are also viable substrates (Table 4, entries 16–18). 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 on a 6.00 g scale was achieved under the standard reaction conditions, with which the alcohol was obtained in 97% isolated yield in 24 h at a S/C ratio of 2000.

The reduction of α-substituted ketones has been explored with iridacycle **33**.[54] Compared with acp derivatives, α-halo-, hydroxyl- and nitrile-substituted ketones are more challenging

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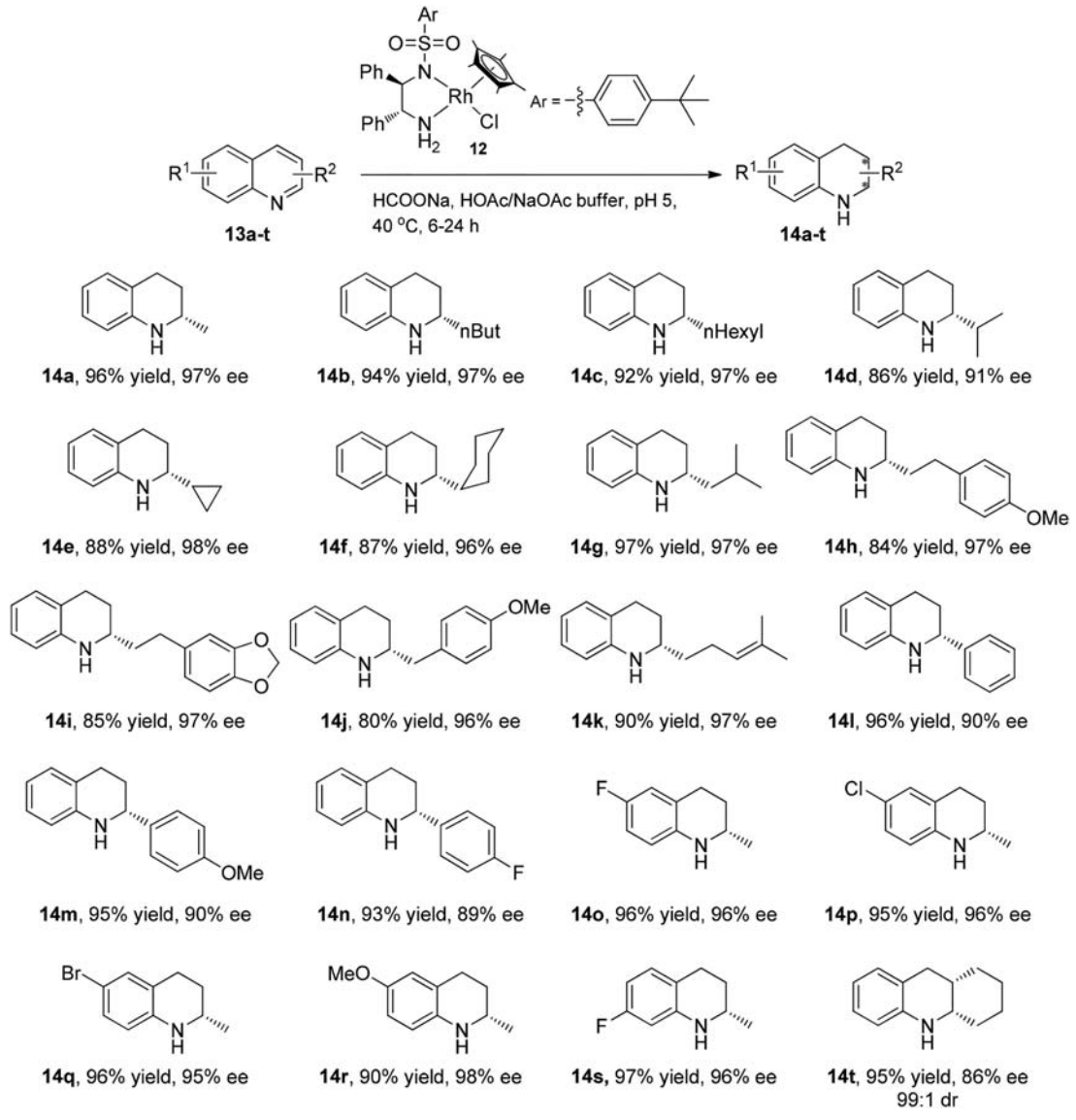
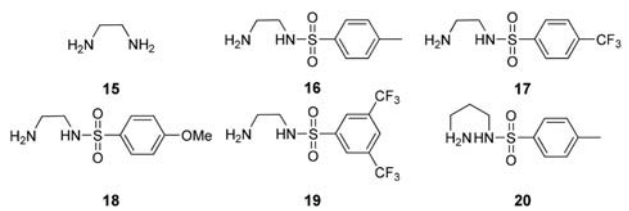


Scheme 3. Examples of ATH of quinolines with rhodium catalyst **12** in water.



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

to reduce, due to the ease of dissociation/decomposition of these α-functional groups under the reaction conditions. The iridacycle appears to tolerate these functionalities well. As illustrated in Table 5, the desired products were obtained with excellent yields for almost all of these problematic ketones.

The much less featured β-keto ethers were also effectively and chemoselectively reduced to the desired β-hydroxyethers with iridacycle **34** (Table 6).[54] Controlling the solution pH is critical, and pH 3–5 is optimal. Under these conditions, keto ethers featuring either aromatic or aliphatic units and aromatic, aliphatic, heterocyclic and fluorinated ethers were all viable and gave excellent yields at a S/C ratio of 10000 on a 2.5 mmol substrate scale without dissociation of any ether groups.

Moreover, the reduction of keto esters with the iridacycle catalysts is also practical.[54] Catalysed by iridacycle **33**, both α- and β-keto esters, including those aromatic and aliphatic ones, have been reduced to the corresponding alcohols with excellent yields (Table 7). These results, together with those mentioned above, demonstrate the wide scope and utility of

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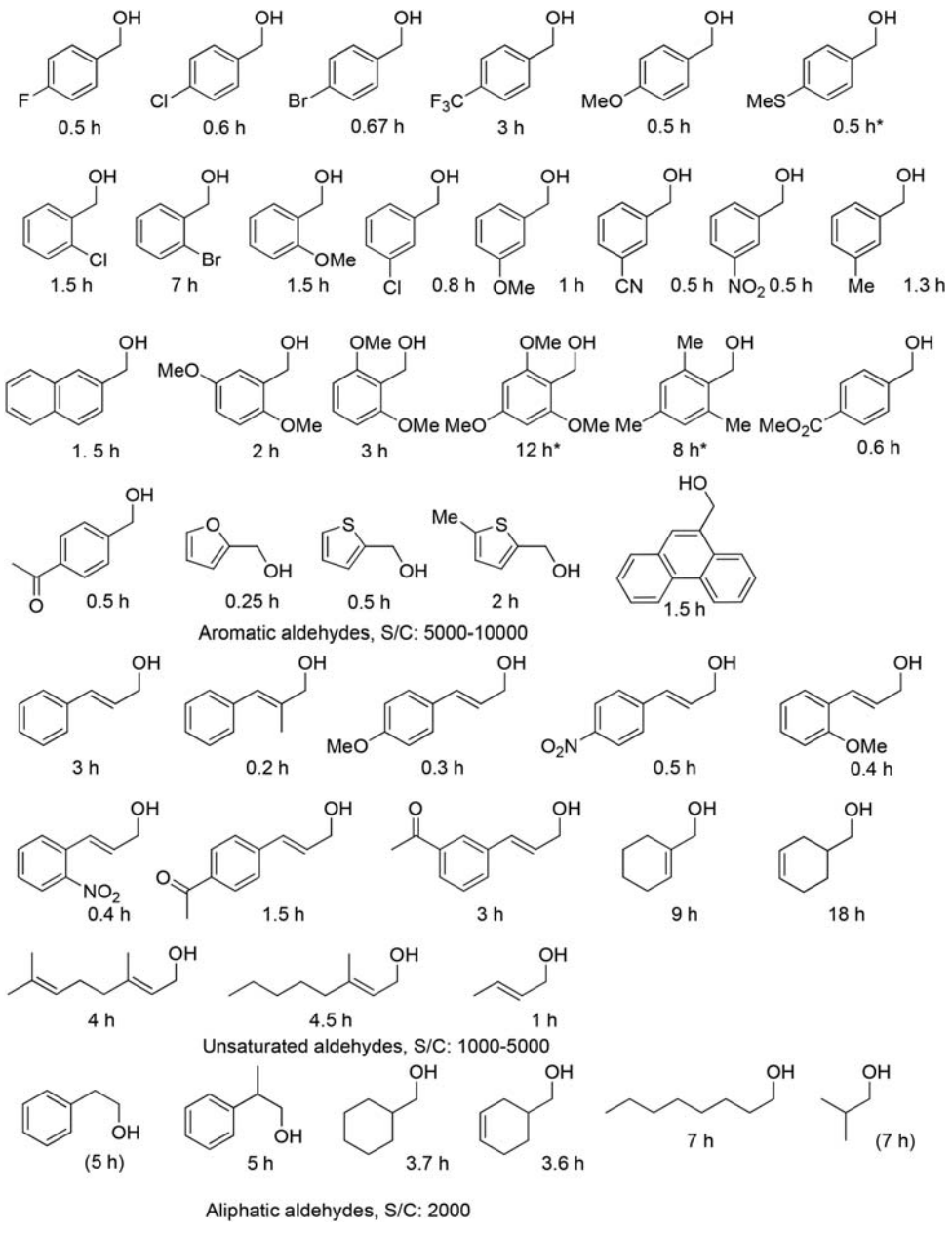

Scheme 5. Examples of TH of aldehydes to alcohols with Ir-**16** by HCOONa in water at 80°C, with full conversion and >85% yields obtained in all cases. * S/C=1000.

the iridacycles in carbonyl reduction and in aqueous-phase organic synthesis.

3.2. TH of N-Heterocycles

In contrast to the situation of ketone reduction, the TH of heterocycles has been much less explored.[62–65] The iridacycle catalysts again show their utility by being capable of reducing an ample variety of N-heterocycles, including quinolines, indoles, isoquinolinium and pyridinium salts, at a high S/C ratio in water.[55] As shown in Table 8, an array of diversely substituted quinolines were reduced by TH in water with catalyst **33**.[55] Large-scale reduction was shown to be feasible. Thus, quinoline (35.8 g) was reduced with 0.01 mol% catalyst at 30 °C in 24 h, affording 67% yield of product.

Indoles can also been reduced with this catalytic system.[55] As shown in Table 9, a range of indoles with both electron-donating and -withdrawing groups were transferred to the corresponding indolines in good yields.

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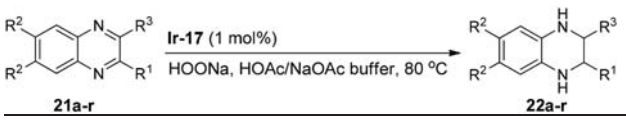
Table 3. TH of quinoxalines with formate in buffered water.[a]



Entry	$R^1/R^2/R^3$	Time [h]	Yield [%][b]	Ref.
1	Me/H/H	0.25	96	[43]
2	Et/H/H	1	97	[43]
3	*i*Bu/H/H	2	96	[43]
4	hexyl/H/H	2	97	[43]
5	cyclohexyl/H/H	6	92	[43]
6	Me/Me/H	1	97	[43]
7	Et/Me/H	1	96	[43]
8	H/H/H	0.25	97	[43]
9	Me/H/Me	4	94	[43]
10[c]	C_6H_5/H/H	10	97	[43]
11[c]	4-F-C_6H_4/H/H	10	97	[43]
12[c]	4-Cl-C_6H_4/H/H	10	95	[43]
13[c]	4-Br-C_6H_4/H/H	10	95	[43]
14[c]	4-MeO-C_6H_4/H/H	10	97	[43]
15[c]	4-C_6H_4-C_6H_4/H/H	10	91	[43]
16[d]	C_6H_5CHCH/H/H	12	95	[43]
17[d]	2-Cl-C_6H_4CHCH/H/H	12	96	[43]
18[d]	3-NO_2-C_6H_4CHCH/H/H	12	95	[43]

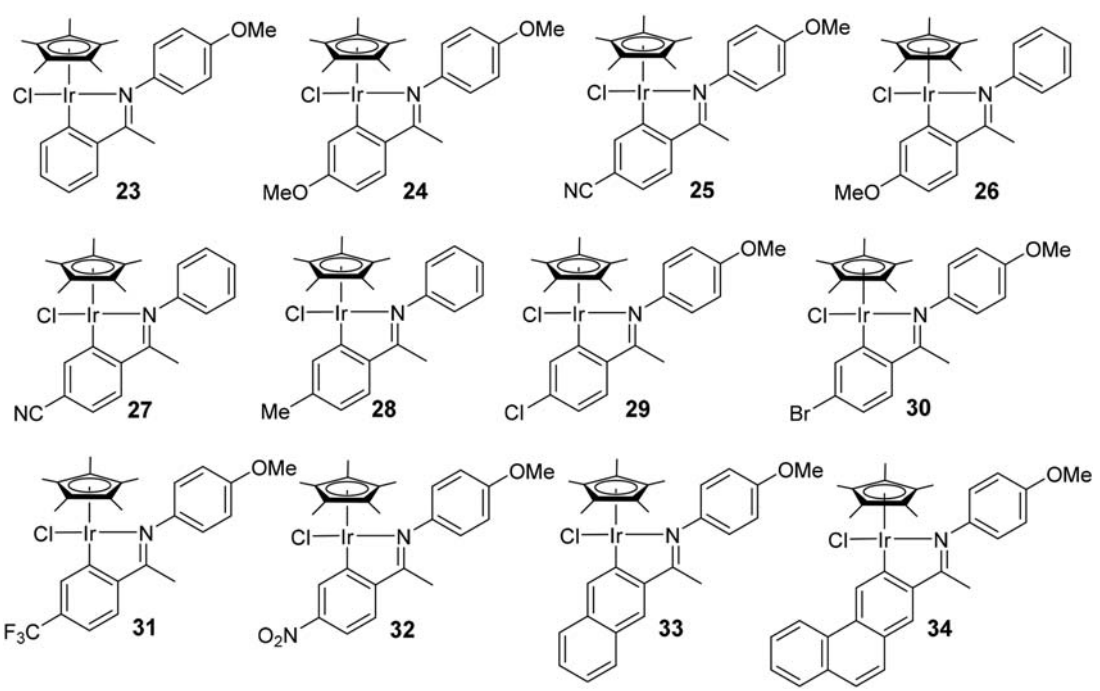
[a] Reaction conditions: quinoxalines **21** (0.5 mmol), $[Cp^*IrCl_2]_2$ (2.5 μmol), **17** (6 μmol), HCOONa (5 mmol), 5 M HOAc/NaOAc buffer (5 mL), pH=5.5, 80°C. [b] Isolated yield. [c] The reaction was carried out at pH 4.3 in 5 M HOAc/NaOAc (5 mL) and EtOAc (0.3 mL). [d] The reaction was carried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

The iridacycles appear to be ineffective in the TH of isoquinolines and pyridines. However, quaternisation of the nitrogen atom in these substrates led to the full reduction of the N-heterocyclic rings.[55] As shown in Table 10, an array of isoquinolinium and pyridinium salts were reduced in excellent yields. The versatility of these cyclometallated iridium catalysts have been further demonstrated by the efficient TH of other heterocycles and imines.[55]

3.3. RA of Ketones and Aldehydes

Aqueous-phase RA reactions are scarce in the literature. This is not surprising because water is generally thought to be adverse for the formation of imines, which are key intermediates in RA reactions. Drying agents are sometimes used to remove water generated from the imine formation step.[66,67] Due to the high activity observed with our iridacycle catalysts for RA in organic solvents,[46] we were interested in developing a greener version of the reaction by replacing the organic solvent with water.

In our initial study of aqueous RA, we chose **24** as a catalyst and sodium formate as a hydrogen source for RA of acp with *p*-anisidine.[47] Imine formation from the ketone and amine and 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. Both the catalytic activity and selectivity were influenced dramatically by the solution pH. At pH 4.8, the best selectivity



Scheme 6. Selected examples of cyclometallated iridium catalysts.

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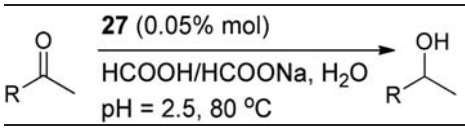
Table 4. TH of ketones with the cyclometallated iridium 27 in water.[a]



Entry	R	Time [h]	Yield [%][b]	Ref.
1	C_6H_5	4	96	[53]
2[c]	4-Me-C_6H_5	12	87	[53]
3[d]	4-OMe-C_6H_5	12	79	[53]
4	4-NO_2-C_6H_5	4	97	[53]
5	4-CF_3-C_6H_5	4	95	[53]
6	4-CN-C_6H_5	12	91	[53]
7[c]	4-F-C_6H_5	12	89	[53]
8[e]	4-Cl-C_6H_5	12	89	[53]
9[e]	4-Br-C_6H_5	12	94	[53]
10	3-NO_2-C_6H_5	4	96	[53]
11[c]	3-Br-C_6H_5	12	93	[53]
12[c]	3-CF_3-C_6H_5	12	91	[53]
13[e]	3,5-$(CF_3)_2$-C_6H_5	12	90	[53]
14[e]	2-F-C_6H_5	12	91	[53]
15	2-Naphthyl	4	89	[53]
16[e]	$C_6H_5(CH_2)_2$	12	97	[53]
17[c,f]	$CH_3(CH_2)_5$	12	100	[53]
18[c,f]	-$(CH_2)_5$-	12	100	[53]
19[g]	C_6H_5	24	97	[53]

[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.

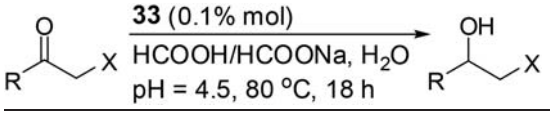
was observed without sacrificing too much of the activity. A series of iridacycles (**25**–**33**) were subsequently examined and complex **33** was most active. Under the optimal conditions, 95% yield was obtained for the reaction of acp with *p*-anisidine.

Firstly, aromatic ketones with various amines were examined for RA with catalyst **33** in the aqueous HCOOH/HCOONa system. The results are shown in Table 11. Excellent yields were obtained for aromatic ketones with both electron-withdrawing and -donating substituents in 2 h with S/C of 1000 (Table 11, entries 1–10).

The reactions of aliphatic ketones with various amines were next investigated (Table 12). Higher activities were generally observed for aliphatic ketones. An S/C of 2000 can be employed for most of the substrates. Again, aromatic amines with the electron-withdrawing CF_3 substituent showed lower activities. Although a good yield was obtained for benzylamine under standard conditions, other aliphatic amines and secondary amines showed poorer activities.

Aldehydes were more reactive than ketones in general (Table 13). Over 90% yield was obtained for most of the aromatic aldehydes reacting with *para*-anisidine at S/C of 2000 in 2 h. Aliphatic amines generally showed better activity in reactions with aldehydes than those with ketones. The lower

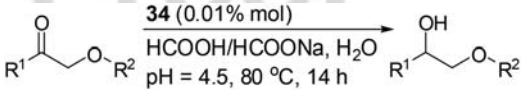
Table 5. TH of α-substituted ketones with 33 in water.[a]



Entry	R	X	Yield [%][b]	Ref.
1	C_6H_5	OH	93	[54]
2	C_6H_5	Cl	94	[54]
3	4-OMe-C_6H_5	Cl	92	[54]
4	4-F-C_6H_5	Cl	93	[54]
5[c]	C_6H_5	α,α-Cl_2	87	[54]
6	C_6H_5	F	95	[54]
7	C_6H_5	α,α,α-F_3	96	[54]
8	C_6H_5	CN	90	[54]
9	4-Me-C_6H_5	CN	92	[54]
10	4-F-C_6H_5	CN	91	[54]
11	2-Thionyl	CN	89	[54]
12	2-Furanyl	CN	90	[54]
13	C_6H_5	$OC(O)C_6H_5$	96	[54]
14	C_6H_5	-$N(CH_2)_2O(CH_2)_2$-	88	[54]
15	C_6H_5	-$N(CH_2)_5$-	86	[54]
16[d]	C_6H_5	α,α-$(OMe)_2$	94	[54]

[a] Reaction conditions: ketone (2.5 mmol), catalyst (0.001 mmol), pH 4.5 aqueous HCOOH–HCOONa solution (3 mL), 80°C, 18 h. [b] Isolated yield. [c] S/C=200. [d] Yield determined by ^{1}H NMR spectroscopy.

Table 6. TH of α-substituted ketones with 34 in water.[a]



Entry	R^1	R^2	Yield [%][b]	Ref.
1	C_6H_5	4-Cl-C_6H_5	93	[54]
2	C_6H_5	4-OMe-C_6H_5	91	[54]
3	C_6H_5	2-naphthyl	97	[54]
4	C_6H_5	2,6-Me_2-C_6H_5	95	[54]
5	C_6H_5	3-pyridine	89	[54]
6	4-Cl-C_6H_5	C_6H_5	97	[54]
7	4-CN-C_6H_5	C_6H_5	97	[54]
8	4-OMe-C_6H_5	C_6H_5	93	[54]
9	C_6H_5	$(CF_3)_2$	87	[54]
10	C_6H_5	$CH_2(CF_2)_2CF_3$	86	[54]
11	Me	C_6H_5	98	[54]
12	Me	2,6-Me_2-C_6H_5	97	[54]
13	Me	3-pyridine	91	[54]
14	–$(CH_2)_4$–	Et	90	[54]

[a] Reaction conditions: keto ethers (2.5 mmol), catalyst (0.01 mol%), pH 4.5 aqueous HCOOH–HCOONa solution (3 mL), 80°C, 14 h. [b] Isolated yield.

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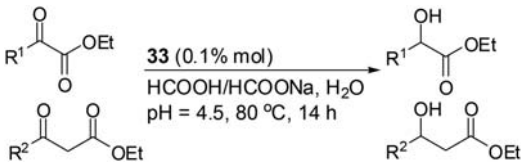
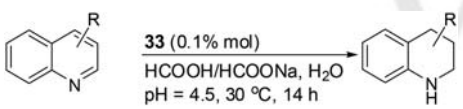
Table 7. TH of α-and β-keto esters with 33 in water.[a]



Entry	R^1 or R^2	Yield [%][b]	Ref.
1[c]	R^1=Me	91	[54]
2	R^1=CF_3	92	[54]
3	R^1=C_6H_5	96	[54]
4	R^2=C_6H_5	94	[54]
5	R^2=3-NO_2-C_6H_5	91	[54]
6	R^2=3-Me-C_6H_5	94	[54]
7	R^2=3,4,5-$(OMe)_3$-C_6H_5	92	[54]
8	R^2=CF_3	95	[54]

[a] Reaction conditions: keto esters (2.5 mmol), catalyst (0.1 mmol%), pH 4.5 aqueous HCOOH–HCOONa solution (3 mL), 80°C, 14 h. [b] Isolated yield. [c] Yield determined by ^{1}H NMR spectroscopy.

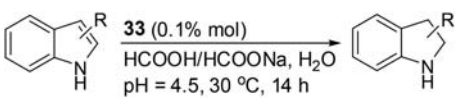
Table 8. TH of quinolines with 33 in water.[a]



Entry	R	Yield [%][b]	Ref.
1	2-Me	96	[55]
2	3-Me	93	[55]
3[c]	4-Me	90	[55]
4	H	90	[55]
5[c]	2-C_6H_5	84	[55]
6	2-Me,6-F	97	[55]
7	2-Me,6-Cl	97	[55]
8	2-Me,6-Br	95	[55]
9	2-Me,7-F	98	[55]
10	2-Me,8-Cl	92	[55]
11	2-Me,6-Me	95	[55]
12	2-Me,6-OMe	96	[55]
13	2-Me,6-OBn	94	[55]
14	2-Me,6-OCH_2CH=CH_2	93	[55]
15	2-Me,6-CF_3	98	[55]
16[c,d]	2-Me,6-NHBoc	90	[55]
17[c]	2-Me,6-C(O)$N(Et)_2$	91	[55]
18	2-Me,6-CO_2Me	92	[55]
19	2-Me,6-COOH	82	[55]
20	2-Me,6-(2-furyl)	95	[55]
21	2-Me,6-(2-thiophyl)	96	[55]
22[c]	2-Me,6-(4-pyridyl)	82	[55]
23	2-Me,5,7-Me_2-	95	[55]
24[c,e]	2-Me,4-C_6H_5	84	[55]

[a] Reaction conditions: quinoline (2.5 mmol), catalyst (0.1 mmol%), pH 4.5 aqueous HCOOH–HCOONa solution (3 mL), 30°C, 14 h. [b] Isolated yield. [c] Reaction was carried out at reflux. [d] Yield determined by ^{1}H NMR spectroscopy. [e] 0.5 mol% catalyst was used.

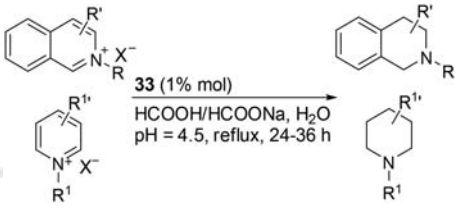
Table 9. TH of indoles with 33 in water.[a]



Entry	R	Yield [%][b]	Ref.
1	H	96	[55]
2	5-OMe	94	[55]
3	2-Me	92	[55]
4[c]	2-Me, 5-Cl	78	[55]

[a] Reaction conditions: indole (2.5 mmol), catalyst (0.1 mmol%), pH 4.5 aqueous HCOOH–HCOONa solution (3 mL), 30°C, 16 h. [b] Isolated yield. [c] 0.5 mol% catalyst at reflux and with the addition of MeOH (1 mL).

Table 10. TH of isoquinolinium and pyridinium salts with 33 in water.[a]



Entry	R,R' or R^1, $R^{1'}$	X	Yield [%][b]	Ref.
1	R=Bn, R'=8-C_6H_5	Br	90	[55]
2	R=Et, R'=H	I	95	[55]
3[c]	R=Et, R'=8-Et	I	98	[55]
4[c]	R=Et, R'=2-Me	I	97	[55]
5	R=Et, R'=5-Me	I	99	[55]
6	R=Et, R'=5-Br	I	91	[55]
7	R^1=Bn, $R^{1'}$=2-C_6H_5	Br	90	[55]
8[d]	R^1=Bn, $R^{1'}$=2-C(OH)$(C_6H_5)_2$	Br	72	[55]
9	R^1=Bn, $R^{1'}$=2-CH_2NHCbz	Br	90	[55]
10	R^1=Bn, $R^{1'}$=2-CH_2NHBoc	Br	94	[55]
11	R^1=Bn, $R^{1'}$=2-(4-OMe-C_6H_5)	Br	81	[55]
12[c]	R^1=Bn, $R^{1'}$=3-COOEt	Br	82	[55]
13	R^1=Bn, $R^{1'}$=4-Bn	Br	92	[55]
14	R^1=Bn, $R^{1'}$=4-CF_3	Br	82	[55]
15	R^1=Bn, $R^{1'}$=4-COOEt	Br	80	[55]

[a] Reaction conditions: isoquinolinium or pyridinium salt (2.5 mmol), catalyst (1 mmol%), pH 4.5 aqueous HCOOH–HCOONa solution (3 mL), reflux, 24–36 h. [b] Isolated yield. [c] Yield determined by ^{1}H NMR spectroscopy.

steric hindrance of the aldehydes compared with the ketones renders their reaction with secondary amines much easier. To demonstrate the potential of the catalytic system in the practical synthesis of amines, higher S/C ratios were tested in the reaction of benzaldehyde with *para*-anisidine. At pH 4.6, the reaction with a S/C of 1×10^5 (250 mmol scale) afforded

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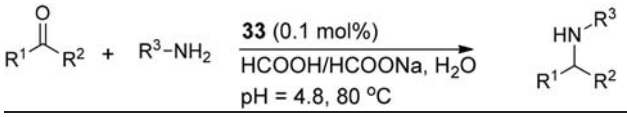
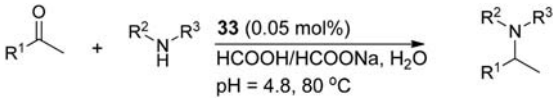
Table 11. RA of aromatic ketones with amines in water.[a]



Entry	R^1	R^2	R^3	Time [h]	Yield [%][b]	Ref.
1	C_6H_5	Me	4-MeO-C_6H_5	2	95	[47]
2	4-Me-C_6H_5	Me	4-MeO-C_6H_5	2	98	[47]
3	4-MeO-C_6H_5	Me	4-MeO-C_6H_5	2	95	[47]
4	4-F-C_6H_5	Me	4-MeO-C_6H_5	2	94	[47]
5	4-Cl-C_6H_5	Me	4-MeO-C_6H_5	2	98	[47]
6	4-Br-C_6H_5	Me	4-MeO-C_6H_5	2	98	[47]
7	4-CN-C_6H_5	Me	4-MeO-C_6H_5	2	98	[47]
8	4-CF_3-C_6H_5	Me	4-MeO-C_6H_5	2	96	[47]
9	4-NO_2-C_6H_5	Me	4-MeO-C_6H_5	2	93	[47]
10	2-naphthyl	Me	4-MeO-C_6H_5	2	92	[47]
11[c]	C_6H_5	CH_2CO_2Me	4-MeO-C_6H_5	12	71	[47]
12	C_6H_5	Me	C_6H_5	2	82	[47]
13	C_6H_5	Me	4-Me-C_6H_5	2	91	[47]
14	C_6H_5	Me	4-F-C_6H_5	2	93	[47]
15	C_6H_5	Me	4-Cl-C_6H_5	10	77	[47]
16[c]	C_6H_5	Me	4-Br-C_6H_5	24	59	[47]
17	C_6H_5	Me	$C_6H_5CH_2$	4	87	[47]

[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 12. 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	[47]
2	$C_6H_5CH_2CH_2$	C_6H_5/H	2	99	[47]
3	$C_6H_5CH_2CH_2$	4-Me-C_6H_5/H	2	98	[47]
4	$C_6H_5CH_2CH_2$	4-F-C_6H_5/H	2	98	[47]
5	$C_6H_5CH_2CH_2$	4-Cl-C_6H_5/H	2	99	[47]
6[c]	$C_6H_5CH_2CH_2$	4-Br-C_6H_5/H	2	96	[47]
7	$C_6H_5CH_2CH_2$	4-CF_3-C_6H_5/H	2	79	[47]
8	$C_6H_5CH_2CH_2$	$C_6H_5CH_2$/H	2	97	[47]
9	$C_6H_5CH_2CH_2$	$CH_3(CH_2)_{10}CH_2$/H	2	54	[47]
10[c]	$C_6H_5CH_2CH_2$	$CH_3(CH_2)_6CH_2$/H	6	85	[47]
11	$C_6H_5CH_2CH_2$	-$(CH_2)_6$-/H	48	52	[47]
12[d]	$C_6H_5CH_2CH_2$	C_6H_5/Me	24	64	[47]
13[c]	C_6H_5CHCH	4-MeO-C_6H_5/H	4	93	[47]
14	Me	4-MeO-C_6H_5/H	2	98	[47]
15	$CH_3CH_2CH_2$	4-MeO-C_6H_5/H	2	88	[47]
16	$CH_3(CH_2)_4CH_2$	4-MeO-C_6H_5/H	2	98	[47]

[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.

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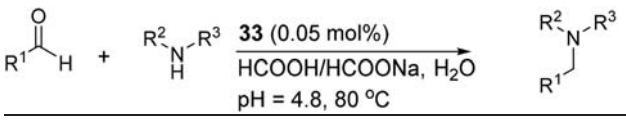
Table 13. RA of aldehydes with amines in water.[a]



Entry	R^1	R^2/R^3	Time [h]	Yield [%][b]	Ref.
1	C_6H_5	4-MeO-C_6H_5/H	2	98	[47]
2[c]	C_6H_5	4-MeO-C_6H_5/H	48	95	[47]
3	4-Me-C_6H_5	4-MeO-C_6H_5/H	2	98	[47]
4	4-MeO-C_6H_5	4-MeO-C_6H_5/H	2	95	[47]
5	4-F-C_6H_5	4-MeO-C_6H_5/H	2	97	[47]
6	4-Cl-C_6H_5	4-MeO-C_6H_5/H	2	79	[47]
7	4-Br-C_6H_5	4-MeO-C_6H_5/H	2	92	[47]
8	4-CF_3-C_6H_5	4-MeO-C_6H_5/H	2	96	[47]
9	4-NO_2-C_6H_5	4-MeO-C_6H_5/H	4	97	[47]
10	3-Br-C_6H_5	4-MeO-C_6H_5/H	2	97	[47]
11	C_6H_5	C_6H_5/H	5	97	[47]
12	C_6H_5	4-Me-C_6H_5/H	2	94	[47]
13	C_6H_5	4-F-C_6H_5/H	2	98	[47]
14[d]	C_6H_5	4-Br-C_6H_5/H	2	95	[47]
15	C_6H_5	$C_6H_5CH_2$/H	2	95	[47]
16	C_6H_5	$CH_3(CH_2)_6CH_2$/H	2	97	[47]
17[d]	C_6H_5	$CH_3(CH_2)_{10}CH_2$/H	2	83	[47]
18[d]	C_6H_5	-$(CH_2)_6$-/H	4	93	[47]
19[d]	C_6H_5	C_6H_5/Me	4	72	[47]
20[d]	C_6H_5	$C_6H_5CH_2$/Me	5	98	[47]

[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=100000, 48 h; yield determined by ^{1}H NMR spectroscopy. [d] S/C=1000.

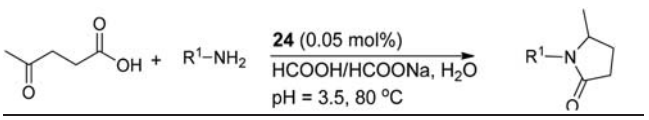
95% yield in 48 h. This is the highest S/C ratio ever reported for RA reactions (Table 13, entry 2).

3.4. RA of Levulinic Acids

More challenging applications of the iridacycle catalysts have been demonstrated in the RA of levulinic acid (LA) to form pyrrolidinones by TH in water.[49] LA can be obtained by simple acidic dehydration of renewable carbohydrates and has been identified as a biomass-derived platform chemical. The RA of LA with formic acid as a hydrogen source would be ideal because formic acid is a by-product during the production of LA.

By using our iridacycle catalysts, we disclosed the first true TH system for RA of LA to produce pyrrolidinones using formic acid as the hydrogen source. As with the RA reactions outlined above, this reaction was also affected strongly by solution pH; pH 3.5 was optimum for **24**-catalysed RA of LA with *para*-anisidine. As seen from the results in Table 14, RA afforded good yields for a range of aromatic amines. In particular, those with relatively electron-donating substituents gave higher yields than those with electron-withdrawing substituents.

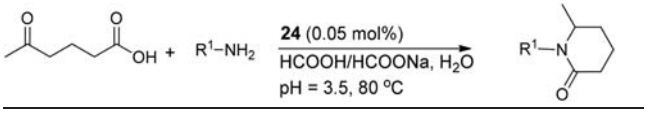
Table 14. RA of LA in water with iridacycle 24.[a]



Entry	R^1	Time [h]	Yield [%][b]	Ref.
1	4-MeO-C_6H_5	2	94	[49]
2	4-Me-C_6H_5	2	93	[49]
3	C_6H_5	2	91	[49]
4	4-F-C_6H_5	4	88	[49]
5	4-Cl-C_6H_5	4	73	[49]
6	4-Br-C_6H_5	4	86	[49]
7	4-OCF_3-C_6H_5	4	72	[49]
8[c]	3-MeO-C_6H_5	12	76	[49]
9	3,4-$(Me)_2$-C_6H_5	12	82	[49]
10	$C_6H_5CH_2$	4	86	[49]
11	4-MeO-$C_6H_5CH_2$	4	94	[49]
12	3-MeO-$C_6H_5CH_2$	12	94	[49]
13[d]	2-MeO-$C_6H_5CH_2$	24	96	[49]
14	3,4-$(MeO)_2$-$C_6H_5CH_2$	24	94	[49]
15	4-F-$C_6H_5CH_2$	12	91	[49]
16[e]	$CH_3(CH_2)_6CH_2$	12	88	[49]
17[f]	$CH_3(CH_2)_9CH_2$	12	73	[49]

[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 a solvent, azeotropic HCOOH/Et_3N as a hydrogen source, with S/C=500.

Table 15. 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	[49]
2	4-F-C_6H_5	12	97	[49]
3	4-MeO-$C_6H_5CH_2$	24	82	[49]
4	4-F-$C_6H_5CH_2$	12	81	[49]
5[c]	$CH_3(CH_2)_6CH_2$	12	86	[49]

[a] For reaction conditions, see Table 14. [b] Isolated yield. [c] S/C=500.

The utility 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.[49] The results are summarised in Table 15.

4. Concluding Remarks

In the past ten years or so, we have developed several catalytic systems for aqueous-phase TH and ATH of carbonyl

compounds, starting with Noyori–Ikariya-type catalysts. Nitrogen heterocycles were also found to be reducible. During the course of our studies, a new class of catalysts, iridacycles, were found. These iridacycles have since found broad applications in catalysis. Of relevance to the objective of this article is that they are capable of catalysing aqueous-phase TH of carbonyls and RA reactions, including extension into biomass-derived platform molecules. A chiral version would certainly make these iridacycles more attractive. Throughout our endeavour, water is shown to be an enabling medium for TH reactions of various features. Not only can it accelerate reduction, it also allows one to control the reaction through the pH. Performing optimally only in a certain pH window in water, Noyori–Ikariya-type catalysts and iridacycles provide illuminating examples.

Acknowledgements

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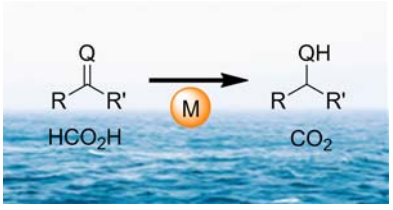

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