

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

22 **1. Introduction**

23 Transfer hydrogenation (TH) has attracted a great deal of
24 attention in recent years, finding numerous applications in
25 synthetic chemistry.^[1–9] As with other catalytic reactions, TH
26 is usually conducted in organic solvents. This is in contrast
27 with enzyme-catalysed TH, which uses formate as a hydrogen
28 source and takes place in an aqueous environment.^[10] The
29 development of aqueous TH reactions is not only fundamen-
30 tally interesting in terms of understanding enzymatic catalysis,
31 but also offers economic and environmental benefits because
32 water is cheap and non-toxic. Research into aqueous TH reac-
33 tions started around the 1980s,^[11,12] and great progress has

been made since the 1990s.^[7,13–17] Herein, we provide a sum- 34
mary of our own work on TH in aqueous media. 35

2. TH with Noyori–Ikariya-Type Catalysts in Water 36

2.1. ATH of Ketones 38

Due to the importance of chiral compounds, extensive atten- 39
tion has been paid to developing asymmetric transfer hydroge- 40
nation (ATH) systems. A milestone in the history of ATH was 41
the discovery of the Ru-TsDPEN (TsDPEN = *N*-(*p*-toluene- 42
sulfonyl)-1,2-diphenylethylenediamine) catalyst for the asym- 43
metric reduction of aromatic ketones by Noyori, Ikariya, 44
Hashiguchi, and co-workers in 1995.^[18] This and related 45
Noyori–Ikariya-type catalysts have found broad applications. 46
Giving enantiomeric excesses (*ee*) up to 99% and operating 47
through a novel metal–ligand bifunctional mechanism, they 48
have since inspired intense research into ATH.^[19–27] One 49
direction is the development of aqueous ATH systems based 50
on these catalysts. 51

Our group has had a long interest in asymmetric catalysis. 52
In one projects, we developed a method for the immobilisation 53
of chiral diamine ligands,^[28] which could be used as a platform 54
to build supported chiral catalysts. We started our journey 55
with TH reactions by using a poly(ethylene glycol) (PEG)-sup- 56
ported complex, Ru-1, for ATH in a HCOOH–Et₃N 57

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58 mixture.^[28,29] Complex Ru-1 catalysed the ATH of ketones
 59 effectively, but unexpectedly catalyst recycling by solvent
 60 extraction of the chiral alcohol product was possible only when
 61 water was present as a co-solvent. In its absence, much
 62 reduced conversions and *ee* values were observed, indicat-
 63 ing catalyst decomposition. This finding prompted us to
 64 examine the behaviour of sulfonamide ligands **2** and **3**
 F1 65 (Scheme 1) in acetophenone (acp) reduction by HCOONa
 66 in neat water. Pleasingly, we found that, without any mod-
 67 ification, Noyori-Ikariya catalyst Ru-2, derived in situ
 68 from [RuCl₂(*p*-cymene)]₂ and **2**, enabled efficient ATH in
 69 neat water. The reaction was significantly faster than that
 70 in organic media and afforded excellent enantioselectiv-
 71 ities.^[30] Thus, following the addition of 5 equivalents of
 72 HCOONa and acp with a molar substrate-to-catalyst (S/
 73 C) ratio of 100, the ketone was fully converted into
 74 (*R*)-1-phenylethanol in 95% *ee* after 1 h of reaction time
 75 at 40 °C. In comparison, the reaction run in the
 76 HCOOH-NEt₃ (F/T) azeotrope afforded a conversion of
 77 less than 2% in 1 h, with full conversion requiring more
 78 than 10 h (97% *ee*) at 40 °C. This initial finding has since
 79 proven to be quite general, in that other ligands (Scheme
 80 1) designed for organic solvents are also effective for ATH
 81 in water with no need for modification or organic sol-
 T1 82 vents.^[31–37] In Table 1, we summarise the results obtained
 83 with various metal catalysts based on Ru, Rh and Ir, in
 84 the ATH of the benchmark substrate acp.

In comparison with ATH in the azeotropic mixture of
 HCOOH-NEt₃ 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 per-
 formed with HCOOH-Et₃N in water, providing the ratio of
 HCOOH/Et₃N 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*RhCl₂]₂ and
 [Cp*IrCl₂]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.



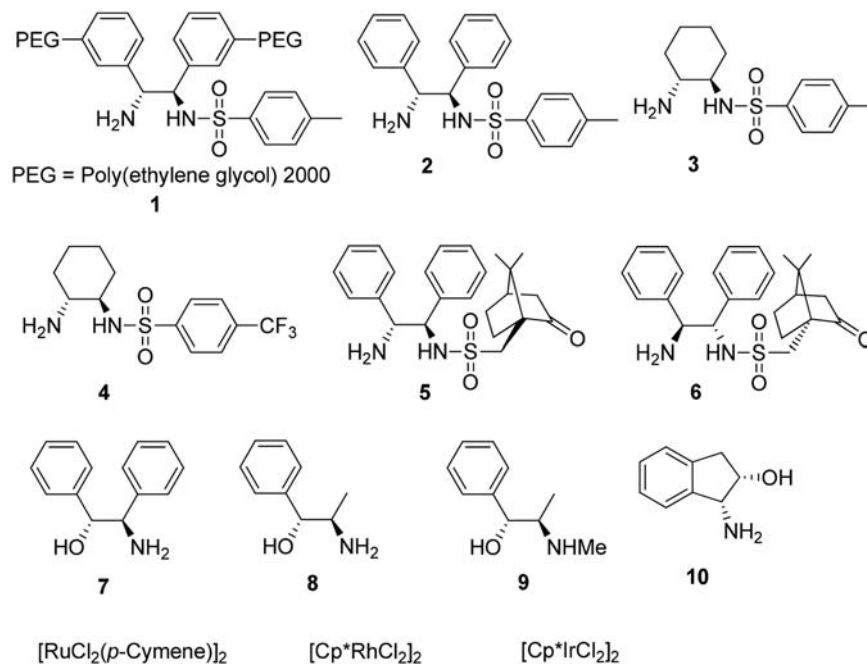
Chao Wang received his B. S. degree from Hunan Normal University in 2004 and M.S. degree from Chengdu Institute of Organic Chemistry (Graduate School of Chinese Academy of Sciences) in 2007 in P.R. China. He then moved to the UK to pursue his Ph.D. degree at the University of Liverpool with Prof. Jianliang 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.





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 be 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 $[\text{Cp}^*\text{IrCl}_2]_2$ 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 $[\text{Cp}^*\text{IrCl}_2]_2$ and **17**, afforded turnover frequencies of up to $1.3 \times 10^5 \text{ h}^{-1}$ 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 $[\text{Cp}^*\text{IrCl}_2]_2$ (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

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 ₂ O	100	1.5	>99	97	[32]
5	Ru-2	F/T-H ₂ O	1000	9	>99	96	[32]
6	Ru-2	F/T-H ₂ O	5000	57	98	96	[32]
7	Ru-2	F/T-H ₂ O	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.

167 Ir-17, although electron-deficient Ir-17 generally displayed a
168 higher catalytic activity than that of Ir-16. The same aldehyde
169 substrates have also been reduced with H₂ in water with Ir-17
170 as the catalyst.^[42]

171 2.4. TH of Quinoxalines

172 The same iridium catalyst, Ir-17, has also been explored for
173 the TH of quinoxalines in a project in collaboration with Pro-
T3 174 fessors Xu and Fan.^[43] As shown in Table 3, a variety of qui-
175 noxaline derivatives were successfully reduced, in a buffered

aqueous formate solution, to the corresponding tetrahydroqui- 176
noaxalines in good to excellent yields under mild conditions, 177
with or without inert gas protection. Again, the pH of the solu- 178
tion was crucial for the reduction (see Table 3 for details). 179

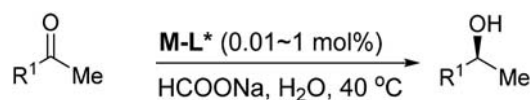
3. TH with Iridacycles in Water 180

The Noyori-Ikariya-type catalysts can be applied to the ATH/ 181
TH of cyclic imine bonds (C=N) in aqueous media.^[44,45] 182
This prompted us to try to apply this protocol to ATH/TH of 183
acyclic imines. Disappointingly, the reduction was not success- 184
ful under many reaction conditions screened. However, a very 185
interesting cyclometallated iridium complex was observed in 186
the TH of 4-methoxy-*N*-(1-phenylethylidene)aniline, result- 187
ing from the in situ reaction of [Cp*IrCl₂]₂ with the imine 188
substrate.^[46] A variety of cyclometallated iridium complexes, 189
iridacycles, have since been synthesised (Scheme 6) and proven 190 F6
to be highly efficient catalyst in a range of reactions, such as 191
transfer hydrogenative reductive amination (RA),^[47-49] hydro- 192
genation of acyclic imines^[50,51] and heterocycles,^[52] aqueous 193
TH of carbonyl groups^[53,54] and heterocycles,^[55] dehydroge- 194
nation of formic acid^[56] and heterocycles,^[57] and alkylation of 195
amines with alcohols and amines.^[58] The key intermediates 196
for TH, the iridium hydrides, have been isolated and charac- 197
terised.^[59] More recently, the mechanistic details of the hydro- 198
genation of imines with these iridacycles have been revealed by 199
a kinetic study and computational modelling.^[60] A significant 200
advantage of these catalysts is that they are easy to synthesise 201
and stable in air. 202

3.1. TH of Ketones and Aldehydes 203

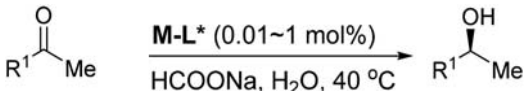
Our previous work on aqueous-phase ketone reduction 204
showed that water could accelerate ketone reduction, and the 205
solution pH had a dramatic effect on both the catalytic activity 206
and enantioselectivity, when using Noyori-Ikariya-type cata- 207
lysts.^[32,36] We envisioned that TH of ketones with the cyclo- 208
metallated iridium complexes might also be feasible in water, 209
and the reduction rate may vary with the solution pH as well. 210

Using formate as a reductant, we first investigated the 211
reduction of acp with precatalysts **24** and **25** in water.^[53] TH 212
did take place, even at a high S/C ratio of 2000, but only under 213
certain acidic conditions. The highest reaction rate was 214
observed at pH 3.5 for **24** and pH 2.5 for **25**. These optimal 215
values are quite different from those observed with the previ- 216
ous Noyori-Ikariya catalysts, which perform best at neutral 217
pH.^[32,36] This difference is most likely to be because reduction 218
with the iridacycles necessitate activation of the ketone by an 219
acidic medium, which provides hydrogen-bonding hydroxo- 220
nium ions, whereas the Noyori-Ikariya catalyst needs basic 221
conditions to generate the active 16e⁻ catalytic intermediate 222
and is bifunctional, in which the ligand NH proton activates 223

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

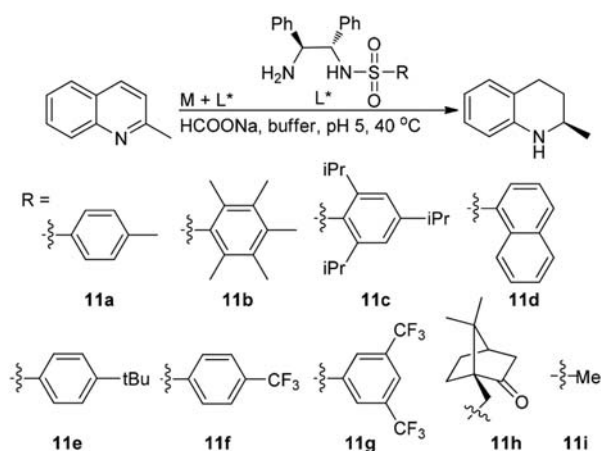
Entry	R ¹	Catalyst/[H]/S/C	Time [h]	ee [%] ^[b]	Ref.
1	4-Me-C ₆ H ₅	Ru-2/HCOONa/100	2	90	[30]
2	4-Me-C ₆ H ₅	Rh-2/HCOONa/100	6	93	[35]
3	4-Me-C ₆ H ₅	Rh-3/HCOONa/100	0.5	92	[33]
4	4-Me-C ₆ H ₅	Rh-4/HCOONa/100	0.5	91	[38]
5	4-Me-C ₆ H ₅	Ir-5/HCOONa/1000	8.5	92	[31]
6	4-OMe-C ₆ H ₅	Ru-2/HCOONa/100	2	95	[30]
7	4-OMe-C ₆ H ₅	Ru-2/HCOOH-Et ₃ N/100	5	97	[32]
8	4-OMe-C ₆ H ₅	Rh-2/HCOONa/100	20	97	[35]
9	4-OMe-C ₆ H ₅	Rh-3/HCOONa/100	0.5	93	[33]
10	4-OMe-C ₆ H ₅	Ir-5/HCOONa/1000	22	97	[31]
11	4-Cl-C ₆ H ₅	Ru-1/HCOONa/100	1.2	89	[29]
12	4-Cl-C ₆ H ₅	Ru-2/HCOONa/100	2	91	[30]
13	4-Cl-C ₆ H ₅	Ru-2/HCOOH-Et ₃ N/1000	11	93	[32]
14	4-Cl-C ₆ H ₅	Rh-2/HCOONa/100	0.4	94	[35]
15	4-Cl-C ₆ H ₅	Rh-2/HCOONa/1000	3	94	[35]
16	4-Cl-C ₆ H ₅	Rh-3/HCOONa/100	0.17	94	[33]
17	4-Cl-C ₆ H ₅	Rh-4/HCOONa/100	0.17	92	[38]
18	4-Cl-C ₆ H ₅	Ir-5/HCOONa/1000	2	96	[31]
19	4-CF ₃ -C ₆ H ₅	Ru-2/HCOONa/100	2	94	[30]
20	4-CF ₃ -C ₆ H ₅	Ru-2/HCOOH-Et ₃ N/100	1.3	95	[32]
21	4-CF ₃ -C ₆ H ₅	Rh-2/HCOONa/1000	1.8	94	[35]
22	4-CF ₃ -C ₆ H ₅	Rh-3/HCOONa/100	0.17	91	[33]
23	4-Br-C ₆ H ₅	Ru-2/HCOONa/1000	18	93	[30]
24	4-Br-C ₆ H ₅	Rh-2/HCOONa/1000	4	95	[32]
25	4-Br-C ₆ H ₅	Rh-3/HCOONa/100	0.25	94	[33]
26	4-Br-C ₆ H ₅	Ir-5/HCOONa/1000	1.8	95	[31]
27	4-CN-C ₆ H ₅	Ru-2/HCOOH-Et ₃ N/100	1.5	93	[32]
28	4-CN-C ₆ H ₅	Rh-2/HCOONa/1000	4.5	92	[35]
29	4-CN-C ₆ H ₅	Rh-3/HCOONa/100	0.4	90	[33]
30	4-NO ₂ -C ₆ H ₅	Ru-2/HCOOH-Et ₃ N/100	2	85	[32]
31	4-NO ₂ -C ₆ H ₅	Rh-2/HCOONa/100	0.5	88	[35]
32	4-NO ₂ -C ₆ H ₅	Rh-3/HCOONa/100	0.75	87	[33]
33	4-NO ₂ -C ₆ H ₅	Ir-5/HCOONa/1000	2	93	[31]
34	3-OMe-C ₆ H ₅	Ru-2/HCOONa/100	2	94	[30]
35	3-OMe-C ₆ H ₅	Ru-2/HCOOH-Et ₃ N/100	2.5	95	[32]
36	3-OMe-C ₆ H ₅	Rh-2/HCOONa/100	0.5	98	[35]
37	3-OMe-C ₆ H ₅	Rh-3/HCOONa/100	0.5	93	[33]
38	3-OMe-C ₆ H ₅	Ir-5/HCOONa/1000	3	98	[31]
39	2-OMe-C ₆ H ₅	Ru-2/HCOONa/100	2	72	[30]
40	2-OMe-C ₆ H ₅	Rh-2/HCOONa/100	24	81	[35]
41	2-OMe-C ₆ H ₅	Rh-3/HCOONa/100	1	79	[33]
42	2-OMe-C ₆ H ₅	Ir-5/HCOONa/1000	21	85	[31]
43	2-Me-C ₆ H ₅	Ru-2/HCOONa/100	6	80	[30]
44	2-Me-C ₆ H ₅	Rh-3/HCOONa/100	1	80	[33]
45	2-Me-C ₆ H ₅	Ir-5/HCOONa/1000	29	93	[31]
46	2-Cl-C ₆ H ₅	Ru-1/HCOONa/100	1.5	85	[29]
47	2-Cl-C ₆ H ₅	Ru-2/HCOONa/100	2	89	[30]

Table 2. (Continued)



Entry	R ¹	Catalyst/[H]/S/C	Time [h]	ee [%] ^[b]	Ref.
48	2-Cl-C ₆ H ₅	Rh-2/HCOONa/100	1	71	[35]
49	2-Cl-C ₆ H ₅	Rh-3/HCOONa/100	0.3	77	[33]
50	2-Cl-C ₆ H ₅	Ir-5/HCOONa/1000	3	88	[31]
51 ^[c]	C ₆ H ₅	Ru-2/HCOONa/100	2	86	[30]
52 ^[c]	C ₆ H ₅	Rh-3/HCOONa/100	1	92	[33]
53 ^[c]	C ₆ H 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.

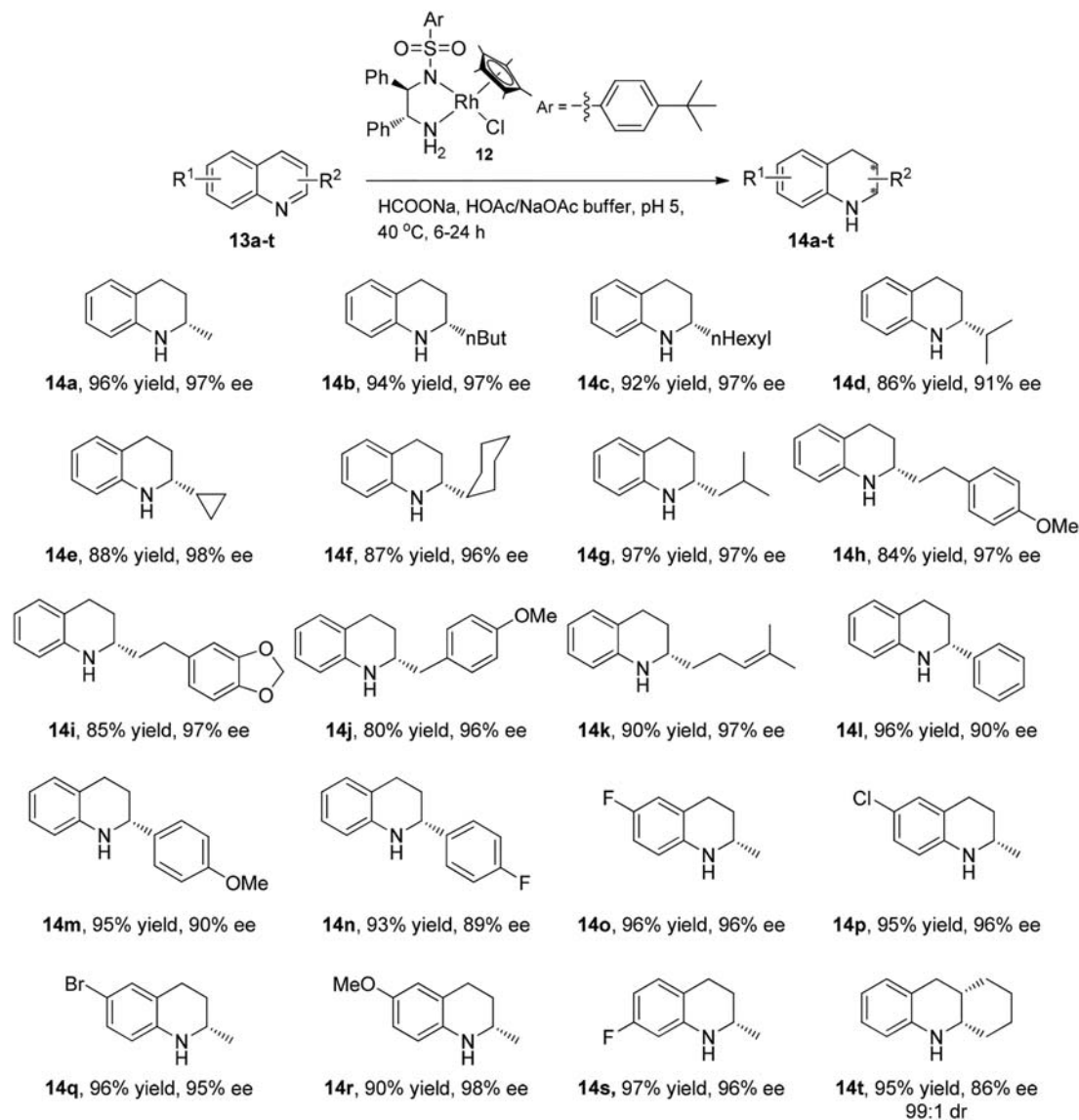


Scheme 2. Diamine ligands studied for the ATH of quinolines in water.

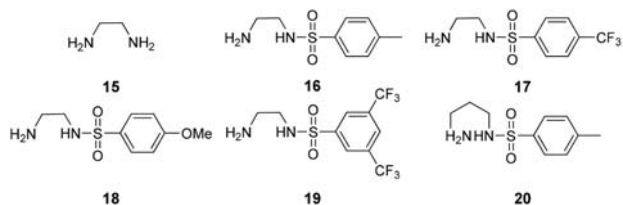
the substrate.^[61] However, when the pH becomes too low, the active catalytic species, iridium hydride, will be protonated. Hence, there should be an optimal pH value to balance the two competing reactions.

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



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

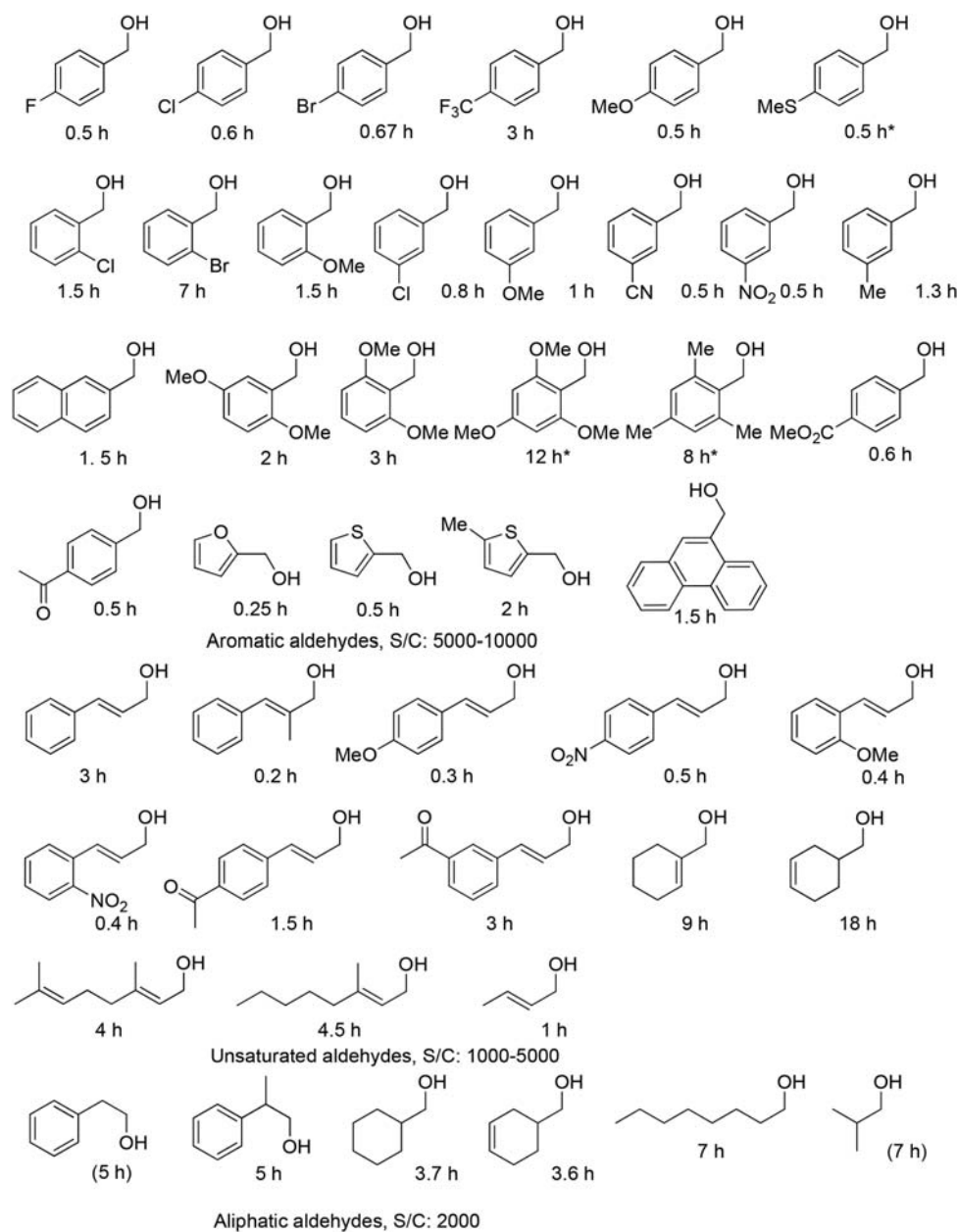


Scheme 4. Selected diamine ligands used for TH of aldehydes in water.

240 to reduce, due to the ease of dissociation/decomposition of
 241 these α -functional groups under the reaction conditions. The
 242 iridacycle appears to tolerate these functionalities well. As illus-
 T5 243 trated in Table 5, the desired products were obtained with
 244 excellent yields for almost all of these problematic ketones.

245 The much less featured β -keto ethers were also effectively
 246 and chemoselectively reduced to the desired β -hydroxyethers
 247T6 with iridacycle **34** (Table 6).^[54] Controlling the solution pH is
 248 critical, and pH 3–5 is optimal. Under these conditions, keto
 249 ethers featuring either aromatic or aliphatic units and aromatic
 250 aliphatic, heterocyclic and fluorinated ethers were all viable
 251 and gave excellent yields at a S/C ratio of 10000 on a 2.5
 252 mmol substrate scale without dissociation of any ether groups.

253 Moreover, the reduction of keto esters with the iridacycle
 254 catalysts is also practical.^[54] Catalysed by iridacycle **33**, both
 255 α - and β -keto esters, including those aromatic and aliphatic
 256 ones, have been reduced to the corresponding alcohols with
 257T7 excellent yields (Table 7). These results, together with those
 258 mentioned above, demonstrate the wide scope and utility of



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.

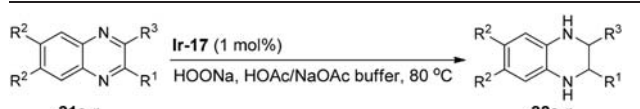
259 the iridacycles in carbonyl reduction and in aqueous-phase
260 organic synthesis.

261 3.2. TH of N-Heterocycles

262 In contrast to the situation of ketone reduction, the TH of het-
263 erocycles has been much less explored.^[62–65] The iridacycle
264 catalysts again show their utility by being capable of reducing
265 an ample variety of N-heterocycles, including quinolines,
266 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 cata-
lyst **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 be reduced with this catalytic sys-
tem.^[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.

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>i</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 ₆ H ₅ /H/H	10	97	[43]
11 ^[c]	4-F-C ₆ H ₄ /H/H	10	97	[43]
12 ^[c]	4-Cl-C ₆ H ₄ /H/H	10	95	[43]
13 ^[c]	4-Br-C ₆ H ₄ /H/H	10	95	[43]
14 ^[c]	4-MeO-C ₆ H ₄ /H/H	10	97	[43]
15 ^[c]	4-C ₆ H ₄ -C ₆ H ₄ /H/H	10	91	[43]
16 ^[d]	C ₆ H ₅ CHCH/H/H	12	95	[43]
17 ^[d]	2-Cl-C ₆ H ₄ CHCH/H/H	12	96	[43]
18 ^[d]	3-NO ₂ -C ₆ H ₄ CHCH/H/H	12	95	[43]

[a] Reaction conditions: quinoxalines **21** (0.5 mmol), [Cp*IrCl₂]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 iso- 276
quinolines and pyridines. However, quaternisation of the 277
nitrogen atom in these substrates led to the full reduction of 278
the N-heterocyclic rings.^[55] As shown in Table 10, an array of 279
isoquinolinium and pyridinium salts were reduced in excellent 10
yields. The versatility of these cyclometallated iridium catalysts 280
have been further demonstrated by the efficient TH of other 281
heterocycles and imines.^[55] 282
283

3.3. RA of Ketones and Aldehydes

Aqueous-phase RA reactions are scarce in the literature. This is 284
not surprising because water is generally thought to be adverse 285
for the formation of imines, which are key intermediates in RA 286
reactions. Drying agents are sometimes used to remove water 287
generated from the imine formation step.^[66,67] Due to the 288
high activity observed with our iridacycle catalysts for RA in 289
organic solvents,^[46] we were interested in developing a greener 290
version of the reaction by replacing the organic solvent with 291
water. 292
293

In our initial study of aqueous RA, we chose **24** as a cata- 294
lyst and sodium formate as a hydrogen source for RA of acp 295
with *p*-anisidine.^[47] Imine formation from the ketone and 296
amine and subsequent imine reduction are known to benefit 297
from acidic conditions. With this in mind, we first examined 298
the effect of the pH value of the solution on the model reaction. 299
Both the catalytic activity and selectivity were influenced 300
dramatically by the solution pH. At pH 4.8, the best selectivity 301

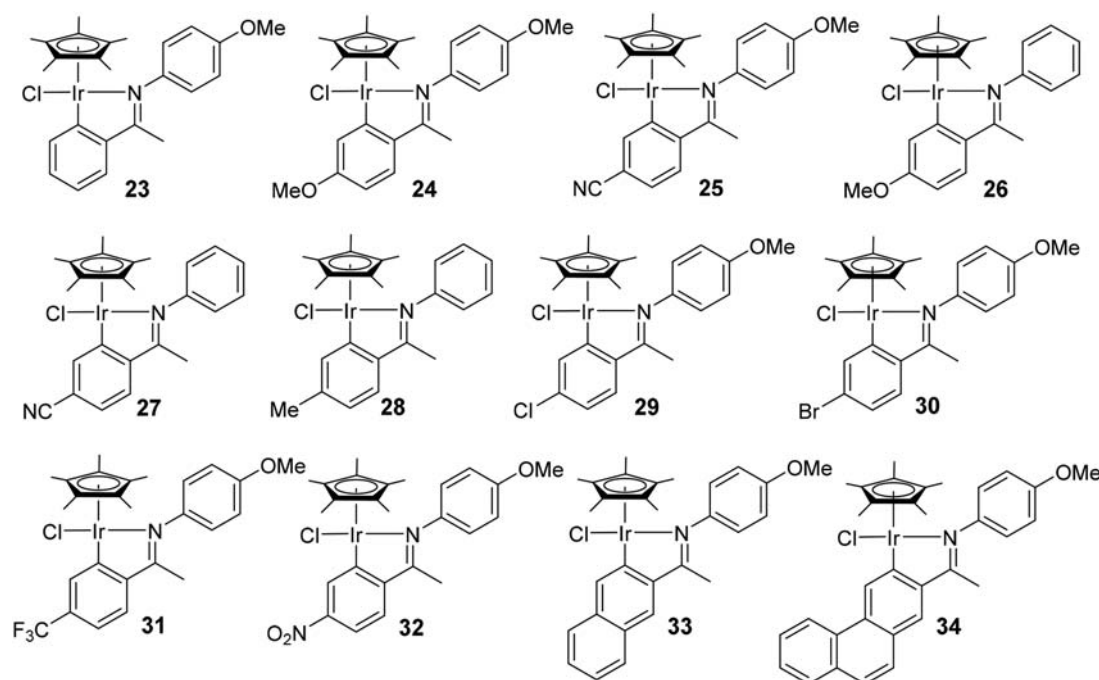
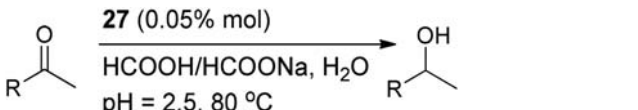
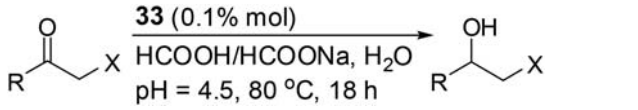
**Scheme 6.** Selected examples of cyclometallated iridium catalysts.

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


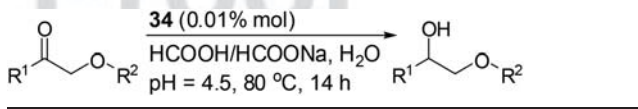
Entry	R	Time [h]	Yield [%] ^[b]	Ref.
1	C ₆ H ₅	4	96	[53]
2 ^[c]	4-Me-C ₆ H ₅	12	87	[53]
3 ^[d]	4-OMe-C ₆ H ₅	12	79	[53]
4	4-NO ₂ -C ₆ H ₅	4	97	[53]
5	4-CF ₃ -C ₆ H ₅	4	95	[53]
6	4-CN-C ₆ H ₅	12	91	[53]
7 ^[e]	4-F-C ₆ H ₅	12	89	[53]
8 ^[e]	4-Cl-C ₆ H ₅	12	89	[53]
9 ^[e]	4-Br-C ₆ H ₅	12	94	[53]
10	3-NO ₂ -C ₆ H ₅	4	96	[53]
11 ^[c]	3-Br-C ₆ H ₅	12	93	[53]
12 ^[c]	3-CF ₃ -C ₆ H ₅	12	91	[53]
13 ^[e]	3,5-(CF ₃) ₂ -C ₆ H ₅	12	90	[53]
14 ^[e]	2-F-C ₆ H ₅	12	91	[53]
15	2-Naphthyl	4	89	[53]
16 ^[e]	C ₆ H 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 ₆ H 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.

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


Entry	R	X	Yield [%] ^[b]	Ref.
1	C ₆ H ₅	OH	93	[54]
2	C ₆ H ₅	Cl	94	[54]
3	4-OMe-C ₆ H ₅	Cl	92	[54]
4	4-F-C ₆ H ₅	Cl	93	[54]
5 ^[d]	C ₆ H ₅	α,α -Cl ₂	87	[54]
6	C ₆ H ₅	F	95	[54]
7	C ₆ H ₅	α,α,α -F ₃	96	[54]
8	C ₆ H ₅	CN	90	[54]
9	4-Me-C ₆ H ₅	CN	92	[54]
10	4-F-C ₆ H ₅	CN	91	[54]
11	2-Thionyl	CN	89	[54]
12	2-Furanyl	CN	90	[54]
13	C ₆ H ₅	OC(O)C ₆ H ₅	96	[54]
14	C ₆ H ₅	-N(CH ₂) ₂ O(CH ₂) ₂ -	88	[54]
15	C ₆ H ₅	-N(CH ₂) ₅ -	86	[54]
16 ^[d]	C ₆ H 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 ¹H NMR spectroscopy.

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


Entry	R ¹	R ²	Yield [%] ^[b]	Ref.
1	C ₆ H ₅	4-Cl-C ₆ H ₅	93	[54]
2	C ₆ H ₅	4-OMe-C ₆ H ₅	91	[54]
3	C ₆ H ₅	2-naphthyl	97	[54]
4	C ₆ H ₅	2,6-Me ₂ -C ₆ H ₅	95	[54]
5	C ₆ H ₅	3-pyridine	89	[54]
6	4-Cl-C ₆ H ₅	C ₆ H ₅	97	[54]
7	4-CN-C ₆ H ₅	C ₆ H ₅	97	[54]
8	4-OMe-C ₆ H ₅	C ₆ H ₅	93	[54]
9	C ₆ H ₅	(CF ₃) ₂	87	[54]
10	C ₆ H ₅	CH ₂ (CF ₂) ₂ CF ₃	86	[54]
11	Me	C ₆ H ₅	98	[54]
12	Me	2,6-Me ₂ -C ₆ H 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.

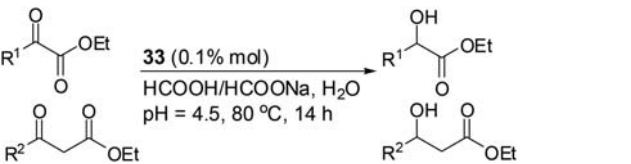
aromatic aldehydes reacting with *para*-anisidine at S/C of 2000 in 2 h. Aliphatic amines generally showed better activity in reactions with aldehydes than those with ketones. The lower

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).

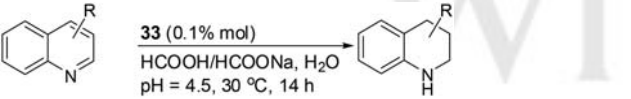
The reactions of aliphatic ketones with various amines were next investigated (Table 12). Higher activities were generally observed for aliphatic ketones. An S/C of 2000 can be employed for most of the substrates. Again, aromatic amines with the electron-withdrawing CF₃ substituent showed lower activities. 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

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


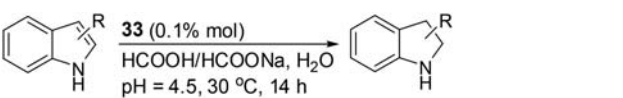
Entry	R ¹ or R ²	Yield [%] ^[b]	Ref.
1 ^[c]	R ¹ =Me	91	[54]
2	R ¹ =CF ₃	92	[54]
3	R ¹ =C ₆ H ₅	96	[54]
4	R ² =C ₆ H ₅	94	[54]
5	R ² =3-NO ₂ -C ₆ H ₅	91	[54]
6	R ² =3-Me-C ₆ H ₅	94	[54]
7	R ² =3,4,5-(OMe) ₃ -C ₆ H ₅	92	[54]
8	R ² =CF ₃	95	[54]

[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 ¹H NMR spectroscopy.

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


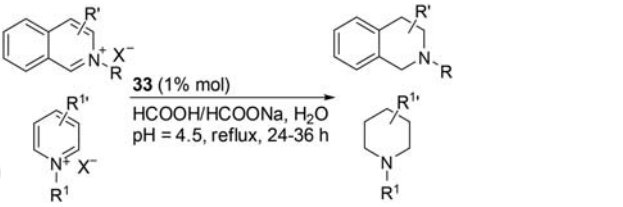
Entry	R	Yield [%] ^[b]	Ref.
1	2-Me	96	[55]
2	3-Me	93	[55]
3 ^[c]	4-Me	90	[55]
4	H	90	[55]
5 ^[c]	2-C ₆ H ₅	84	[55]
6	2-Me,6-F	97	[55]
7	2-Me,6-Cl	97	[55]
8	2-Me,6-Br	95	[55]
9	2-Me,7-F	98	[55]
10	2-Me,8-Cl	92	[55]
11	2-Me,6-Me	95	[55]
12	2-Me,6-OMe	96	[55]
13	2-Me,6-OBn	94	[55]
14	2-Me,6-OCH ₂ CH=CH 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 ₂ Me	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 ₆ H 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 ¹H 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 ₆ H 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 ₆ H ₅	Br	90	[55]
8 ^[d]	R ¹ =Bn, R ^{1'} =2-C(OH)(C ₆ H ₅) ₂	Br	72	[55]
9	R ¹ =Bn, R ^{1'} =2-CH ₂ NHCbz	Br	90	[55]
10	R ¹ =Bn, R ^{1'} =2-CH ₂ NHBoc	Br	94	[55]
11	R ¹ =Bn, R ^{1'} =2-(4-OMe-C ₆ H 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 ¹H 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

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

$$\text{R}^1-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}^2 + \text{R}^3-\text{NH}_2 \xrightarrow[\text{pH} = 4.8, 80^\circ\text{C}]{\text{33 (0.1 mol\%)} \\ \text{HCOOH/HCOONa, H}_2\text{O}} \text{R}^1-\overset{\text{HN}-\text{R}^3}{\text{C}}-\text{R}^2$$

Entry	R ¹	R ²	R ³	Time [h]	Yield [%] ^[b]	Ref.
1	C ₆ H ₅	Me	4-MeO-C ₆ H ₅	2	95	[47]
2	4-Me-C ₆ H ₅	Me	4-MeO-C ₆ H ₅	2	98	[47]
3	4-MeO-C ₆ H ₅	Me	4-MeO-C ₆ H ₅	2	95	[47]
4	4-F-C ₆ H ₅	Me	4-MeO-C ₆ H ₅	2	94	[47]
5	4-Cl-C ₆ H ₅	Me	4-MeO-C ₆ H ₅	2	98	[47]
6	4-Br-C ₆ H ₅	Me	4-MeO-C ₆ H ₅	2	98	[47]
7	4-CN-C ₆ H ₅	Me	4-MeO-C ₆ H ₅	2	98	[47]
8	4-CF ₃ -C ₆ H ₅	Me	4-MeO-C ₆ H ₅	2	96	[47]
9	4-NO ₂ -C ₆ H ₅	Me	4-MeO-C ₆ H ₅	2	93	[47]
10	2-naphthyl	Me	4-MeO-C ₆ H ₅	2	92	[47]
11 ^[c]	C ₆ H ₅	CH ₂ CO ₂ Me	4-MeO-C ₆ H ₅	12	71	[47]
12	C ₆ H ₅	Me	C ₆ H ₅	2	82	[47]
13	C ₆ H ₅	Me	4-Me-C ₆ H ₅	2	91	[47]
14	C ₆ H ₅	Me	4-F-C ₆ H ₅	2	93	[47]
15	C ₆ H ₅	Me	4-Cl-C ₆ H ₅	10	77	[47]
16 ^[c]	C ₆ H ₅	Me	4-Br-C ₆ H ₅	24	59	[47]
17	C ₆ H ₅	Me	C ₆ H ₅ CH 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.

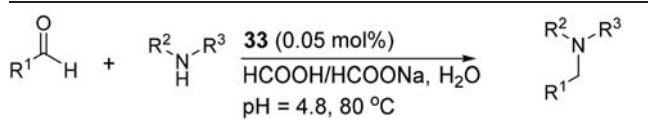
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Table 12. RA of aliphatic ketones with amines in water.^[a]

$$\text{R}^1-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}^2 + \text{R}^2-\overset{\text{R}^3}{\text{N}}-\text{H} \xrightarrow[\text{pH} = 4.8, 80^\circ\text{C}]{\text{33 (0.05 mol\%)} \\ \text{HCOOH/HCOONa, H}_2\text{O}} \text{R}^1-\overset{\text{R}^2-\text{N}-\text{R}^3}{\text{C}}-\text{R}^2$$

Entry	R ¹	R ² /R ³	Time [h]	Yield [%] ^[b]	Ref.
1	C ₆ H ₅ CH ₂ CH ₂	4-MeO-C ₆ H ₅ /H	2	98	[47]
2	C ₆ H ₅ CH ₂ CH ₂	C ₆ H ₅ /H	2	99	[47]
3	C ₆ H ₅ CH ₂ CH ₂	4-Me-C ₆ H ₅ /H	2	98	[47]
4	C ₆ H ₅ CH ₂ CH ₂	4-F-C ₆ H ₅ /H	2	98	[47]
5	C ₆ H ₅ CH ₂ CH ₂	4-Cl-C ₆ H ₅ /H	2	99	[47]
6 ^[c]	C ₆ H ₅ CH ₂ CH ₂	4-Br-C ₆ H ₅ /H	2	96	[47]
7	C ₆ H ₅ CH ₂ CH ₂	4-CF ₃ -C ₆ H ₅ /H	2	79	[47]
8	C ₆ H ₅ CH ₂ CH ₂	C ₆ H ₅ CH ₂ /H	2	97	[47]
9	C ₆ H ₅ CH ₂ CH ₂	CH ₃ (CH ₂) ₁₀ CH ₂ /H	2	54	[47]
10 ^[c]	C ₆ H ₅ CH ₂ CH ₂	CH ₃ (CH ₂) ₆ CH ₂ /H	6	85	[47]
11	C ₆ H ₅ CH ₂ CH ₂	-(CH ₂) ₆ -/H	48	52	[47]
12 ^[d]	C ₆ H ₅ CH ₂ CH ₂	C ₆ H ₅ /Me	24	64	[47]
13 ^[c]	C ₆ H ₅ CHCH	4-MeO-C ₆ H ₅ /H	4	93	[47]
14	Me	4-MeO-C ₆ H ₅ /H	2	98	[47]
15	CH ₃ CH ₂ CH ₂	4-MeO-C ₆ H ₅ /H	2	88	[47]
16	CH ₃ (CH ₂) ₄ CH ₂	4-MeO-C ₆ H 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.

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


Entry	R ¹	R ² /R ³	Time [h]	Yield [%] ^[b]	Ref.
1	C ₆ H ₅	4-MeO-C ₆ H ₅ /H	2	98	[47]
2 ^[c]	C ₆ H ₅	4-MeO-C ₆ H ₅ /H	48	95	[47]
3	4-Me-C ₆ H ₅	4-MeO-C ₆ H ₅ /H	2	98	[47]
4	4-MeO-C ₆ H ₅	4-MeO-C ₆ H ₅ /H	2	95	[47]
5	4-F-C ₆ H ₅	4-MeO-C ₆ H ₅ /H	2	97	[47]
6	4-Cl-C ₆ H ₅	4-MeO-C ₆ H ₅ /H	2	79	[47]
7	4-Br-C ₆ H ₅	4-MeO-C ₆ H ₅ /H	2	92	[47]
8	4-CF ₃ -C ₆ H ₅	4-MeO-C ₆ H ₅ /H	2	96	[47]
9	4-NO ₂ -C ₆ H ₅	4-MeO-C ₆ H ₅ /H	4	97	[47]
10	3-Br-C ₆ H ₅	4-MeO-C ₆ H ₅ /H	2	97	[47]
11	C ₆ H ₅	C ₆ H ₅ /H	5	97	[47]
12	C ₆ H ₅	4-Me-C ₆ H ₅ /H	2	94	[47]
13	C ₆ H ₅	4-F-C ₆ H ₅ /H	2	98	[47]
14 ^[d]	C ₆ H ₅	4-Br-C ₆ H ₅ /H	2	95	[47]
15	C ₆ H ₅	C ₆ H ₅ CH ₂ /H	2	95	[47]
16	C ₆ H ₅	CH ₃ (CH ₂) ₆ CH ₂ /H	2	97	[47]
17 ^[d]	C ₆ H ₅	CH ₃ (CH ₂) ₁₀ CH ₂ /H	2	83	[47]
18 ^[d]	C ₆ H ₅	-(CH ₂) ₆ -/H	4	93	[47]
19 ^[d]	C ₆ H ₅	C ₆ H ₅ /Me	4	72	[47]
20 ^[d]	C ₆ H ₅	C ₆ H ₅ CH ₂ /Me	5	98	[47]

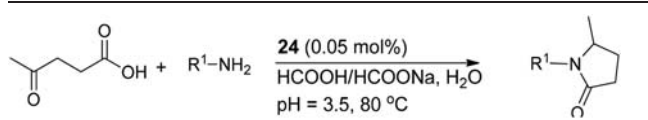
[a] Reaction conditions: Aldehyde (5 mmol), amine (10 mmol), HCOOH/HCOONa solution (pH 4.8, 8 mL), 80 °C. [b] Isolated yield. [c] pH 4.6, S/C=100000, 48 h; yield determined by ¹H NMR spectroscopy. [d] S/C=1000.

332 95% yield in 48 h. This is the highest S/C ratio ever reported
333 for RA reactions (Table 13, entry 2).

34 3.4. RA of Levulinic Acids

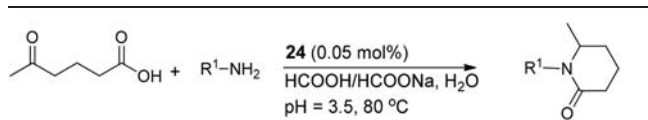
335 More challenging applications of the iridacycle catalysts have
336 been demonstrated in the RA of levulinic acid (LA) to form pyr-
337 rolidinones by TH in water.^[49] LA can be obtained by simple
338 acidic dehydration of renewable carbohydrates and has been
339 identified as a biomass-derived platform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

342 By using our iridacycle catalysts, we disclosed the first true
343 TH system for RA of LA to produce pyrrolidinones using formic
344 acid as the hydrogen source. As with the RA reactions out-
345 lined above, this reaction was also affected strongly by solution
346 pH; pH 3.5 was optimum for **24**-catalysed RA of LA with *para*-
347 anisidine. As seen from the results in Table 14, RA afforded
348 good yields for a range of aromatic amines. In particular, those
349 with relatively electron-donating substituents gave higher yields
350 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 ₆ H ₅	2	94	[49]
2	4-Me-C ₆ H ₅	2	93	[49]
3	C ₆ H ₅	2	91	[49]
4	4-F-C ₆ H ₅	4	88	[49]
5	4-Cl-C ₆ H ₅	4	73	[49]
6	4-Br-C ₆ H ₅	4	86	[49]
7	4-OCF ₃ -C ₆ H ₅	4	72	[49]
8 ^[c]	3-MeO-C ₆ H ₅	12	76	[49]
9	3,4-(Me) ₂ -C ₆ H ₅	12	82	[49]
10	C ₆ H ₅ CH ₂	4	86	[49]
11	4-MeO-C ₆ H ₅ CH ₂	4	94	[49]
12	3-MeO-C ₆ H ₅ CH ₂	12	94	[49]
13 ^[d]	2-MeO-C ₆ H ₅ CH ₂	24	96	[49]
14	3,4-(MeO) ₂ -C ₆ H ₅ CH ₂	24	94	[49]
15	4-F-C ₆ H ₅ CH ₂	12	91	[49]
16 ^[e]	CH ₃ (CH ₂) ₆ CH ₂	12	88	[49]
17 ^[f]	CH ₃ (CH ₂) ₉ CH 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/Et₃N 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 ₆ H ₅	12	84	[49]
2	4-F-C ₆ H ₅	12	97	[49]
3	4-MeO-C ₆ H ₅ CH ₂	24	82	[49]
4	4-F-C ₆ H ₅ CH ₂	12	81	[49]
5 ^[c]	CH ₃ (CH ₂) ₆ CH 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

359 compounds, starting with Noyori–Ikariya-type catalysts.
 360 Nitrogen heterocycles were also found to be reducible. During
 361 the course of our studies, a new class of catalysts, iridacycles,
 362 were found. These iridacycles have since found broad applica-
 363 tions in catalysis. Of relevance to the objective of this article is
 364 that they are capable of catalysing aqueous-phase TH of car-
 365 bonyls and RA reactions, including extension into biomass-
 366 derived platform molecules. A chiral version would certainly
 367 make these iridacycles more attractive. Throughout our
 368 endeavour, water is shown to be an enabling medium for TH
 369 reactions of various features. Not only can it accelerate reduc-
 370 tion, it also allows one to control the reaction through the pH.
 371 Performing optimally only in a certain pH window in water,
 372 Noyori–Ikariya-type catalysts and iridacycles provide illumina-
 373 tating examples.

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