Aqueous-phase asymmetric transfer hydrogenation of ketones – a greener approach to chiral alcohols

Xiaofeng Wu and Jianliang Xiao*

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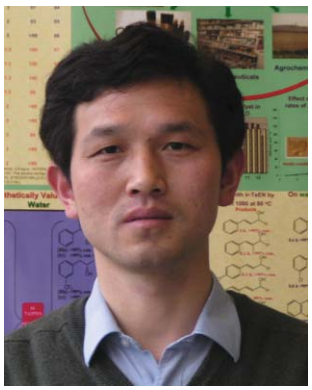
Asymmetric transfer hydrogenation (ATH) has emerged as a practical, powerful alternative to asymmetric hydrogenation for the production of chiral alcohols, one of the most valuable intermediates in chemical synthesis. In the last a few years, ATH in neat water has proved to be viable, affording chiral alcohols in fast rates, high productivity and high enantioselectivity. The reduction can be carried out with unmodified or tailor-made catalysts by using mild, readily available formate salt as reductant with no organic solvents required, thus providing a simple, economic and green pathway for alcohol production. This Feature Article attempts to present an account of the progress made on aqueous-phase transfer hydrogenation (TH) reactions, with a focus on ATH. The coverage includes a brief background of the chemistry, TH and ATH reactions in water, and the mechanistic aspects of the aqueous-phase reduction.

1 Introduction

Chirality or handedness is one of the most important symbols of nature and living organisms. Life itself depends on chirality because biological systems recognise molecules with specific chirality. Among small chiral molecules, chiral alcohols occupy a central place in the synthesis of pharmaceuticals, flavour, aroma and agricultural chemicals, and speciality materials. Chiral alcohols can be accessed by enantioselective chemical reduction of the corresponding ketones by methods shown in Scheme 1, and this remains pivotal in organic synthesis both in the laboratory and in industry. In addition, they are increasingly prepared by enzymatic reduction using the cofactor NAD(P)H as hydrogen donor.

The past two decades have witnessed the development of some of the most successful and general catalysts for both the asymmetric hydride reduction[1] and enantioselective hydrogenation.[2] Recently asymmetric transfer hydrogenation (ATH) has emerged

Liverpool Centre for Materials and Catalysis, Department of Chemistry, University of Liverpool, Liverpool, UK L69 7ZD.
E-mail: j.xiao@liv.ac.uk; Fax: (+44) 151 7943589;
Tel: (+44) 151 7942937

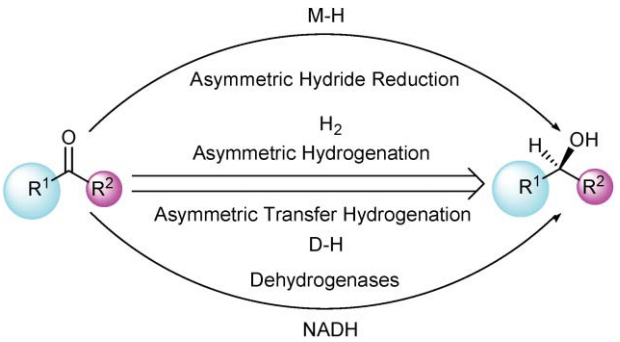


Xiaofeng Wu

Xiaofeng Wu graduated from East China University of Science and Technology (ECUST) (Shanghai, China), obtaining a BSc in applied chemistry in 1995. He was then appointed to a teaching position and promoted to a Lecturer at the same university in 1999. He did his MSc study in organic chemistry under the joint direction of Prof. G. Rong of ECUST and Prof. M. Shi of the Shanghai Institute of Organic Chemistry during the period of 1999–2002. After obtaining the MSc degree, he was awarded the Fuji Otsuka Fund Research Fellowship and took part in the total synthesis of a natural product in the group of Prof. K. Shishido at the University of Tokushima in Japan. Since 2004, he has been working on his PhD under the supervision of Prof. Xiao at the University of Liverpool, with a project focusing on the chemistry of asymmetric transfer hydrogenation in water. His scientific interest includes organic synthesis, organometallics, and catalysis.

Jianliang Xiao received his BSc in chemical engineering at the Northwest University in Xi'an in 1982. This was followed by a MSc in catalytic engineering with Profs C. Wu and J. Wang at the Research Institute of Petroleum Processing in Beijing. Feeling a chemistry background would benefit his interest in heterogeneous catalysis, he went to the University of Alberta for a PhD in organometallic chemistry under Prof. Martin Cowie. After a two-year postdoctoral appointment with Prof. Dick Puddephatt, he joined the ERATO Molecular Catalyst Project as a Researcher to learn homogeneous catalysis under Prof. R. Noyori. In 1996, he took up a Principal Scientist position at the Leverhulme Centre for Innovative Catalysis in the University of Liverpool. He was appointed to a Lectureship in the Chemistry Department in 1999; this was followed by promotion to Reader and then full Professor. He is a visiting professor at the Dalian Institute of Chemical Physics and Northwest University and sits on the Advisory/Editorial Boards of several organisations. His research interest focuses on understanding the molecular basis of catalysis and on developing catalytic methodologies for more efficient and greener organic synthesis.

Jianliang Xiao



Scheme 1 Synthesis of chiral alcohols *via* catalytic asymmetric reduction of ketones.

as a powerful, practical and versatile tool for the enantioselective reduction of carbonyl compounds.[2d,3] The method is attractive as an alternative to asymmetric hydrogenation because it requires neither the hazardous hydrogen gas nor pressure vessels and it is easy to execute. Furthermore, there are a number of chemicals that are easily available and can be used as hydrogen donors, D–H, among which 2-propanol (IPA) and the azeotropic mixture of formic acid and triethylamine (F–T; 2.5 $HCOOH/NEt_3$ molar ratio) have been most frequently used. Still further, it allows for reduction that cannot be effected under the conditions of hydrogenation. In the past, the application of ATH has been hampered by its low TONs and TOFs. This challenge has largely been met by the advent of new catalysts and new reaction conditions in the last a few years, and there have been a number of excellent reviews summarizing the achievements including mechanistic understanding made thus far.[2d,3] In this feature article, we focus on a more specific aspect of the recent development made by us and other research groups, *viz* in-water ATH of ketones and transfer hydrogenation (TH) of aldehydes.[4,5] None of the available review articles are specific on aqueous-phase reduction.

Enabling catalysis in water contributes to one of the most important and challenging fields of modern chemistry, green synthesis.[6] As solvent for organic reactions, water bears a number of attractive physicochemical properties over traditional organic solvents: it is non-flammable, non-explosive, non-toxic and non-carcinogenic. In addition, water is also one of the least expensive and most easily accessible solvents. Unsurprisingly, a great number of aqueous phase catalytic reactions have been documented.[6a,d,h,i,7] A disadvantage often associated with catalysis in water is the need for water soluble ligands/catalysts and the decrease in catalytic activity and/or stereoselectivity on going from organic solvents to water.[6] However, the low solubility of organic molecules in water has been harnessed to design hydrophobicity directed organic synthesis and catalysis, furnishing reaction rates and selectivities superior to those in organic media.[6b,8] And as will be seen, water-insoluble ligands can be extremely effective in aqueous TH or ATH reactions.

2 Background and recent progress of TH in non-aqueous media

2.1 History

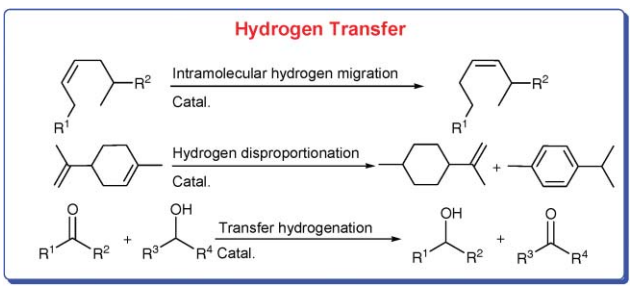
TH is the reduction of an unsaturated molecule by a hydrogen donor other than H_2 with the aid of a catalyst. This process is but one of several possible hydrogen transfer reactions classified by Braude and Linstead in 1954, as exemplified by the reactions in Scheme 2.[9] TH reactions can be effected by a variety of means including heterogeneous, homogeneous and enzymatic catalysis.

Catalytic hydrogen transfer was first demonstrated by Knoevenagel and Bergdolt in 1903, who observed that dimethyl 1,4-dihydroterephthalate disproportionated readily to dimethyl terephthalate and *cis*-hexahydroterephthalate under the catalysis of palladium black.[10] The reduction of ketones and aldehydes by TH, *i.e.* the Meerwein–Ponndorf–Verley (MPV) reduction, first appeared in 1925.[11] In the following three decades, a great deal of progress was made in developing heterogeneous palladium and nickel catalysts for TH reactions. TH by transition metal complexes did not appear until the 1960s, however, when the modern homogeneous catalysis started. The initial discovery was due to Henbest, Mitchell and co-workers.[12] An iridium hydride complex was used as catalyst for the reduction of cyclohexanone and α,β-unsaturated ketones. A few years later, Sasson and Blum disclosed TH by a ruthenium catalyst, $[RuCl_2(PPh_3)_3]$, and developed biphasic TH of ketones and aldehydes with this catalyst.[13] However, the reaction necessitated a high temperature of 200 °C in most cases and gave low TOFs. In 1991, Chowdhury and Backvall reported a breakthrough – the TH reaction with the same catalyst could be accelerated 10^3–10^4 times by adding a small amount of a base, NaOH.[14]

The asymmetric version of the reaction, ATH, appeared first as enantioface discriminating reduction in the 1970s from the groups of Ohkubo and Sinou, who explored the catalysis with $[RuCl_2(PPh_3)_3]$ in the presence of either a chiral monophosphine or a chiral hydrogen donor.[15] Since then, a wide range of metal complexes coupled with various chiral phosphorus and nitrogen ligands have been explored to catalyze the ATH of ketones and olefins.[3c,h,j,k,m] However, the optical yields of products were generally low before the 1990s, with few ee values exceeding 90%.[3k,m]

2.2 Recent development

There is little doubt that the last decade has witnessed the most celebrated achievements in TH/ATH chemistry, highlighted by the advent of highly active, selective and productive catalytic systems.[2,3,16] Among the catalysts developed for ATH, the most important and significant are Ru(II) complexes containing monotosylated 1,2-diamines, discovered by Hashiguchi,



Scheme 2 Hydrogen transfer reactions illustrated with examples.

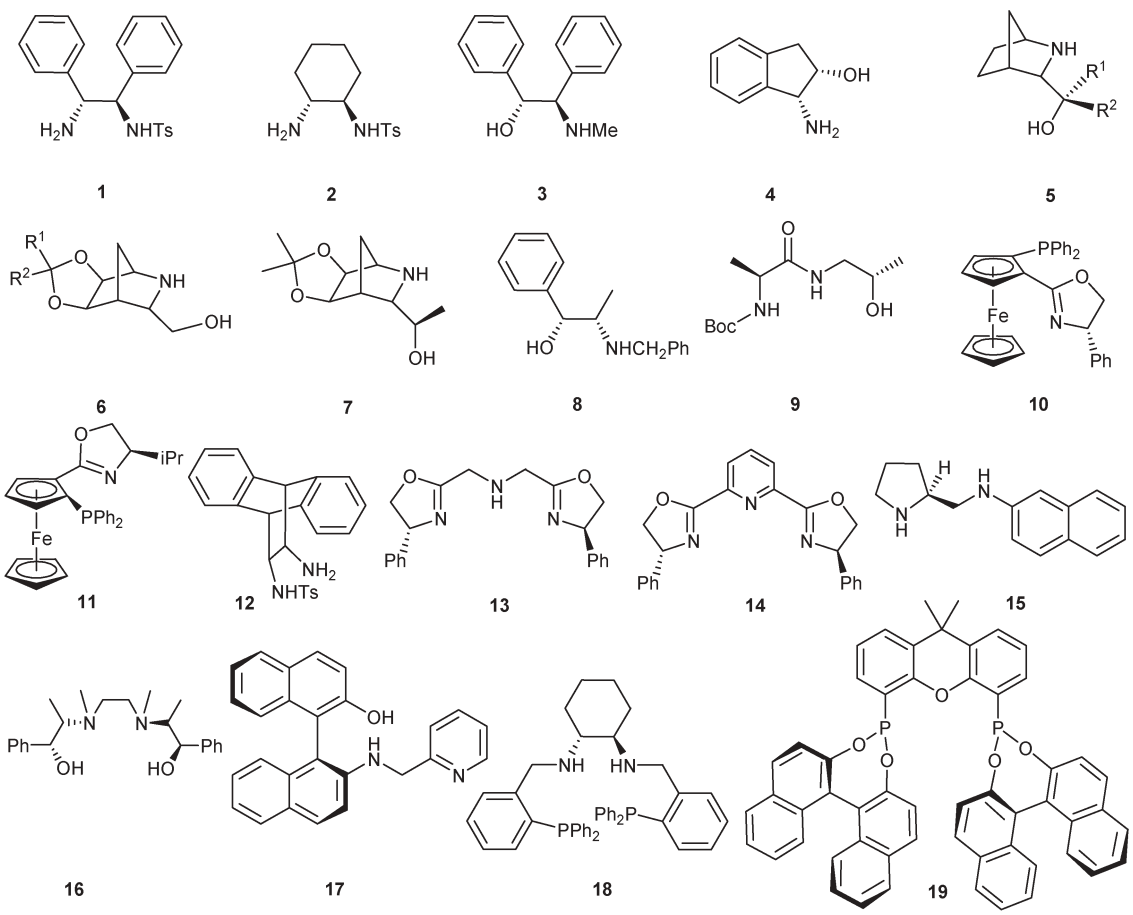
Ikariya, Noyori and co-workers in 1995.[17] The application of these chiral ligands, represented by *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine (TsDPEN), has led to the reduction of a number of aromatic ketones and imines with outstanding conversions and ee's.[2a,3j,18] Not long after this, Knochel and co-workers demonstrated the application of monotosylated diaminocyclohexane (TsCYDN) and diaminoferrocene in ATH of ketones,[19a,b] and the CATHY™ series of catalysts were disclosed by Blacker.[19c] Following on from these pioneering studies, a great number of related ligands and catalysts have been developed.[3] In Scheme 3 are shown some of the most effective ligands, all affording ee's >90% in the enantioeselective reduction of a benchmark substrate, acetophenone (acp).

Alongside the diamines, β-amino alcohols have emerged as another type of efficient ligands. Noyori and co-workers showed that there is a significant ligand-acceleration effect of **3** on the ATH of ketones with Ru(II) catalysis, and the N–H moiety is necessary for an efficient reduction.[18d] Wills[20a] and Andersson[21a] demonstrated that stereochemically rigid β-amino alcohols, *e.g.* **4–7**, work very well in ATH of ketones in IPA, outperforming **1** or **2** in some cases. In particular, the ATH of ketones with Ru-**7** led to excellent reaction rates and enantioselectivities in IPA,[21b,c] furnishing TOF up to 8500 h^{-1} and enantioselectivity in 96% ee. In general, however, these amino alcohol ligands appear to be incompatible with the F–T reduction system.[3c,h]

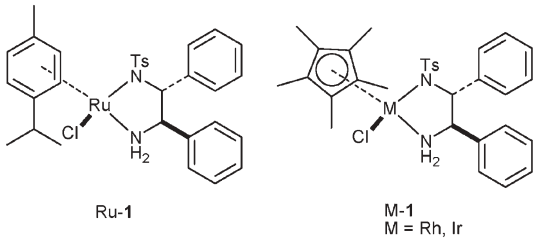
Remarkable advancement in ATH is still emerging. The BINOL-derived diphosphite **19** was recently shown by Li and Reetz to be efficient in Ru(II) catalyzed ATH of both aromatic and aliphatic ketones, although the ee's were lower for the latter.[22a] Mikami reported an achiral, benzophenone-derived phosphine that showed excellent asymmetric induction in the presence of a chiral diamine activator in rhodium-catalysed ATH of ketones.[22b] Very recently, Ru-**1** was discovered by Okuma and Noyori to be efficient for the asymmetric hydrogenation of 4-chromanone and its derivatives in methanol, providing a long-sought catalyst capable of both hydrogenation and transfer hydrogenation.[22c]

In most cases, the ATH reactions with these ligands are performed by in situ reacting the ligands with a metal compound, typical examples being $[RuCl_2(p\text{-cymene})]_2$ and $[Cp^*MCl_2]_2$ (M = Rh, Ir), using IPA or F–T as both the hydrogen source and solvent. In a few cases, the structures of precatalysts and catalytic intermediates have been determined by X-ray diffraction.[18b,23] Scheme 4 schematically shows the structures of Ru(II), Rh(III) and Ir(III) incorporating the TsDPEN **1**.[18b,23]

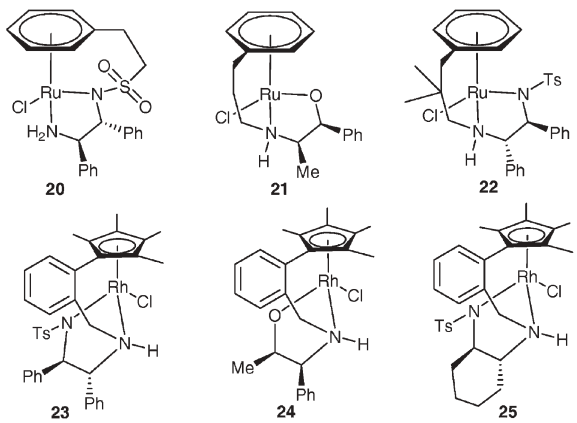
It is noted that catalysts derived from these ligands have the arene rings disintegrated from the amino ligands. In order to achieve improved enantiocontrol by locking the chiral elements of the ligands, Wills recently developed a series of tethered catalysts, in which the monotosylated diamine or



Scheme 3 Representative ligands for ATH of ketones.



Scheme 4 Precatalysts formed by TsDPEN **1**.

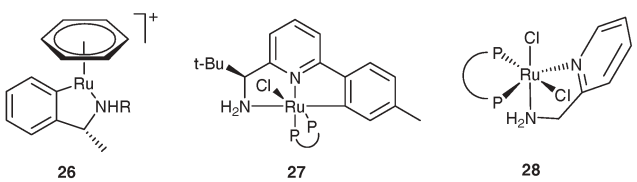


Scheme 5 Tethered ruthenium and rhodium catalysts.

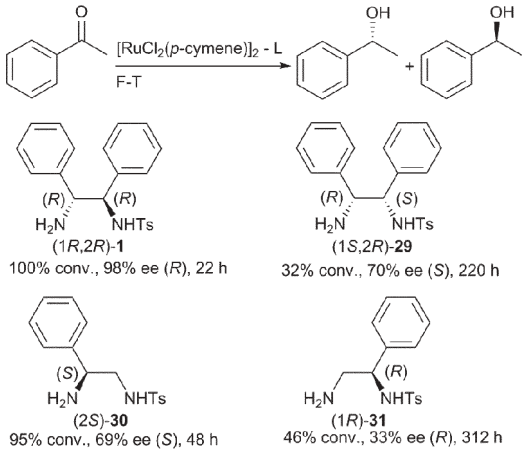
amino alcohol was bound to the η^6- or η^5-arene group (**20–25**, Scheme 5).[5a,24] These catalysts have proved to be more enantioselective than Ru-**1** or Rh-**2** in some cases.

TH reactions could also be effected by the ruthenacycles **26**[25] and **27**[26] and the somewhat related **28** developed by the groups of de Vries and Baratta (Scheme 6). Of particular note is that **27** afforded superlative activity in the TH of acp, with TOF over 1×10^6 h^{-1} being observed.[26b,c]

There appears to be a correlation between the structure factors of ligands and enantioselectivity of corresponding catalysts in ATH of ketones.[3e,27] The study of Wills into tosylated diamines is illustrative, which revealed that ligands with one chiral centre gave products with the same configuration as that of the ligand being used (**30** *vs.* **31**, Scheme 7), while the ligands containing two chiral centres produced alcohols with the configuration following the stereochemistry of the carbon bound to the tosylamine (**1** *vs.* **29**, Scheme 7).[27a] Thus the chirality of product appears to be dependent on the absolute configuration of this carbon centre, with a matched combination of chirality at the two stereogenic centres affording a higher ee and faster rate.[21b,27a,b,28]



Scheme 6 Ruthenacycle and related catalysts.



Scheme 7 Correlation between the configuration of ligand and product.

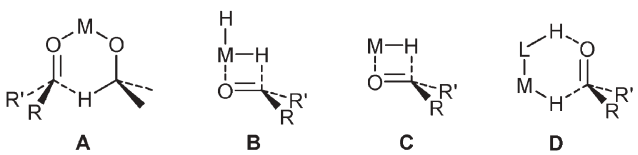
2.3 Mechanism of ATH reactions

Depending on the nature of metal centre, ligands, and substrates, hydrogen transfer from a catalyst to a carbonyl molecule may take different pathways, as shown in Scheme 8. The widely-accepted mechanistic pathway for main group metals is "direct hydrogen transfer" as illustrated by **A**.[3b,29a] With transition metal catalysts, two main pathways have been proposed, a dihydride (**B**) and a monohydride mechanism (**C**, **D**).[29b,c] The monohydridic transfer may proceed *via* an inner sphere pathway involving ketone coordination to the metal (**C**) or an outer sphere variant without substrate–metal bonding (**D**). Still further, the hydrogen transfer proceeding *via* **D** can be concerted[3j,17,18b,29d] or stepwise.[3b,29e,f] In addition, the reduction of imines may occur through an ionic mechanism involving a monohydride but without imine coordination.[29g–i]

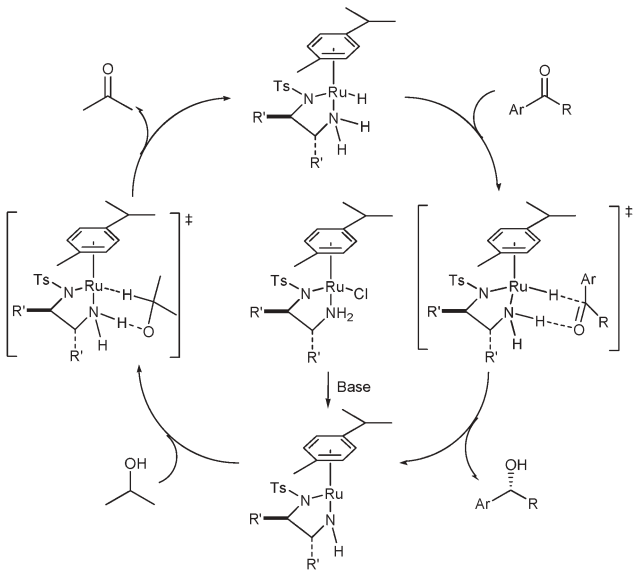
The concerted mechanism appears to be dominant with catalysts containing Lewis acidic or hydrogen bond donating ligands and is best represented in Noyori's metal–ligand bifunctional catalysis. This involves a simultaneous transfer of a hydride from the metal and a proton from the ligand without prior coordination of substrate to the metal, and it is believed to operate in most of the ATH reactions effected by amino and aminoalcohol ligands. The full catalytic cycle is outlined in Scheme 9.[3i,j,17,18b]

3 TH and ATH in aqueous media

The most popular solvents for the ATH reactions have been IPA[17] and the azeotropic F–T mixture,[18c,30] which supply the hydrogen at the same time. Whilst formic acid and its salts are viable hydrogen sources and soluble in water, and aqueous



Scheme 8 Proposed transition states in hydrogen transfer to a ketone.



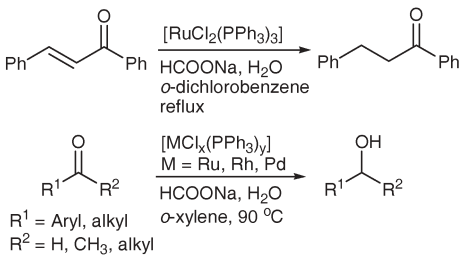
Scheme 9 ATH of ketones by IPA *via* Noyori's metal–ligand bifunctional catalysis.

formate has been used by enzymes for reduction reactions for millions of years, it is all surprising that little attention had been paid to using water as solvent for ATH prior to 2004. To some degree this reflects the limited research into aqueous achiral transfer hydrogenation undertaken in the past decades.

3.1 Achiral TH of ketones and aldehydes in aqueous media

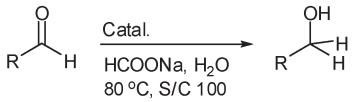
Organometallic catalysis in aqueous media has attracted interest since the 1970s, with pioneering work being carried out by Joo, Sasson and Sinou.[6c,31] In spite of the well-documented studies of aqueous-phase hydrogenation, TH in water had been less developed until a few years ago. In the 1980s, Sasson and co-workers reported aqueous-organic biphasic TH of C=C double bonds[31e] and carbonyl groups (Scheme 10).[31c,d] Up to 76% conversion was obtained for the aldehyde reduction with $[RuCl_2(PPh_3)_3]$ in 30 min; the reduction was less effective for ketones, however.

Transition metal catalyzed TH of aldehydes in neat water was first carried out by Joo and co-workers.[31a,b,f] Unsaturated aldehydes were reduced to unsaturated alcohols by HCOONa with a ruthenium catalyst bearing a water-soluble phosphine (Table 1). The reduction was efficient, with most reactions completed in a few hours, including those involving multi-substituted aromatic aldehydes. For example, 2,6-dichloro-benzaldehyde was converted into the corresponding alcohols



Scheme 10 TH in the presence of water.

Table 1 TH of aldehydes with water-soluble catalyst by HCOONa in water[a]

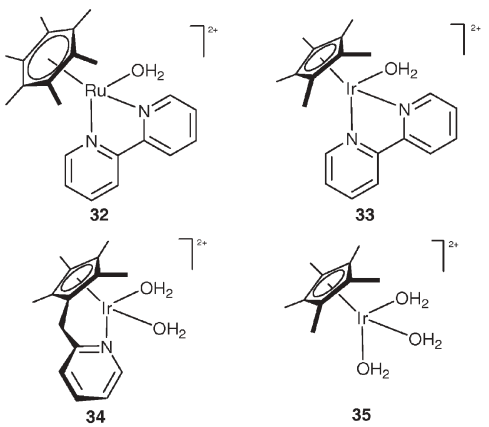


Entry	Substrate	Time/h	Conv. (%)	Yield (%)
1	bza[b]	1.5	>99	94
2	4-Me-bza	1.5	>99	99
3	4-MeO-bza	1.5	99	90
4	4-Br-bza	1.5	>99	94
5	2,6-di-Cl-bza	1.5	100	96
6	3,4,5-tri-MeO-bza	8	99	91
7	4-NMe_2-bza	1.5	99	98
8	2-NO_2-bza	2	100	90
9	*trans*-Cinnamaldehyde	2	98	92
10	Crotonaldehyde[c]	2.5	N/A	78
11	1-Citronellal	4	93	90
12	Citral[d]	7	98	95
13	2-Naphthaldehyde	3.5	100	98
14	Pyrrole-2-carbaldehyde	5	>99	66

[a] *Conditions*: 0.01 mmol $[RuCl_2(m\text{TPPMS})_2]$, (*m*TPPMS = *meta*-sulfophenyldiphenylphosphine), 0.1 mmol *m*TPPMS, 1 mmol aldehyde, 5 M HCOONa in 3 mL water, 80 °C. [b] bza = benzaldehyde. [c] 30 °C; side reaction at 80 °C.[31a,b] [d] Mixture of *cis* and *trans* (2 : 1). No isomerization was observed.

in 1.5 h without hydrodechlorination occurring (entry 5, Table 1), and the reduction of α,β-unsaturated aldehydes was chemoselective, only furnishing unsaturated alcohols as the product (entries 9–12, Table 1). However, there was no reaction for substrates containing an OH group, *e.g.* 2-hydroxybenzaldehyde. Among the various catalysts tested, $[RuCl_2(m\text{TPPMS})_2]$ was found to be the most efficient.[6c,31a,f] Subsequent work from Sinou *et al.* demonstrated the TH as well as ATH of unsaturated carboxylic acids to saturated carboxylic acids by formate in water, using a rhodium catalyst containing water-soluble phosphines.[31g]

Recently, Ogo, Watanabe and co-workers reported the TH of ketones and aldehydes by HCOONa or HCOOH in water with water-soluble half-sandwich Ru(II) and Ir(III) complexes (**32–35**, Scheme 11).[32e–i] The reduction was shown to be solution pH-dependent, an important finding reminiscent of that made by Joo and others on aqueous hydrogenation



Scheme 11 Water-soluble Ru- and Ir-catalysts for pH-dependent TH.

Table 2 TH of carbonyl compounds with **32**[a] or **33**[b] by HCOONa in water

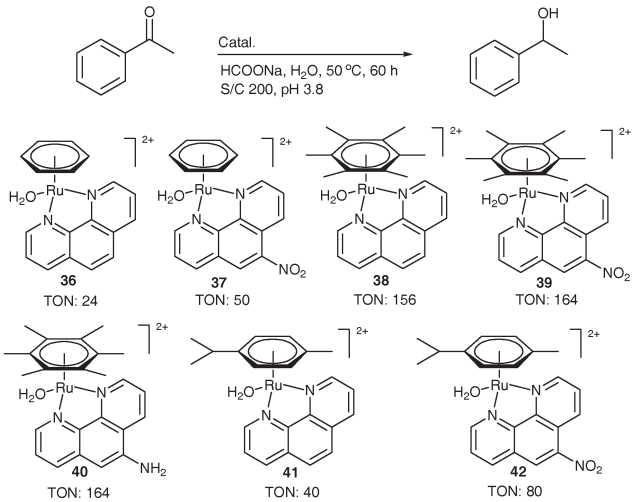
Entry	Substrate	Catalyst	Time/h	Yield (%)	TOF[d]
1	Cyclohexanone	**32** (pH 4.0)	4	99	98
2	2-Butanone		6	97	58
3	Pyruvic acid		4	99	96
4	4′-acebenzsulf ass[c]		3	98	103
5	acp		4	98	75
6	2-CF_3-acp		4	99	153
7	α-Tetralone		13	97	21
8	Cyclohexanone	**33** (pH 2.0)	1	99	376
9	acp		1	97	343
10	2-CF_3-acp		1	99	525
11	Butanone		4	99	150
12	Pyruvic acid		1	98	481
13	4′-SO_3Na-acp		1	99	419
14	1-Tetralone		3	98	203

[a] *Conditions*: 0.32 mmol ketones, 0.5% mmol **32**, 3 mL H_2O, 1.92 mol HCOONa, 70 °C, pH 4.0.[32f] [b] *Conditions*: 0.32 mmol substrates, 0.5% mmol **33**, 3 mL H_2O, 0.32 mol HCOOH, 70 °C, pH 2.0.[32e] [c] 4′-acebenzsulf ass = 4′-acetylbenzenesulfonic acid sodium salt. [d] Turnover frequency: mol mol^{-1} h^{-1}.

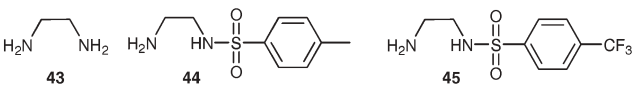
reactions.[6c,32] Both water-soluble and insoluble substrates were reduced, and in the favoured pH window, TOFs up to 525 mol mol^{-1} h^{-1} were obtained with the Ir(III) catalyst (**33**, Scheme 11) and 153 mol mol^{-1} h^{-1} with the Ru(II) catalyst (Table 2). In both cases, decreasing or increasing the pH by *ca.* 1 unit led to much reduced reaction rates. The different Lewis acidity of the Ir-catalysts (**33** < **34** < **35**, Scheme 11) resulted in the favourite pH window for TH being different (also see section 4.1).[32h] At around the same time, a water-soluble molybdocene monohydride, [$Cp_2Mo(H)OTf$], was found to catalyze the TH of ketones and aldehydes in water, again with pH-dependent characteristics. Acetone could be converted into isopropanol in about 8 h at 40 °C in water, and the reduction of benzaldehyde under the same conditions was instantaneous.[33]

More recently, Suss-Fink and co-workers reported a series of water-soluble ruthenium-arene complexes containing chelating 1,10-phenanthroline ligands (**36–42**, Scheme 12).[34a] These complexes were found to catalyze TH of ketones in aqueous solution using formic acid as hydrogen source; the hexamethylbenzene derivatives (**38–40**, Scheme 12) displayed higher activity. For instance, TONs up to 164 were obtained in the reduction of acp as shown in Scheme 12.[34a] Substitution at the 5-position of phenanthroline ligand increased the activity of the hexamethylbenzene complexes slightly (**39**, **40** *vs.* **38**) but doubled the performance of the benzene and cymene variants (**37** *vs.* **36** and **42** *vs.* **41**). The activity of **39** and **40** was about the same despite the different electronic effects of the 5-substituent. On the other hand, when the water-soluble *m*TPPMS was used instead of phenanthroline, similar half-sandwich Ru(II) complexes displayed much reduced activity on going from IPA to water.[34b]

The half-sandwich catalysts above are unlikely to enable metal–ligand bifunctional catalysis. This explains, to some degree, why the reduction rates are generally low. Very recently, we demonstrated that diamine ligands, having a $-NH_2$ functionality and hence capable of activating a carbonyl substrate, exerted a remarkable accelerating effect on the



Scheme 12 TH of acp with Ru–1,10-phenanthroline complexes in water (anion = tetrafluoroborate).



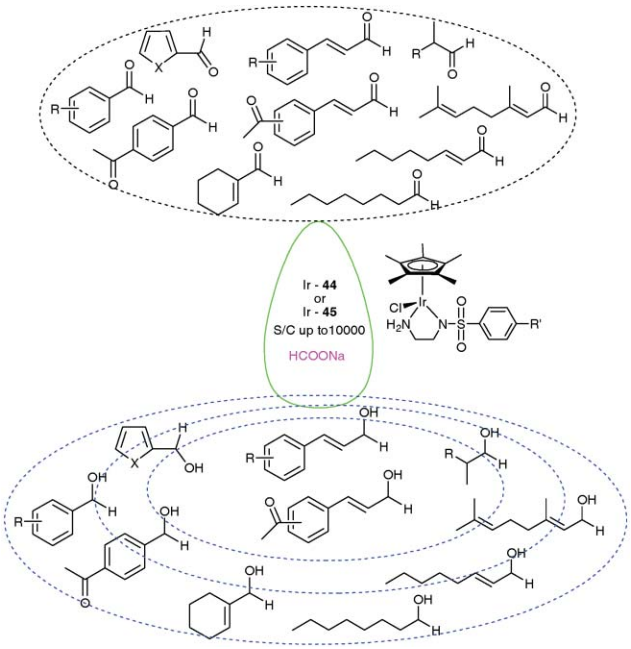
Scheme 13 Ligands for TH of aldehydes in water.

Ir(III)-catalyzed reduction of a wide range of aldehydes by HCOONa in neat H_2O.[4g] In particular, the catalyst Ir-**45** formed in situ from [Cp^*IrCl_2]$_2$ and **45** afforded TOFs of up to 1.3×10^5 h^{-1} in the TH of aldehydes (Scheme 13 and Table 3). In contrast, when carried out in IPA or F–T, a much slower reduction resulted (entries 10, 11, Table 3). The catalyst 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. For example, 4-acetylbenzaldehyde was reduced only to 4-acetylphenylethanol, and the reduction of 4-acetylcinnamaldehyde took place without affecting the ketone and

Table 3 Comparison of TH of benzaldehyde by HCOONa in water[a]

Entry	Catalyst[b]	Time/h	Conv. (%)	TOF[c]/mol mol^{-1} h^{-1}
1	Ru	25	32	2
2	Rh	25	35	3
3	Ir	25	70	20
4	Ru-**43**	1	1.2	12[d]
5	Rh-**43**	1	74	900
6	Ir-**43**	1	99	1800
7	Ru-**44**	2	99	1000
8	Rh-**44**	0.33	99	6000
9	Ir-**44**	0.08	>99	12000
10	Ir-**44**/IPA[e]	1	2.6	26[d]
11	Ir-**44**/F–T[f]	1	1.5	15[d]
12	Ir-**44**[g]	1.5	>99	20400
13	Ir-**44**[h]	0.9	>99	28800
14	Ir-**45**[h]	0.3	>99	42000
15	Ir-**45**[i]	1	98	132000

[a] *Conditions*: 65 °C, 5 equiv. HCOONa at S/C = 1000 in 10 mL water.[4g] [b] Ru = [$RuCl_2$(*p*-cymene)]$_2$, Rh = [Cp^*RhCl_2]$_2$, Ir = [Cp^*IrCl_2]$_2$. [c] Based on 5 min conversion. [d] Based on 1 h conversion. [e] IPA used as hydrogen source and solvent, 3.2% conversion in 8 h. [f] F–T used, 9% conversion in 8 h. [g] S/C = 1×10^4. [h] 80 °C, S/C = 1×10^4. [i] 80 °C, S/C = 5×10^4.



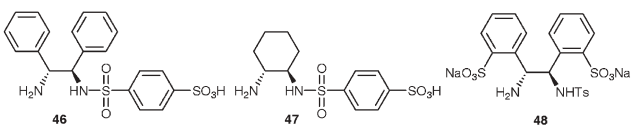
Scheme 14 TH of aldehydes with Ir-catalysts by HCOONa in water and air at 80 °C.

olefin double bonds. Furthermore, the reduction can be performed in the air, necessitating no inert gas protection throughout. Selected examples are presented in Scheme 14.

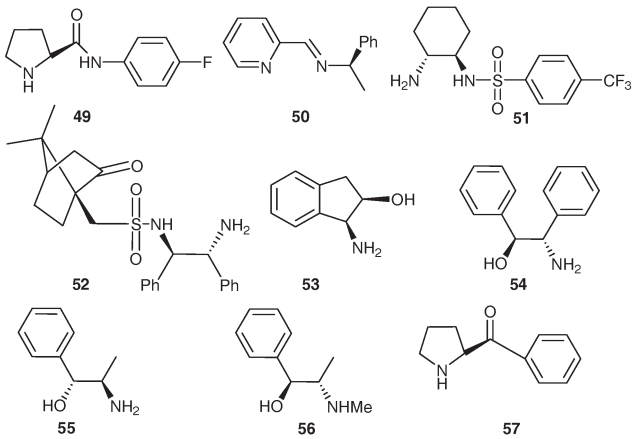
An interesting observation arising from the aldehyde reduction was that no reaction was detected with water-soluble substrates under the conditions employed. For example, the water-soluble 4-carboxybenzaldehyde or its sodium salt could not be reduced; but its ester analogue, methyl 4-formyl benzoate, was reduced in a short time of 40 min with Ir-**44** at 80 °C at a S/C ratio of 5000. This suggests that the catalysis takes place ''on water'' rather than in water in these biphasic reactions. However, the observation does not exclude the possibility of an in-water reaction that is inhibited by the high concentration of substrate.[31c,35a] Aqueous-phase TH of aldehydes has been less investigated in the past,[3c,6j,k,16c,35] partly due to concern over possible decarbonylation of the substrates and poisoning of the catalyst by the resulting CO.[35a] This on-water catalysis represents a most effective, chemoselective and simple means for aldehyde reduction.[3c,6j,k,16c,35]

3.2 ATH of ketones in aqueous media

As with most other catalytic reactions using water as solvent, the ATH of ketones started with searching for water-soluble catalysts. And as would be expected, this was achieved by synthesising ligands that dissolve in water (Scheme 15). However, recent studies by us and other groups have



Scheme 15 Water-soluble ligands for aqueous-phase ATH.



Scheme 16 Unmodified ligands for aqueous-phase ATH.

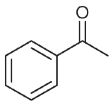
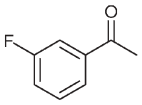
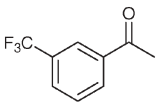
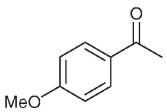
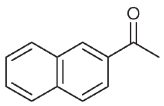
demonstrated that unmodified, water-insoluble ligands can deliver superior activity and enantioselectivity in ATH of ketones in water.[4a,c–g,5a,b,f,m,p–r,34a] Scheme 16 shows the water-insoluble ligands that are effective in enabling aqueous phase ATH. Ligands **1–4** and **18** in Scheme 3 have also proved effective.

Williams, Blacker and co-workers were the first to explore the ATH of ketones with water-soluble, Noyori–Ikariya type catalysts in 2001.[5n,o] The reaction was performed using catalyst containing a sulfonated TsDPEN or TsCYDN ligand (**46** and **47**, Scheme 15) in IPA with water (up to 51%) added. The catalyst was in situ generated by reacting the ligand with the chloro dimer, $[RuCl_2(p\text{-cymene})]_2$ or $[Cp^*MCl_2]_2$ (M = Rh, Ir). Table 4 give the results of ATH of ketones with these two ligands in IPA in the presence of water (15% v/v). While good to excellent ee's were achieved, the reaction took a relatively long time to complete under the chosen conditions. It was shown that the reaction went faster with increasing volume of water in the case of the Ir(III) catalysts. For example, the reduction of 3′-fluoroacetophenone with the Ir-**47** catalyst gave in 2.5 h a 82% conversion when the water content was 34%, and a 94% conversion when the water level was increased to 51%, and when the water was dropped to 15%, the same reaction afforded a 99% conversion in 26 h (entry 8, Table 4); the enantioselectivities remained virtually unchanged, however, at 93–94% ee.

At about the same time, Chung and co-workers communicated the ATH of aromatic ketones by formate in neat water, using a water-soluble catalyst formed by combining $[RuCl_2(p\text{-cymene})]_2$ with a (*S*)-proline amide ligand (**49**, Scheme 16).[5m,p] The reduction was carried out with or without a surfactant, with better results obtained in its presence. As is seen from Table 5, the reaction afforded good conversions with moderate to good ee's at 40 °C. These results represent the first examples of ATH in water with no organic co-solvents. Water-soluble Rh(III)–Schiff base complexes were later reported by Himeda *et al.* to catalyse ATH of ketones in aqueous formic acid/sodium formate solution (**50**, Scheme 16), affording moderate to good reaction rates and ee's.[5l]

Recently the group of Deng developed a novel, highly water-soluble ligand **48** (Scheme 15).[5k] ATH of ketones catalysed by Ru-**48** showed good activity and moderate to excellent

Table 4 ATH of ketones with water-soluble ligands in IPA in the presence of water[a]

Entry	Ketone	Catalyst	Time/h	Conv. (%)	Ee (%)
1		Ru-**46**	48	96	94
2		Ru-**47**	48	91	88
3		Rh-**46**	24	92	97
4		Ir-**47**	140	90	82
5		Rh-**47**	18	94	95
6		Ir-**47**	26	88	96
7		Ir-**46**	51	83	85
8		Ir-**47**	26	99	94
9		Ru-**46**	24	90	87
10		Ru-**47**	24	91	81
11		Rh-**46**	18	98	95
12		Rh-**47**	4	99	94
13		Ir-**46**	43	95	86
14		Ir-**47**	4	98	93
15		Ru-**46**	42	31	91
16		Ru-**47**	42	35	83
17		Rh-**46**	42	9	94
18		Rh-**47**	42	65	95
19		Ir-**46**	150	22	78
20		Ir-**47**	141	80	95
21		Ru-**46**	72	94	95
22		Ru-**47**	48	87	90
23		Rh-**46**	64	81	82
24		Rh-**47**	48	95	96
25		Ir-**46**	139	77	73
26		Ir-**47**	45	96	96

[a] *Conditions*: 2 mmol ketones, 0.01 mmol M-Ligand, 10 mL IPA, 2 mL water, 0.28 mmol K^{t}OBu in IPA (2.8 mL of 0.1 M solution), 22 °C.[5n,o]

enantioselectivity in the presence of a surfactant SDS (Table 6). Moreover, the catalyst, as it was designated for, can be recycled twice without loss of enantioselectivity.

A common feature of these investigations, like those in other areas of aqueous-phase catalysis, is to make the catalysts soluble in water, and to circumvent the problem of low solubility of most organic substrates in water, surfactants are usually called on. And this was also how we started our study into ATH in water. In a previous project, we developed a method for immobilization of chiral diamine ligands, which

Table 5 ATH of ketones with Ru-**49** by HCOONa in water[a]

Entry	Ketone	Time/h	Conv. (%)	Ee[c] (%)
1	acp[b]	18	98.3	68.6
2	2′-Me-acp	18	44	90.6
3	2′-Br-acp	15	67	89
4	2′-Cl-acp	18	69	88
5	3′-MeO-acp	17	75.4	58.8
6	4′-MeO-acp	16	95	60
7	2-Me-acp	18	62.9	53.7
8	2-Naphthone	18	85.3	89.4
9	4′,5′-di-MeO-acp	20	96.2	41.1[d]
10	3′,5′-di-MeO-acp	19	99	94.1[d]

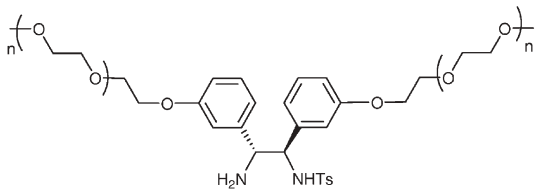
[a] *Conditions*: S/C = 400, Ru/**49** = 1, 5 equiv. HCOONa, 0.02 equiv. SDS, 40 °C.[5p] [b] acp = acetophenone. [c] *R* product. [d] The configuration was not determined.

Table 6 ATH of ketones with Ru-**48** by HCOONa in water[a]

Entry	Ketone	Catalyst	Time/h	Conv. (%)	Ee[c] (%)
1	acp[b]	Ru-**48**	24	>99	95
2		Rh-**48**	24	92	84
3		Ir-**48**	24	10	58
4	4′-Me-acp	Ru-**48**	24	>99	94
5	4′-F-acp		24	>99	92
6	2′-F-acp		24	>99	87
7	4′-NO_2-acp		24	88	88
				100[d]	88
8	2′-NO_2-acp		24	99	83
				100[d]	81
9	2-Me-acp		24	19	80
10	2-Acetonaphthone		24	13	92
				69[d]	94
11	1-Indanone		24	66	83
12	1-Tetralone		24	21	98
13	2-Acetylthiophene		24	72	95

[a] *Conditions*: S/C = 100, Ru/**48** = 1/1.1, 5 equiv. HCOONa, 0.04 equiv. SDS, 40 °C.[5k] [b] acp = acetophenone. [c] *R* product. [d] The reaction was carried out in a DCM/H_2O biphasic system under the same conditions.

could then be used as a platform to build supported chiral catalysts.[36] Of relevance here is that we demonstrated the water-soluble PEG-supported (PEG = polyethylene glycol 2000) **58** to be effective in the Ru(II)-catalyzed ATH in F–T; but unexpectedly the catalyst recycle *via* solvent extraction of the alcohol product was possible only when water was present as co-solvent. In its absence, much reduced conversions and ee's were observed, indicating catalyst decomposition.[36a] This finding prompted us to examine the behaviour of **58** and **1** in ketone reduction by HCOONa in neat water. While Ru-**58** was shown to be highly effective in neat water (*vide infra*), the Noyori–Ikariya catalyst Ru-**1** that contains a water-insoluble ligand gave surprising results. This was, to some degree, due to the fact that few reports were available on ATH in neat water at that time when the research started.[5k–p]



58
PTsDPEN

In our initial endeavor, acp was chosen as a model substrate to explore the feasibility of reduction with Ru-**1** in neat water. The precatalyst was generated by reacting **1** with $[RuCl_2(p\text{-cymene})]_2$ in water at 40 °C for 1 h. Much to our surprise, following the addition of 5 equiv. HCOONa and acp, the ketone was fully converted into (*R*)-1-phenylethanol in 95% ee in a 1 h reaction time. In comparison, the reaction run in the F–T afforded a conversion of less than 2% in 1 h, with full conversion requiring more than 10 h (Fig. 1).[4a] Several other structurally diverse ketone substrates were subsequently examined, showing again the reduction in water to be considerably faster, although the enantioselectivities observed with the F–T azeotrope were slightly higher. This initial finding has since been proved to be quite general, that is, water enables fast and enantioselective asymmetric reduction of

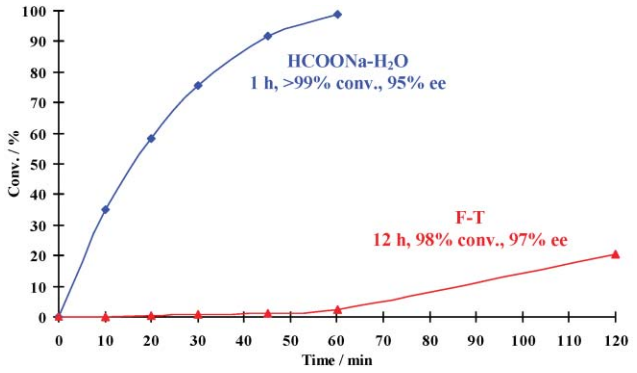
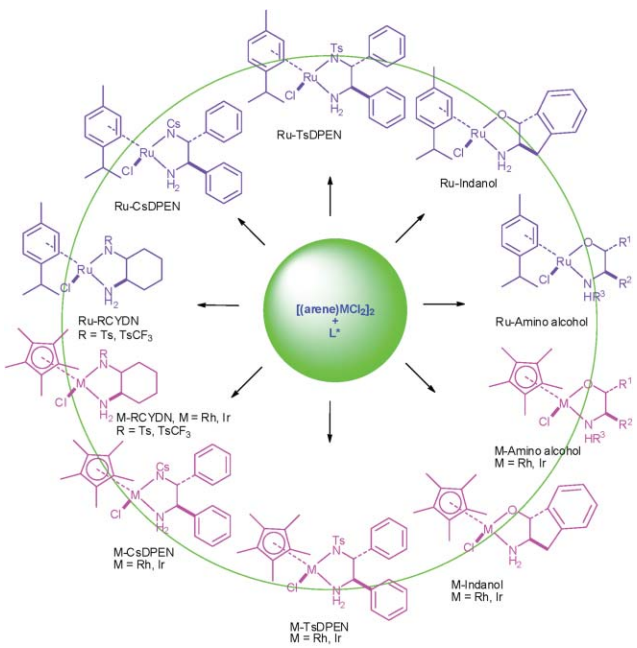


Fig. 1 Comparison of the ATH of acp catalysed by Ru–**1** in HCOONa–H_2O (■) and in the azeotropic F–T (▲). Reactions were carried out at 40 °C, using 1 mmol of acp at a S/C ratio of 100 in 2 mL of solvent.

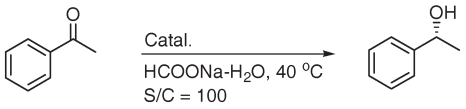
unfunctionalized ketones by HCOONa with a range of metal–diamine catalysts.

Scheme 17 shows the precatalysts that we have used and have proved to effectively catalyse ATH of aryl ketones in neat water. They are generally prepared in situ by reacting the unmodified ligand with one of the metal dimers aforementioned in water at the temperature for ATH reactions without adding a base. The structure of Ru-TsDPEN prepared under such conditions has been confirmed by X-ray diffraction to be the same as the one obtained in IPA.[18b] These precatalysts show varying solubilities in water, with those containing rhodium and iridium being more soluble than the ruthenium ones. Presumably their water solubility stems from chloride-water exchange, resulting in the formation of monoaqua cations (*vide infra*).[37] However, they show much higher solubility in ketones and alcohols, most of which that are covered in this article are insoluble in water. Hence, the



Scheme 17 Precatalysts for ATH of ketones by HCOONa in water.

Table 7 ATH of acp with unmodified metal catalysts by HCOONa in water[a]



Entry	Catalyst	Time/h	Conv. (%)	Ee (%)	Config.
1	Ru-**1**	1	99	95	*R*
2	Ru-**2**	2	99	85	*R*
3	Rh-**2**	0.25	>99	95	*R*
4	Rh-**2**[b]	0.25	99	96	*R*
5	Ir-**2**	3	99	93	*R*
6	Ru-**51**	2.5	99	81	*R*
7	Rh-**51**	0.25	99	94	*R*
8	Rh-**51**[b]	0.25	99	94	*R*
9	Ir-**51**	1.5	99	92	*R*
10	Ru-**52**	2	99	97	*R*
11	Rh-**52**	0.7	99	99	*R*
12	Rh-**52**[b]	0.7	99	99	*R*
13	Ir-**52**	0.7	99	97	*R*
14	Ru-**53**	12	84	71	*S*
15	Rh-**53**	20	92	55	*S*
16	Ir-**53**	5	>99	27	*S*
17	Ru-**54**	10	95	50	*R*
18	Rh-**54**	20	85	41	*R*
19	Ir-**54**	1.5	100	27	*R*
20	Ru-**55**	5	97	60	*S*
21	Rh-**55**	5	63	31	*S*
22	Ru-**56**	3.5	>99	73	*R*
23	Rh-**56**	22	77	68	*R*
24	Ir-**56**	2.5	100	54	*R*

[a] Reactions were carried out at 40 °C, using 1 mmol of acp, 5 equiv. HCOONa, S/C 100 and 2 mL water. [b] The reactions were carried out in the open air without degassing or inert gas protection throughout.

reaction is biphasic, with the catalysis probably taking place "on water" as aforementioned in the TH of aldehydes.

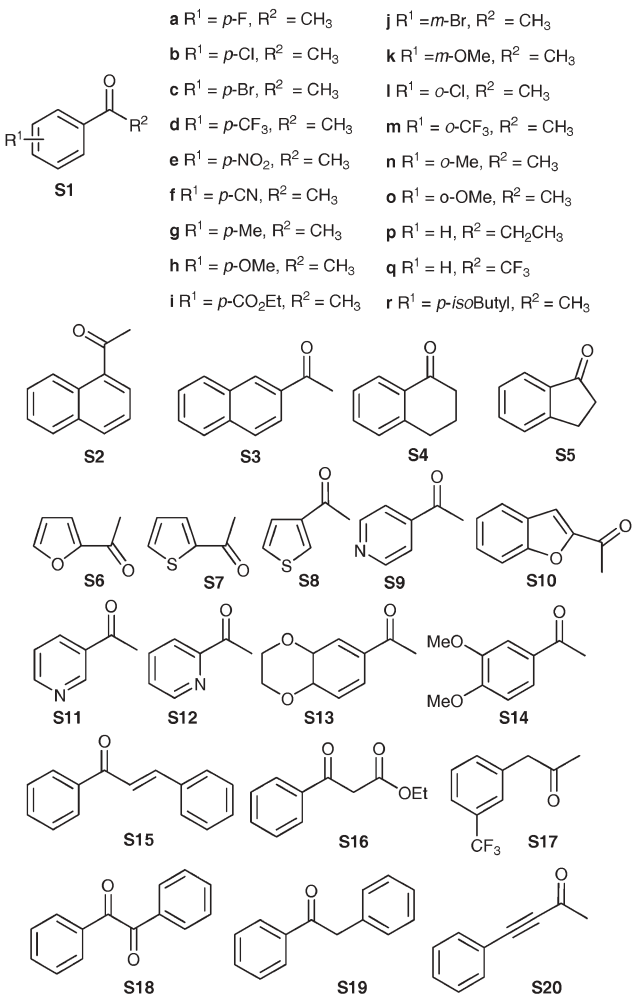
The performance of these catalysts in the ATH of the benchmark substrate acp is shown in Table 7. The monotoylsated diamines, TsDPEN (**1**, Scheme 3), TsCYDN (**2**, Scheme 3), and CF_3TsCYDN (**51**, Scheme 16) and the related CsDPEN (**52**, Scheme 16), which have been shown to be successful ligands for ATH of ketones in IPA or F–T, can all be applied to the ATH of acp by HCOONa in water, with full conversions and up to 99% ee's reached in short reaction times. In general, the reaction in water is faster than in organic solvents, but with similar enantioselectivities. Under the given conditions, the Rh(III) catalysts appear to outperform both Ru(II) and Ir(III) in water in terms of catalytic activity and enantioselectivity, and the camphor-substituted **52** led to the best enantioselectivity (entries 10–13, Table 7). It is noted that the reaction with the Rh–diamine catalysts can be carried out effectively in the open air without degassing and/or inert gas protection throughout, thus making the reduction easier to carry out than reactions catalysed by most organometallic complexes (entries 4, 8 and 12, Table 7).

The β-amino alcohol ligands are believed to be incompatible with formic acid as reductant in the past.[3c,h] Table 7 shows that the ligands **53–56** do catalyse the ATH of acp by HCOONa in water; however, the reduction rates and enantioselectivities were much lower than those obtained with the diamines (entries 14–24, Table 7). The metal complexes

containing (−)-ephedrine (**56**) yielded better results than others in terms of rates and/or ee's (entries 22–24, Table 7), and in general the iridium catalysts exhibited a higher activity (entries 16, 19 and 24, Table 7). Recently, (−)-ephedrine hydrochloride has been employed as ligand for ATH of ketones in water, affording results comparable to the Ru-**56** catalyst.[5f]

It has also been reported that Cr(II) coordinated with L-amino acid (alanine, valine, leucine, aspartic acid, glutamic acid, histidine) catalyses the ATH of ketones in aqueous DMF or formamide solution. The reaction gave good yields but only moderate ee's (up to 58%).[5j] More recently, Singaram and co-workers reported Ru(II)-catalysed ATH of ketones with terpene-based chiral β-amino alcohol ligands; the reduction could be smoothly carried out in IPA at room temperature but led to unsuccessful reduction on switching to aqueous HCOONa.[5t]

The aqueous-phase protocol has since been applied to a range of ketones. Selected examples are shown in Scheme 18. These substrates can be reduced efficiently with the M-diamines catalysts (M = Ru, Rh or Ir; diamines = **1**, **2**, **51** or **52**) by HCOONa in water. The unfunctionalized aromatic ketones (**S1a–S1r**, **S2–S5**, Scheme 18), heterocyclic ketones (**S6–S12**) and the functionalized or multi-substituted ketones (**S13–S20**) are all viable substrates with this reduction system. The reduction is easy to perform, affording the chiral alcohols with high ee's in a short reaction time for most of the substrates. We frequently used a S/C ratio of 100; however, S/C ratio of up to 10000 has been demonstrated to be feasible.[4c] As mentioned, the ketones are generally water-insoluble; but this does not appear to have negative bearings on the reaction rates.



Scheme 18 Substrates for ATH with unmodified metal catalysts in water.

Table 8 presents selected examples of reduction with formate affected by Ru-**1**, Rh-**2** and Ir-**52**. It is quite evident that all of these catalysts are viable for the ATH reactions in neat water and in general they give much better reaction rates in the aqueous system than in IPA or F–T. Of particular note is the Rh-diamine catalyst, which delivered high conversions for most of the ketones in a short reaction time and in most cases, the enantioselectivities were good to excellent, with ee's reaching up to 99% and TOFs close to 4000 h^{-1} in distilled tap water in the open air.[4d] The CsDPEN ligand **52** is both sterically and electronically different from **1** and **2**, and the carbonyl group introduces an additional functionality into the ligand, which could have some bearing on the reduction. The M-**52** catalyst was found to behave somewhat differently from the M-**1** and M-**2**, with Ir-**52** being the more active rather than rhodium and ruthenium at S/C = 1000.[4h] The protocol works particularly well for some heteroaryl ketones, as shown by the examples (entries 19–22, Table 8). Thus, for instance, the reduction of 2-acetylfuran with Rh-**2** were complete within 5 min, yielding (*R*)-1-(2-furyl)ethanol in 99% ee.

Suss-Fink and co-workers have recently synthesized a series of water-soluble arene–ruthenium complexes containing a *trans*-1,2-diaminocyclohexane ligand (**59–66**, Scheme 19).[5d] These complexes were examined in the ATH of ketones in aqueous media with various degree of success. The results on the reduction of acp are seen in Scheme 19. The complex **63**, an analogue of Ru-**2**, afforded the best performance, giving a good yield and a high ee of 93%. The study reveals again the importance of tosylation of the diamine and substitution on the arene ring to both catalyst activity and enantioselectivity in water.

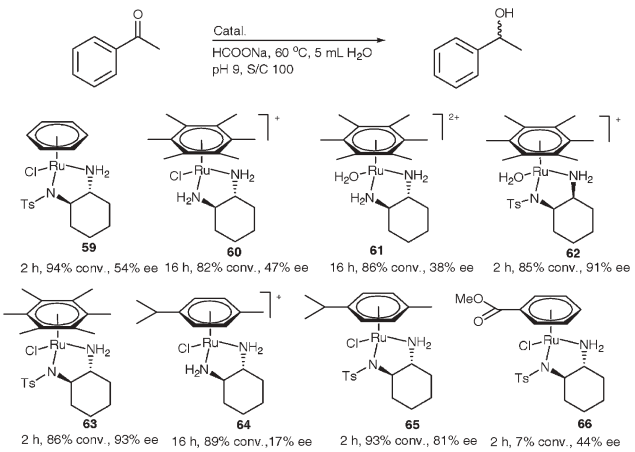
More recently, Gao *et al*. demonstrated that the PNNP ligand **18**, which is highly effective in ruthenium-catalysed ATH of ketones in IPA as shown by Gao, Ikariya and Noyori,[18f] could also be used for the aqueous-phase ATH reactions when combined with $[IrHCl_2(COD)]_2$.[5b,r] As shown in Table 9, the reduction of propiophenone was completed in 9 h with 88% ee at 60 °C at a S/C ratio of 100 in the presence of a phase transfer catalyst (entry 1, Table 9). Moreover, the same reaction could be run without inert gas protection and at a higher S/C ratio of 8000/1. In the latter case, the reaction afforded 80% isolated yield with 85% ee in 101 h. Interestingly, the reduction with the analogous Schiff base ligand led to a much reduced enantioselectivity (34% ee for propiophenone), indicating the importance of the N–H moiety to the reduction.

Very recently, the tethered complex **25** (Scheme 5) was shown by Wills and co-workers to be excellent catalyst for both organic (F–T) and aqueous phase reduction of ketones (Scheme 20).[5a] Thus, acp was reduced by HCOONa in water with **25** to give 100% conversion and 96% ee at 28 °C in 3 h,

Table 8 ATH of ketones with metal–diamine catalysts by HCOONa in water

		Ru-**1**[a]			Rh-**2**[a]			Ir-**52**[b]		
Entry	Ketone	Time/h	Conv. (%)	Ee (%)	Time/h	Conv. (%)	Ee (%)	Time/h	Conv. (%)	Ee (%)
1	**S1a**	1.5[c]	100	92	0.3	>99	94	3.1	99	96
2	**S1b**	2	>99	91	0.2	>99	94	2	99	96
3	**S1d**	2	99	94	0.2	>99	91	N/A	N/A	N/A
4	**S1e**	2[c]	>99	85	0.7	98	87	2	99	93
5	**S1f**	1.5[c]	99	89	0.4	98	90	2	99	94
6	**S1g**	2	98	90	0.5	>99	92	8.5	94	92
7	**S1h**	2	>99	95	0.5	99	93	22	94	97
8	**S1j**	N/A	N/A	N/A	0.25	>99	89	2	>99	93
9	**S1k**	2	98	94	0.5	97	93	3	>99	98
10	**S1l**	2	>99	89	0.3	>99	77	3	98	88
11	**S1m**	6	100	20	N/A	N/A	N/A	N/A	N/A	N/A
12	**S1n**	6	>99	80	1	98	80	29	84	93
13	**S1o**	2	96	72	1	98	79	21	99	85
14	**S1p**	2	>99	86	1	97	92	9.5	98	97
15	**S2**	6	98	87	N/A	N/A	N/A	N/A	N/A	N/A
16	**S3**	3	95	95	0.75	99	95	4	>99	97
17	**S4**	3	97	94	0.5	94	97	N/A	N/A	N/A
18	**S5**	2	93	95	0.3	98	95	N/A	N/A	N/A
19	**S6**	N/A	N/A	N/A	0.08	99	99	N/A	N/A	N/A
20	**S7**	N/A	N/A	N/A	0.25	98	94	N/A	N/A	N/A
21	**S8**	N/A	N/A	N/A	0.75	99	99	N/A	N/A	N/A
22	**S10**	N/A	N/A	N/A	0.17	99	96	0.75	>99	94

[a] Reactions were carried out at 40 °C, using 1 mmol of ketones, 5 equiv. HCOONa, at a S/C ratio of 100 in 2 mL of water. [b] *Conditions*: 40 °C, 10 mmol of ketones, 5 equiv. HCOONa, at S/C ratio of 1000 in 10 mL water. [c] Using HCOOH–NEt_3 in H_2O with initial pH 5–8.



Scheme 19 ATH of ketones with water-soluble Ru complexes in water.

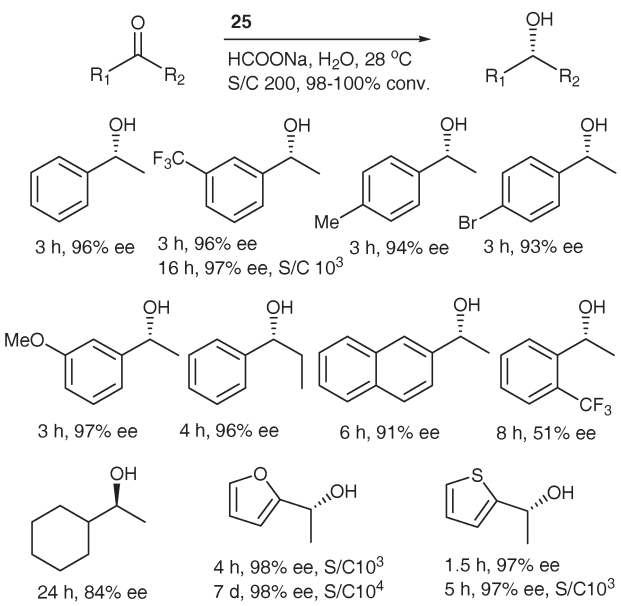
Table 9 ATH of ketones with Ru-**18** by HCOONa in water[a]

Entry	Ketone	Ligand	Time/h	Yield (%)	Ee (%)	Conf.
1	propiophen[b]	(*R*,*R*)	9	99	88	*R*
2	acp	(*R*,*R*)	47	99	62	*S*
3	1-Tetralone	(*S*,*S*)	33	99	99	*R*
4	1-Tetralone	(*R*,*R*)	30	95	99	*S*
5	2-di-Me-acp	(*S*,*S*)	50	99	96	*R*
6	2-di-Me-acp	(*R*,*R*)	39	85	92	*S*
7	2-*n*-Pr-acp	(*R*,*R*)	39	86	88	*R*
8	2-*n*-Bu-acp	(*R*,*R*)	36	99	82	*R*
9	3′-Cl-acp	(*S*,*S*)	47	98	55	*R*
10	4′-Cl-acp	(*R*,*R*)	34	48	76	*S*
11	2′-Me-acp	(*S*,*S*)	39	95	82	*S*
12	3′-Me-acp	(*R*,*R*)	39	98	64	*R*

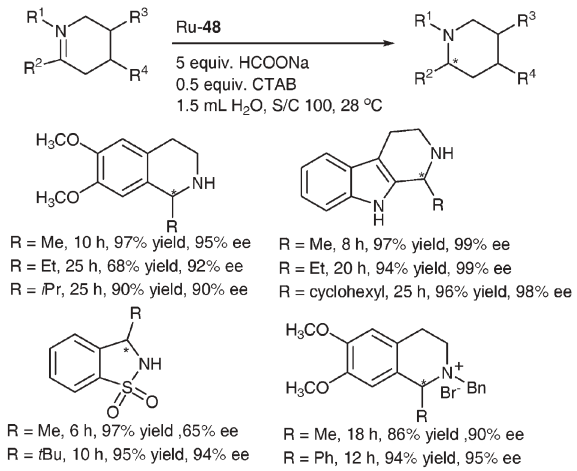
[a] *Conditions*: 5 equiv. HCOONa, 2 mL H_2O, S/C = 100, 5 mol% PPNCl, 60 °C.[5b] [b] propiophen = propiophenone.

and in the case of 2-acetylfuran, the catalyst loading could be reduced to 0.01 mol% with an ee of 98% obtained. Remarkably, the catalyst even allowed for the reduction of aliphatic ketones in water, albeit with slightly lower ee's.

The boundary of the aqueous-phase ATH has recently been extended. Using the water-soluble ligand **48**, Deng and co-workers showed that imines and iminiums could be smoothly reduced by HCOONa with Ru(II) catalysis in water in the presence of CTAB as a phase transfer catalyst (Scheme 21).[5s] The reduction afforded moderate to excellent yields and ee's for both imines and iminiums. However, the catalyst failed to



Scheme 20 ATH of ketones with Ru-**25** by HCOONa in water.



Scheme 21 ATH of imines and inmiums with Ru-**48** in water.

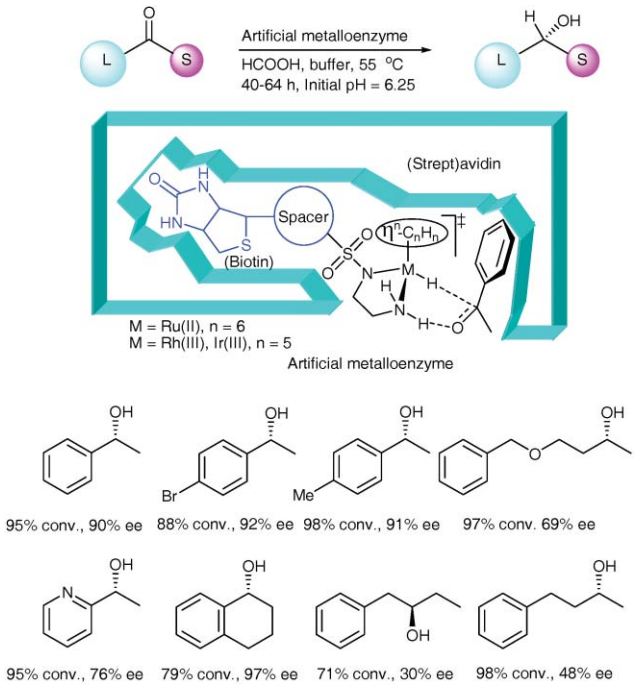
reduce acylic imines, which decomposed under the aqueous conditions.

3.3 ATH of ketones with biomimetic catalysts in water

Unlike the organometallic ATH analogues, ATH of ketones in aqueous media with enzymes and micro-organisms is well documented.[38] A range of aromatic as well as aliphatic ketones can be reduced stereoselectively using alcohol dehydrogenases, microorganisms and whole microbial cells.[38a,39] However, baker's yeast is by far the most widely used microorganism for the ATH of ketones.[38a]

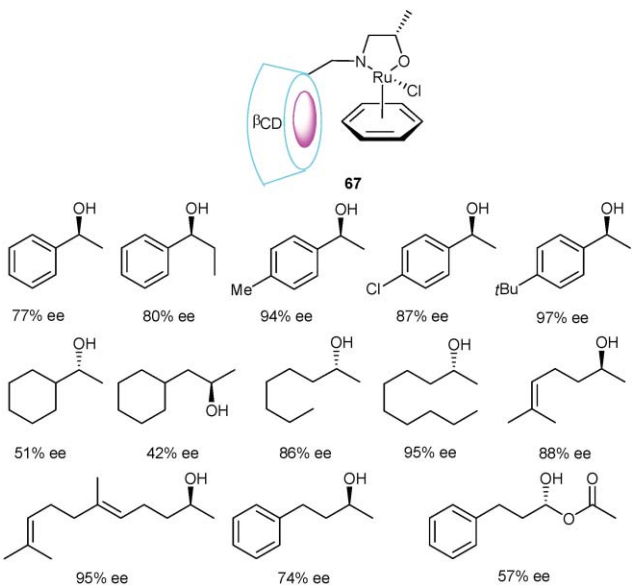
Aiming to broaden the substrate specificity of natural enzymes and discover new enzymes for novel transformations, artificial metalloenzymes, a combination of metal complexes with biocatalysts, has been explored in enantioselective catalysis since the 1970s.[40,41] The opportunity of combined chemogenetic optimization of artificial metalloenzymes, *i.e.* chemically improving the metal centres and genetically modifying the host protein, offers a new strategy to discover more efficient metalloenzymes.[42a] Ward and co-workers have recently demonstrated that incorporation of a biotinylated achiral 1,2-diamine catalyst, an analogue of Ru-**44** and Rh-**44**, into a host protein, avidin or streptavidin, affords a versatile artificial metalloenzyme capable of ATH of ketones in buffered aqueous solution (Scheme 22).[5h,42] The reduction of aromatic ketones went smoothly under optimized conditions, furnishing enantioselectivity of up to 97% ee. Selected chiral products are showed in Scheme 22. To identify the best metalloenzyme with matched active metal site and chiral protein pocket, the metal complex was modified by varying the arene ligand and the spacer group while the host protein was genetically optimized by point mutations. The results suggested that the catalyst activity of these artificial metalloenzyme catalysts is dependent on the localization of the biotinylated metal catalyst, with the properties of the η^6-bound arenes playing a critical role in the enantioselection.

A different approach was adopted by Woggon and co-workers, who reported a Ru(II) catalyst with the amino alcohol ligand attached to β-cyclodextrin (**67**, Scheme 23).[43] ATH of ketones in water can be carried out with the catalyst in a



Scheme 22 ATH of ketones with artificial metalloenzyme in water.

water–DMF mixture, with both aromatic and aliphatic ketones being reducible. Significantly, the later class of substrates could be reduced with ee's up to 95%, a value superior to those obtained with most other metal catalysts but still inferior to those by enzymes.[44] Having a S/C of 10, the TONs were low, however. The excellent enantiodiscrimination against the aliphatic ketones results presumably from the hydrophobic cavity of β-cyclodextrin, in which the aliphatic chain is likely to reside and is thus spatially fixed. To some degree, this mimics an enzymatic reaction in water, with



Scheme 23 ATH of ketones with **67** in water under the conditions: room temperature, 24 h, H_2O–DMF (3 : 1), S/C = 10, giving 50–100% yield.

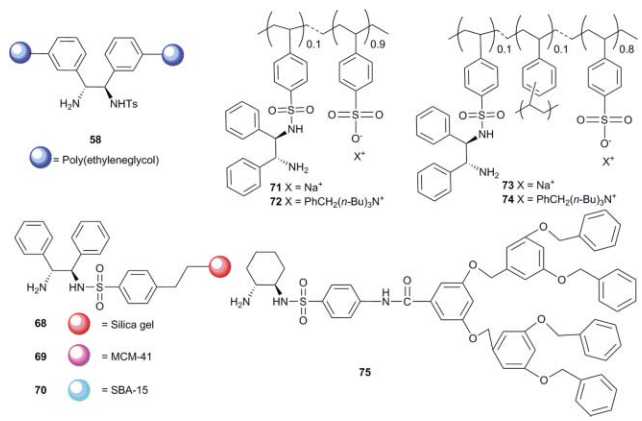
hydrophobic substrates usually reacting at a hydrophobic, active site.

3.4 Water-facilitated catalyst separation and recycle

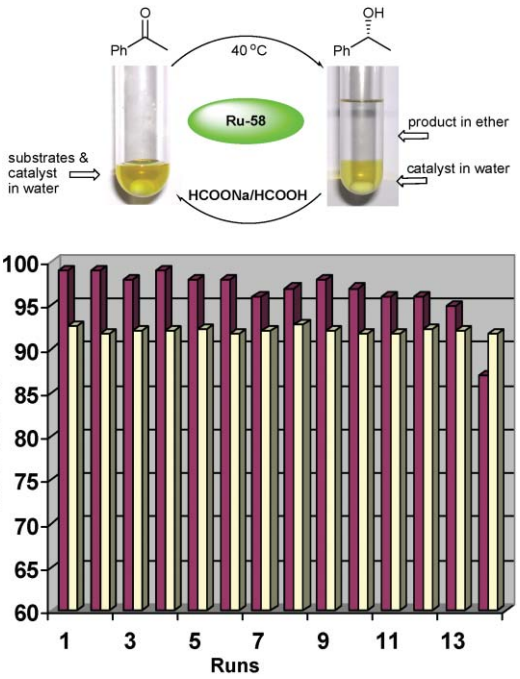
As with most other homogeneous catalysts, most of the chiral M-diamine catalysts discussed are expensive and cannot be easily separated from products. Being simple to operate, economic and green, water as solvent provides one of the most appealing solutions to this problem; catalyst/product separation can be achieved by simple phase separation. This requires the catalysts to be preferentially soluble in water but not in organic media. The arene–metal–diamine catalysts aforementioned are often (partially) soluble in water but insoluble in nonpolar solvents. In this case, the product can be extracted with a solvent such as diethyl ether without recourse to purpose-built water-soluble catalysts, and this has been demonstrated by several groups including ours.[4,5m,p,q] A good example is the reduction catalysed by Ru-**49** (Scheme 16) mentioned earlier, which could be reused up to 6 times without compromising ee's.[5p] Very recently, a similar catalyst, Ru-**57**, was also shown to be effective in the ATH of aromatic ketones and recyclable in water.[5q]

For more practical and easier catalyst/product separation, however, highly water-soluble ligands or those that are supported on solid surfaces are desirable. Examples of such water-soluble ligands are seen in **46–48** (Scheme 15). As discussed in Section 3.2, Ru-**48** has been shown to be an efficient catalyst for ATH of ketones and imines in water. Deng and co-workers further demonstrated that the catalyst could be readily separated from the alcohol product by decantation of the diluted product solution.

Scheme 24 presents examples of supported ligands that have been studied in aqueous ATH. Ligand **58** provides an example of soluble polymer supported catalyst for ATH in water; the hydrophilic polyethylene glycol chain renders the catalyst soluble in water. As with the non-supported Ru-**1**, Ru-**58** is also highly effective for the ATH in water towards a wide range of aromatic ketones, with results comparable to those obtained with Ru-**1**. To demonstrate its recyclability, we carried out the reduction of acp by HCOONa with Ru-**58** in water, with the product extracted with diethyl ether (Scheme 25).[4b] An ICP analysis showed that 0.4 mol% of



Scheme 24 Immobilized ligands for ATH in water.



Scheme 25 Plot of conversion (red bars) and ee (yellow bars) *vs.* number of runs in the ATH of acp with Ru-**58** in water.

ruthenium leached into the organic phase. The recycle was performed by extracting the alcohol with ether, followed by adding a new portion of acp along with 1 equiv. HCOOH. Remarkably, the Peg-immobilized catalyst could be reused 14 times with no loss in enantioselectivity, demonstrating its excellent recyclability and lifetime under aqueous conditions. As indicated earlier, when carried out in the F–T without water, catalyst recycle was possible only for two runs without the rates and ee's being eroded.[36a]

The sulfonated polystyrene-supported diamines **71–74** have been applied to ATH in the presence of $[RuCl_2(p\text{-cymene})]_2$ or $[Cp^*RhCl_2]_2$ (Scheme 24).[5c] Table 10 shows the ATH of ketones with Ru-**72** by HCOONa in water, yielding excellent enantioselectivities. Interestingly, ligands **71** and **73** gave quite lower conversions and ee's, showing the importance of microenvironment within the polymer network to stereoselection. The cross-linked polymer **74** has also proved to be efficient in water; the catalyst can be recycled five times, affording almost the same ee values.

Tu, Deng and co-workers have developed the solid-supported ligands **68–70** (Scheme 24). When applied to Ru(II)-catalysed ATH of ketones, these ligands were effective in both organic and aqueous media, with **68** being more

Table 10 ATH of ketones with Ru-**72** by HCOONa in water[a]

Entry	Ketone	Time/h	Conv. (%)	Ee[b] (%)
1	acp	3	100	98
2	**S1b**	2	90	99
3	**S1p**	2	91	96
4	**S2**	13	97	97

[a] *Conditions*: 1 mmol ketone, 5 equiv. HCOONa, 2 mL water, S/C 100, 40 °C.[5c] [b] *R* products.

Table 11 ATH of ketones with Ru-**68** by HCOONa in water[a]

Entry	Ketone	Run	Time/h	Conv. (%)	Ee[b] (%)
1	acp	1–7	2–60	>99–60	96
2	2′-F-acp	1–8	2–58	>99–91	90
3	2′-Br-acp	1–10	2.5–11	>99–98	92
4	**S1j**	1–11	5–93	>99–98	93
5	**S1k**	1–6	5–58	>99–85	95
6	**S1l**	1–7	2–58	>99–98	92

[a] *Conditions*: 40 °C, S/C = 100, 5.0 equiv. HCOONa, 4 mol% TBAB.[5g] [b] *R* products.

Table 12 ATH of ketones with Rh-**75** by HCOONa in water[a]

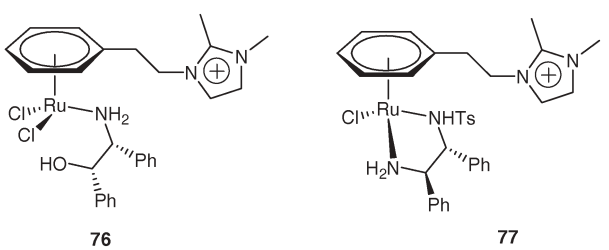
Entry	Ketone	Run	Time/h	Conv. (%)	Ee[b] (%)
1	acp	1–6	0.67–1.5	>99–85	96–94
2	**S1b**	1	0.5	99	93
3	**S1c**	1	0.8	97	92
4	**S1h**	1	1	95	94
5	**S1n**	1	1.5	>99	81
6	**S2**	1	0.8	99	97
7	**S7**	1	0.5	98	96
8	**S9**	1	9	69[c]	57
9	**S12**	1	5	70[c]	91
10	2-acetoxy-acp	1	4	97[c]	72
11	Benzylidenacetone	1	1.3	94[c]	52

[a] *Conditions*: 0.4 mmol ketone, 2.4 mmol HCOONa, 1 mL H_2O, S/C 100, 40 °C.[45a] [b] *R* products. [c] Isolated yield.

efficient than the others. Table 11 gives selected examples of ATH of ketone by HCOONa catalysed with Ru-**68** in water. Although taking a long time to complete in recycle runs even in the presence of a surfactant, the catalyst displayed excellent recyclability in terms of enantioselectivity – up to 11 recycles without loss of ee's.[5g,i]

The same group also reported the dendritic ligands **75** (Scheme 24).[45] In the ATH of ketones by HCOONa in water, the first generation **75** coordinated with rhodium could be reused up to six times without enantioselectivity being eroded (Table 12).[45a] The catalyst can be separated and recycled by simple phase separation. Remarkably, the S/C ratio could be increased to as high as 10000/1.

Apart from water, ionic liquids have been explored to immobilise ATH catalysts and to act as solvents for ATH reactions.[46] Examples are seen in the imidazolium-tagged complexes **76** and **77** developed by Dyson and co-workers (Scheme 26).[46a] The reduction of acp with **76** or **77** was carried out in a F–T and ionic liquid biphasic system and the catalyst could be reused several times by phase separation. The reduction afforded excellent ee's but moderate rates.



Scheme 26 Imidazolium-tagged catalysts for ATH of ketones.

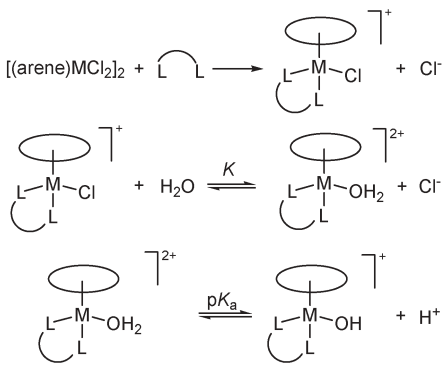
4 Mechanistic aspects of ATH in water

4.1 Precatalysts and intermediates in water

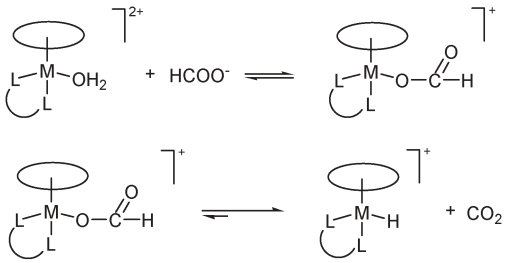
Systematic studies into the mechanisms of aqueous-phase ATH reactions are not yet available. In the last sections, we attempt to give a brief summary of the studies that are pertinent to ATH in water. As is clear from the survey, the most effective catalysts are those derived from Ru(II), Rh(III) and Ir(III). The precatalysts can be easily generated by reacting a chloro dimer with a ligand as aforementioned (Scheme 27). The resulting half-sandwich chloro complexes readily undergo I_a type of aquation to give the mono aqua dications. In several instances, the aquation and anation equilibrium constants have been determined, which generally favour the formation of anation products.[37] In the case of [(arene)Ru(en)Cl][PF_6], the equilibrium constants are in the order of $K \sim 0.01$ M and do not vary significantly with the arene ligand.[37a] The achiral monoaqua complexes have been isolated and structurally characterised in a number of instances.[5d,32e,37a] As with the chloro parents, these aqua complexes exhibit varying solubilities in water. For example, [(η^6-C_6Me_6)Ru(bpy)(H_2O)][SO_4] has a solubility of 136 mg mL^{-1} (pH 3, 25 °C).[32f]

An important reaction of the aqua complexes in water is deprotonation to form hydroxo species, which may stop catalysis from occurring by inhibiting the coordination of formate (Scheme 27). The pK_a values of these half-sandwich complexes are *ca.* 7–8 and interestingly, they do not appear to vary significantly with the central metal atom and its ligands.[37a,b] However, the closely related triaqua complexes [(arene)M(H_2O)$_3$]$^{2+}$ are much more acidic, showing the importance of L^L in attenuating the electrophilic properties of M.

Of direct relevance to TH/ATH in water is the anation of the aqua complex with formate. The resulting formato complexes undergo decarboxylation to give the hydride, the very species that reduces carbonyls to alcohols (Scheme 28). In the case of [(η^6-C_6Me_6)Ru(bpy)(H_2O)]$^{2+}$, Ogo and Watanabe have structurally characterised both the formato and hydrido complexes.[32f] Their work also revealed that the formation of these species is solution-pH dependent, and there appears to be a pH window in which the yields are optimal.[32e,f] This dependence can be traced to: (1) the concentration of free formate. The pK_a of HCOOH is 3.6, below which $HCOO^-$ exists primarily as HCOOH, thus reducing the concentration of formate anions.



Scheme 27 Precatalysts and the related equilibrium in water.



Scheme 28 Formation of formato and hydrido complexes with formate in water.

(2) The concentration of the aqua complexes. The pK_a of the aqua complexes is 7–8, above which hydroxo species is formed, inhibiting coordination of formate. (3) The protonation of the hydride at low pH to give H_2. However, the hydride can be stable in a wide pH window. Take $[Cp^*Ir(bpy)H]^+$ as an example, it was formed in pH 1–9, and protonation to give H_2 was observed only at pH < 1.[32e] The hydride may undergo H/D exchange with D_2O, *via*, for example, a M-(HD) intermediate.[32e,47a] Also of note is that the decarboxylation process is reversible as shown by Ikariya and others.[48] In fact, Ogo and co-workers reported that $[(\eta^6\text{-}C_6Me_6)Ru(bpy)H]^+$ reacted with CO_2 in water to give the corresponding formato complex, from which $HCOO^-$ was formed.[48b]

4.2 Effect of pH on ATH in water

Bearing in mind the pH dependence of the concentration of formate and formato and hydrido complexes, it is hardly surprising that the reaction rates in aqueous TH/ATH reactions vary with solution pH values. Extensive studies have been carried out by Watanabe and Ogo in the achiral reduction of carbonyl compounds by formate with $[(\eta^6\text{-}C_6Me_6)Ru(bpy)(H_2O)]^{2+}$, $[Cp^*Ir(H_2O)_3]^{2+}$ or $[Cp^*Ir(bpy)(H_2O)]^{2+}$ in water, revealing strong dependence of reduction rates on pH.[32e–g] The results have been discussed in section 3.1. Earlier, Joó and recently, Frost showed the effect of pH on asymmetric reduction with H_2.[6c,47b]

Our studies of ATH in water revealed a similar picture.[4c] Following on from the finding that aromatic ketones can be reduced more rapidly by HCOONa in water than in F–T with the Ru-**1** catalyst, we investigated the ATH by the F–T azeotrope in water and found the reduction to be much slower than that in aqueous HCOONa. The most discernable difference between the two systems was the initial solution pH. The azeotrope–water system displayed a pH of 3 at the beginning of the reaction; but the aqueous HCOONa solution was far more basic, having a pH of 7. To determine if the reaction was affected by pH, we measured the initial rates of the reduction of acp in water at various initial solution pH values by adjusting the $HCOOH/NEt_3$ molar ratios.

The initial reaction rates varied indeed with solution pH, as revealed by Fig. 2. Remarkably, an increase of 1 pH unit at *ca.* pH 3.9 resulted in an increase in rate of *ca.* 20 times. Further studies of the reduction starting at pH 2.3 revealed that the reaction was accompanied with a long induction period of *ca.* 9 h. Little reduction occurred during this time; but decomposition of HCOOH into CO_2 and H_2 by the catalyst was

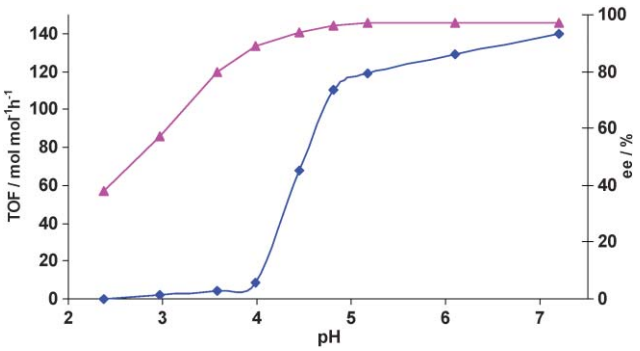


Fig. 2 Plot of initial TOF (■) and ee (▲) *vs.* initial pH values in the ATH of acp with Ru-**1** in water under the conditions: 1 mmol acp, 1 mL water, 40 °C, and S/C 100.

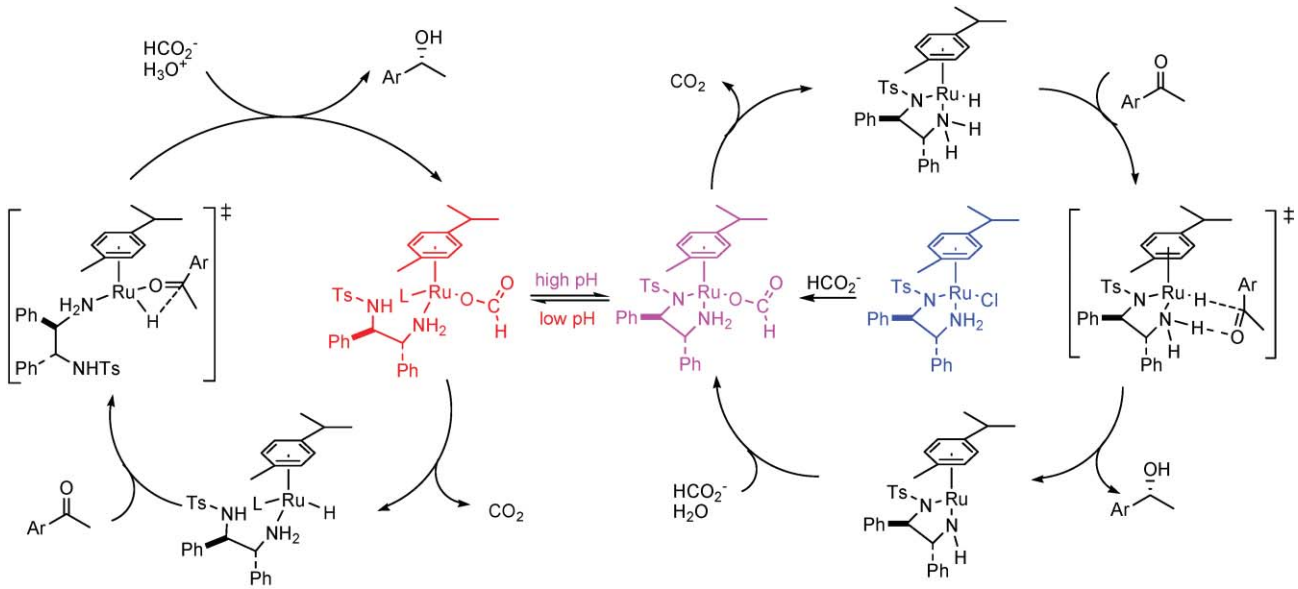
observed and as a consequence, the pH increased with time. Still further, it was found that the enantioselectivity varied with pH, rising quickly from <60% ee at *ca.* pH 2.3 to >90% ee at *ca.* pH 4 (Fig. 2).

These studies suggest that the aqueous-phase ATH proceeds *via* two competing pathways, with one primarily operating under basic conditions, which affords fast rates and high enantioselectivities, whilst the other becoming dominant under acidic conditions, which gives lower rates as well as lower ee's. We proposed that the catalysis operates *via* two catalytic cycles as illustrated in Scheme 29. The one under basic conditions follows Noyori's concerted mechanism[3i,j] whilst the other at low pH starts with protonation of the coordinated TsDPEN **1**. The low rates and low ee's in the case of the latter can thus be interpreted as resulting from the conventional, stepwise reduction of ketones and/or from a similar concerted mechanism with a less-well organized transition state. Additional support for the proposed protonation of ligand arose from the observation that introduction of 1 equiv. (*S*,*S*)-TsDPEN into the catalytic solution containing Ru-(*R*,*R*)-TsDPEN at low pH resulted in almost a racemic alcohol product in the reduction of acp at high pH, due to ligand dissociation and the consequent formation of a mixture of equimolar Ru-(*R*,*R*)-TsDPEN and Ru-(*S*,*S*)-TsDPEN catalysts (Scheme 30).[4c]

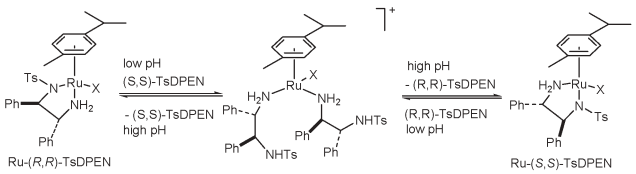
With this finding in hand, faster ketone reduction with $HCOOH–NEt_3$ can be readily implemented when the $HCOOH/NEt_3$ ratio is lowered. Indeed, we showed that a variety of aryl ketones can be reduced with excellent ee's with S/C ratios of up to 10000 in an aqueous solution of HCOOH and NEt_3, in which the amine acted as a pH modulator ensuring that the solution pH was maintained in between 5 to 8 during the reduction.[4c] Faster rates were also observed when the reduction was conducted in a $HCOOH\text{-}NEt_3$ mixture without water but with a reduced $HCOOH/NEt_3$ ratio.[49] More recently, the dependence of ATH reactions on pH in water was also revealed from the work of other groups.[5d,e,t,34a]

5 Conclusions and perspectives

We hope that we have provided enough evidence in this article to show that ATH in water affords an effective, green alternative for fast and enantioselective reduction of prochiral ketones. Of practical significance is that the reduction can be



Scheme 29 Proposed catalytic cycles for the reduction of ketones under acidic and basic conditions, where L may be a water molecule.



Scheme 30 Formation of an equimolar mixture of Ru-(*R*,*R*)/(*S*,*S*)-TsDPEN at low pH.

carried out with unmodified homogeneous metal complexes, tailor-made water-soluble catalysts, supported catalysts, and biomimetic analogues with no organic solvents. The hydrogen source, formate, is cheap and easily available, generating no hazardous waste in the reduction. Apart from these merits, the reduction is easy to conduct, requiring mild reaction conditions and often no inert gas protection. Water plays an important role in the process; it provides a soluble form of formate and enables easy catalyst/product separation, and more significantly, it allows the reduction to be controlled by pH and it appears to stabilise the active catalysts. In many cases, however, the reduction takes place "on water" rather than in water, particularly when carried out with catalysts containing unmodified ligands.

In terms of catalyst activity, productivity and enantioselectivity, there is still space to improve. Although fast and productive catalysts have been developed for ATH reactions, we note that none are yet comparable in TON with the best Noyori hydrogenation catalysts and, as aforementioned, there are reactions that proceed less efficiently on going from organic media to water.[5t,34b] However, ATH has already enabled reactions that are difficult with hydrogenation catalysts, *e.g.* the reduction of tetralone, α-heteroatom substituted aryl ketones and α,β-acetylenic ketones. Concerning the scope of substrates, non-aromatic and aliphatic ketones remain challenging in terms of enantioselectivity.

Unlike hydrogenation and ATH in organic media, little mechanistic measurements and theoretic studies into the ATH in water have been available. This information will be indispensable for the development of more efficient and greener catalysts for aqueous ATH/TH reactions. Of particular interest is to delineate the role of water in the catalytic cycle. Gratifyingly, recent theoretical calculations have shed light on closely related hydrogenation reactions, where the important role of water is clearly indicated.[50]

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