

# Asymmetric Transfer Hydrogenation in Water with Platinum Group Metal Catalysts

Rapid reactions and high enantioselectivities achieved for carbonyl bond reduction

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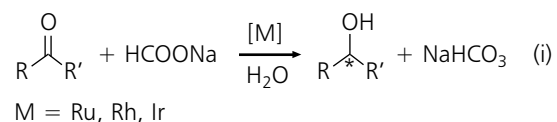
*Asymmetric transfer hydrogenation (ATH) is the reduction of prochiral compounds with a hydrogen donor other than hydrogen gas in the presence of a chiral catalyst. The asymmetric reduction of a wide variety of ketone and aldehyde substrates has been carried out in water using catalysts based on complexes of ruthenium(II), rhodium(III) and iridium(III), affording fast reaction rates and good enantioselectivities without the use of organic solvents and with easy separation of catalyst and product. For ATH of ketones, the Rh(III) complexes appear to perform better than the Ru(II) and Ir(III) complexes in terms of activity, enantioselectivity and substrate scope. However, their performance varies with the choice of ligands, and simple Ir(III)-diamine complexes were found to be excellent catalysts for the reduction of aldehydes.*

## 1. Introduction

The technique of asymmetric transfer hydrogenation (ATH) has emerged as a powerful and practical tool for reduction reactions in both academia and industry, due to its operational simplicity, high reaction rate and enantioselectivity and broad substrate scope (1–24). The subject has been under investigation for more than three decades (25) but until the 1990s enantioselectivities were poor. In 1995, Noyori, Ikariya, Hashiguchi and coworkers published a paper reporting a TsDPEN-coordinated (TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine) Ru(II) complex (Ru-TsDPEN) to be an excellent precatalyst for the asymmetric reduction of aromatic ketones, affording an enantiomeric excess (ee) up to 99% (26, 27). This significant breakthrough has inspired intense research into the chemistry of this class of reactions. As a result, a variety of related metal catalysts have been developed and have since been applied to the asymmetric reduction of various ketones and imines

from academic laboratory research to commercial scale applications (1–24, 28–63).

Among all the catalysts reported so far, those that are based on the platinum group metals (pgms) Ru, Rh and Ir have been the most successful. While other metal catalysts and organocatalysts have been reported, their ATH rates and/or enantioselectivities are generally inferior. Most often, the metal-catalysed ATH reactions are performed in 2-propanol or the azeotropic mixture of formic acid (HCOOH) and triethylamine (NEt<sub>3</sub>) (HCOOH:NEt<sub>3</sub> in the molar ratio 2.5:1), which act as both the solvent and reductant. Using TsDPEN type ligands, we recently discovered that pgm-catalysed ATH reactions can be carried out in water in a highly efficient manner (6, 7, 10, 14, 23, 64–75). The use of water is environmentally advantageous, and the reduction is easy to conduct, requiring no modification to the ligands, no organic solvents, and often no inert gas protection throughout. It also uses one of the most easily available and inexpensive hydrogen sources, sodium formate (HCOONa), thus providing a new viable tool for ketone reduction. Here we present a brief account of the work we have carried out with these catalysts for C=O bond reduction in water (Equation (i)).



## 2. ATH in Water with Platinum Group Metal Catalysts

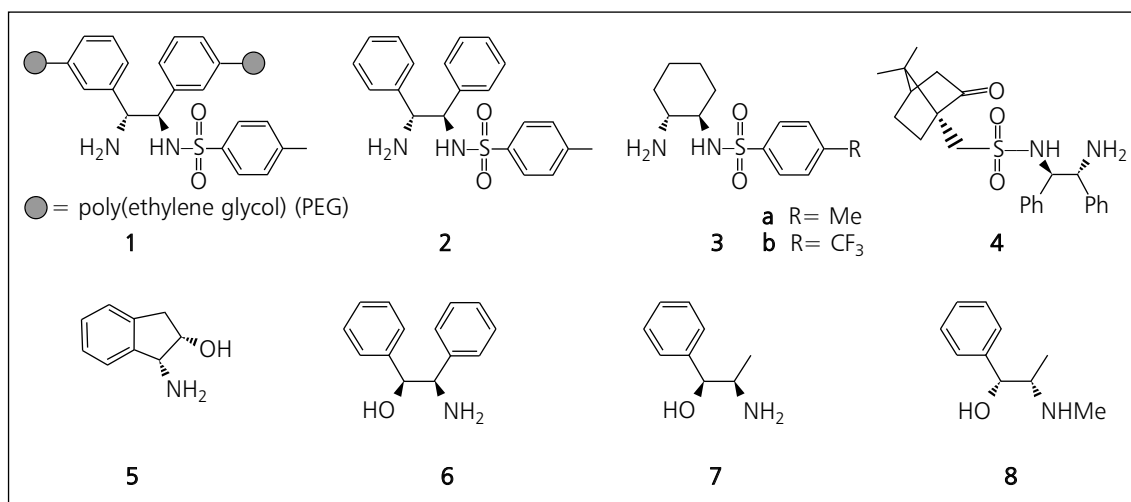
ATH in water is not something new; in fact enzyme-catalysed ATH has been taking place in aqueous media for billions of years. However, most man-made catalysts use organic media. Enabling the use of water as a medium for industrial applications would be an advantage as water is cheap and nontoxic, so it can be used in large amounts without associated environmental or health hazards, a feature of increasing significance for the pharmaceutical and fine chemical industries. Further, the combination of small molecule size and a three-dimensional hydrogen-bonded network results in a large cohesive energy density, a high surface tension and a high heat capacity. These attributes give water its unique structure as a liquid and lead to unique hydrophobic effects in contact with hydrocarbon compounds. These properties have been exploited to benefit reactions, leading to

enhanced reactivities and selectivities and easy separation of the catalyst and product. In the case of ATH in water, significant progress has been recorded in the past few years. For more information about this and other groups' work, the reader is referred to the references cited (6, 7, 10, 14, 23, 64–119).

### 2.1 Ruthenium-Catalysed ATH in Water

Reports on ATH in aqueous media with Ru(II) complexes were initially concerned with organic–water biphasic systems, with effort being focused on the design of water-soluble catalysts (116, 118). However, the resulting catalysts displayed activities and/or enantioselectivities lower than might be expected. Before entering the ATH area, we had developed a method for the immobilisation of chiral diamine ligands, which could be used as a platform to build supported chiral catalysts (120, 121). Of relevance here is that we demonstrated the water-soluble poly(ethylene glycol) (PEG)-supported complex **1** (Scheme I), using PEG with molecular mass 2000 g mol<sup>-1</sup> (PEG 2000), to be effective in the Ru(II)-catalysed ATH in azeotropic HCOOH-NEt<sub>3</sub> mixture; but unexpectedly the catalyst recycle *via* solvent extraction of the chiral alcohol product was possible only when water was present as cosolvent. In its absence, much reduced conversions and ees were observed, indicating catalyst decomposition (120).

This finding prompted us to examine the behaviour of sulfonamide ligands **1** and **2** (Scheme I) in acetophenone reduction by HCOONa in neat water. Rather pleasingly, we found that, without any modification, the Noyori-Ikariya catalyst Ru-**2**, derived *in situ* from [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> and **2**, enables efficient ATH in neat water (74). The reaction was considerably faster than in organic media and afforded excellent enantioselectivities. Thus, following the addition of 5 equivalents of HCOONa and acetophenone with a molar substrate-to-catalyst ratio (S:C) of 100, the ketone was fully converted into (*R*)-1-phenylethanol in 95% ee after 1 h reaction time; in comparison, the reaction run in the HCOOH-NEt<sub>3</sub> azeotrope afforded a conversion of less than 2% in 1 h, with full conversion requiring more than 10 h (97% ee) (74). Several other structurally diverse ketone substrates were subsequently examined, showing again that the reduction in water was considerably faster, although the enantioselectivities observed with the azeotrope were slightly higher (74). This initial finding has since been proved to be quite general, in that other ligands



Scheme 1. Ligands used for asymmetric transfer hydrogenation in aqueous media described in this review

(shown in **Scheme 1**) which were designed for organic solvents are also effective for ATH in water with no need for modification or organic solvents. In **Table I**, we summarise the results obtained with various Ru(II) catalysts, including Ru-1, in the ATH of the benchmark substrate acetophenone. The catalysts were usually generated from the ligand and a Ru precursor at the reaction temperature in water without adding a base, for example Ru-2 from [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> and ligand **2**. The structure of Ru-2 prepared under such conditions has been confirmed by X-ray diffraction to be the same as the one obtained in 2-propanol (65, 68, 122). These precatalysts show varying solubilities in water. Presumably their water solubility stems from chloride–water exchange, resulting in the formation of mono-aqua cations. However, they show much higher solubility in ketones and alcohols, most of which are insoluble in water. Hence, we conclude that the reaction is biphasic and takes place ‘on water’ (in aqueous suspension).

As shown in **Table I**, the monotosylated diamines **1–4** all served as efficient ligands for the ATH of ketones in water, with full conversion and up to 97% ee reached in short reaction times (Entries 3–12, **Table I**). Under the given conditions, the ligands **2** and **4** afforded the best enantioselectivity. The reaction was frequently carried out at an S:C ratio of 100; however, a high S:C ratio of 10,000 has been demonstrated to be feasible (Entry 8, **Table I**). In comparison with ATH in azeotropic HCOOH-NEt<sub>3</sub> with or without water, ATH in aqueous HCOONa is much faster (Entries 3 and 4, **Table I**). This finding prompted us to

explore factors that might lead to these contrasting results (65, 73). The clearest difference between the two systems was found to be the solution pH. Subsequently, the pH value was proved to be critical to the reaction rate and enantioselectivity (see Sections 3.1 and 3.2 of this paper). Indeed, efficient ATH can be performed with HCOOH-NEt<sub>3</sub> in water, provided the ratio of HCOOH:NEt<sub>3</sub> is controlled such that the solution is close to pH neutral (Entries 5–8, **Table I**).

Interestingly, while β-aminoalcohol ligands were believed to be incompatible with formic acid as a reductant for ATH of ketones (12, 20), the commercially available simple β-aminoalcohol ligands **5–8** do catalyse the ATH of acetophenone by HCOONa or HCOOH-NEt<sub>3</sub> in water (70). However, the reduction rates and enantioselectivities were much lower than those obtained with the diamine ligands (Entries 13–16, **Table I**) (70).

The Ru(II)-catalysed ATH has since been applied to a wide range of aromatic ketones (**Scheme II**). The reduction is easy to perform, affording the chiral alcohols with high ee in a short reaction time for most of the substrates at S:C ratios from 100:1 to 1000:1. While the substrate ketones are generally water-insoluble, this does not appear to have a negative effect on the reaction rates. The reduction of most ketones proceeded significantly faster in water than the same transformation in azeotropic HCOOH-NEt<sub>3</sub>. For example, the reduction of *p*-methoxyacetophenone, which is difficult under normal conditions, gave a conversion of >99% and an ee of 95%

with Ru-2 in 2 h at an S:C ratio of 100 and a temperature of 40°C (73, 74). With the azeotropic HCOOH-NEt<sub>3</sub> mixture as the reductant, the same catalyst required about 60 h to complete the reduction (97% ee) at 28°C and an S:C ratio of 200 (26). Likewise, 1-acetonaphthone was reduced to (*R*)-1-(1-naphthyl)-ethanol with Ru-2 by aqueous HCOONa in 98% conversion and 87% ee in 6 h at 40°C and an S:C ratio of 100; but in the azeotropic HCOOH-NEt<sub>3</sub> mixture with Ru-1, a conversion of only 71% was achieved in 30 h at 50°C (120). In the aqueous phase ATH, there appears to be no correlation between the electronic properties of substituents and the enantioselectivity, as shown by the reduction of *para*-OMe- and *para*-CF<sub>3</sub>-acetophenone with Ru-2, which both gave ~95% ee in 2 h.

For practical applications, easy separation of the catalyst and product is necessary. The Ru-1 catalyst allows for this, due to its hydrophilic PEG chain, which retains the catalyst in the water during product extraction with, for example, diethyl ether. In the case of acetophenone reduction, we measured the leached Ru; inductively coupled plasma (ICP) analysis showed that only 0.4 mol% of Ru leached into the organic phase. Remarkably, the PEG-immobilised catalyst could be reused fourteen times with no loss in enantioselectivity, demonstrating its excellent recyclability and lifetime under aqueous conditions. When HCOOH-NEt<sub>3</sub> was used without water, the recycle experiments could not be carried out for more than two runs without the rates and ees being eroded.

Table I

Comparison of Asymmetric Transfer Hydrogenation of Acetophenone Using Ruthenium(II) Catalysts in Water<sup>a</sup>

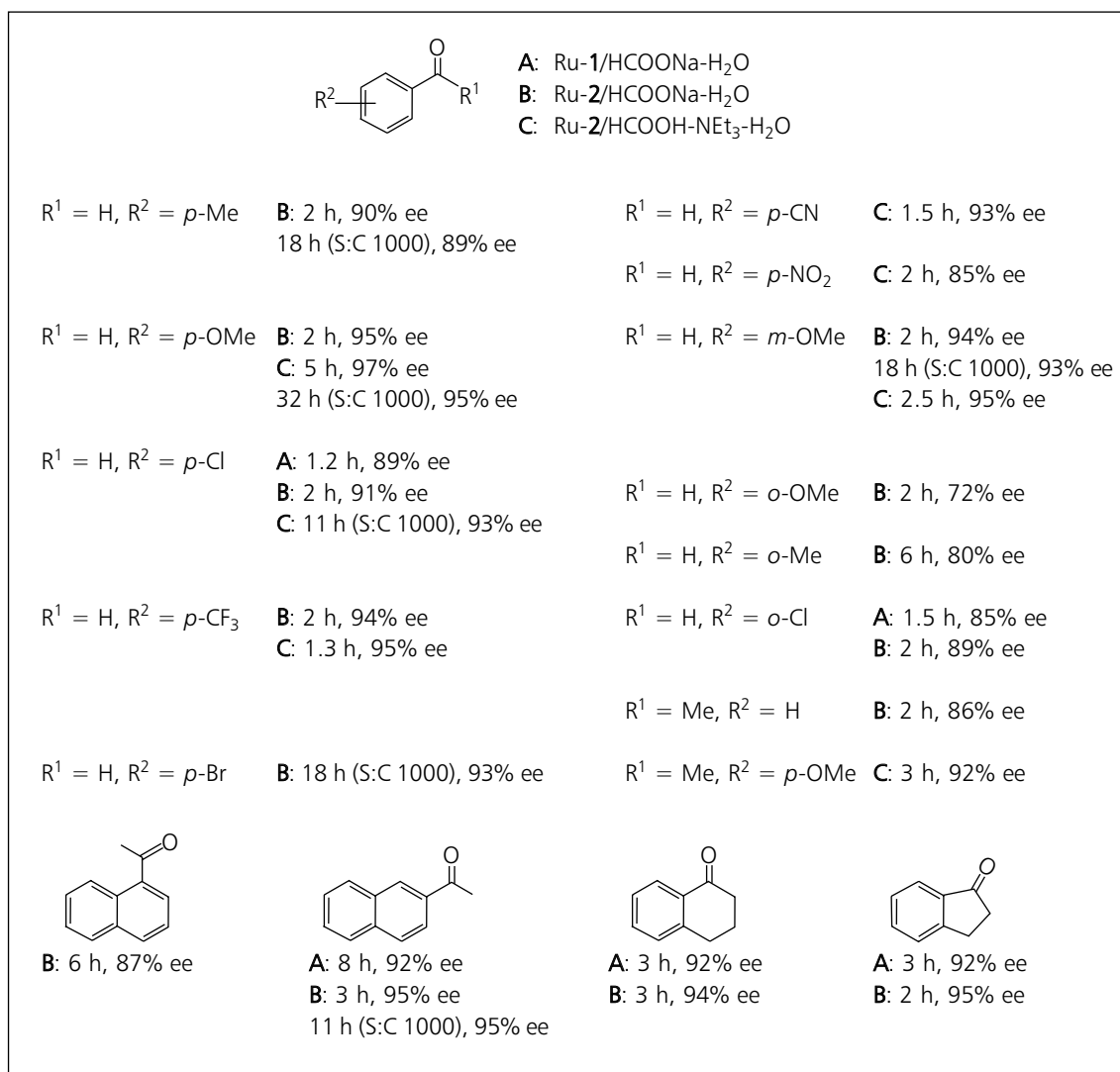
Entry	Catalyst	Hydrogen source <sup>b</sup>	S:C <sup>c</sup>	Time, h	Conversion, %	ee, %	Reference
1	Ru-1	HCOONa	100	1	99	92	(75)
2	Ru-1	HCOONa	1,000	12	>99	89	(75)
3	Ru-2	HCOONa	100	1	>99	95	(65, 74)
4	Ru-2	Azeotrope <sup>d</sup>	100	12	98	97	(73, 74)
5	Ru-2	FA-T/H <sub>2</sub> O	100	1.5	>99	97	(73)
6	Ru-2	FA-T/H <sub>2</sub> O	1,000	9	>99	96	(73)
7	Ru-2	FA-T/H <sub>2</sub> O	5,000	57	98	96	(73)
8	Ru-2	FA-T/H <sub>2</sub> O	10,000	110	98	94	(73)
9	Ru-3a	HCOONa	100	2	99	85	(72)
10	Ru-3b	HCOONa	100	2.5	>99	81	(68, 72)
11	Ru-4	HCOONa	100	2	99	97	(71)
12	Ru-4	HCOONa	1,000	20	95	96	(71)
13	Ru-5	HCOONa	100	12	84	71	(70)
14	Ru-6	HCOONa	100	10	95	50	(70)
15	Ru-7	HCOONa	100	5	97	60	(70)
16	Ru-8	HCOONa	100	3.5	>99	73	(70)

<sup>a</sup> The reaction was carried out at 40°C in 2 ml of water or a mixture of water and formic acid-triethylamine (FA-T in a 1.2:1.0 molar ratio) under inert gas protection

<sup>b</sup> Hydrogen source: 5 equiv. was used unless otherwise specified

<sup>c</sup> S:C is substrate to catalyst molar ratio

<sup>d</sup> Azeotrope refers to an azeotropic HCOOH-NEt<sub>3</sub> mixture (2.5:1 molar ratio)



Scheme II. Selected examples of ruthenium-catalysed asymmetric transfer hydrogenation in water. All the reactions afforded virtually full conversion in the time given. For reaction conditions, see Table I

## 2.2 Rhodium-Catalysed ATH in Water

In organic media, the isoelectronic Rh-2 complex was shown to be highly effective in the reduction of  $\alpha$ -chlorinated ketones and some imines (114, 123); but it was less active than Ru-2 in the reduction of other ketones. Replacing TsDPEN with chiral 1,2-aminoalcohols yields much more active catalysts as shown by Blacker and Mellor (124). However, these catalysts tend to be less enantioselective than Ru-2 and, as with other catalysts using 2-propanol as reductant, their effect depends on the use of a low concentration of substrate unless the resulting products are removed *in situ* (125–127).

The direct application of Rh-2 and related catalysts to the aqueous-phase ATH of ketones had not been reported before our work in 2004. It has since been found that Rh-2 and its analogues also display remarkably enhanced activities and excellent enantioselectivities in the reduction of a wide range of ketones in water (Table II) (66, 72). For example, ATH of acetophenone with Rh-3a, Rh-3b and Rh-4 by HCOONa in water afforded almost full conversions in several minutes, with ees between 94% and 99% at an S:C ratio of 100 (Entries 7–10, Table II) (68, 71, 72). The camphor-substituted 4 led to the best enantioselectivity, affording up to 99% ee (Entries 10 and 11,

**Table II**) (71). In general, as shown in **Table II**, the diamine ligands afford faster reaction rates and better enantioselectivities than aminoalcohol ligands. Furthermore, 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 rendering the reduction easier to perform than reactions catalysed by most other organometallic complexes (Entries 2, 7 and 9, **Table II**). It is also interesting to note that there is little reduction with Rh-2 in the HCOOH-NEt<sub>3</sub> azeotrope in 16 h, and the reduction afforded only 45% conversion with 89% ee in 24 h in 2-propanol (Entries 3 and 4, **Table II**).

A quite broad range of ketones can be effectively reduced with the Rh-diamine catalysts by HCOONa in water (**Scheme III**). Apart from the normal unfunctionalised aromatic ketones which have been successfully reduced with the Ru catalysts, heterocyclic, functionalised and multi-substituted ketones are all viable

substrates with this Rh-catalysed reduction system (**Schemes III and IV**). The reduction is again easy to carry out, affording the chiral alcohols with excellent ees in a short reaction time for most of the substrates. For example, most of the reduction reactions with Rh-3a or Rh-3b finished within several minutes. Thus, 2-acetyl furan was completely reduced to (*R*)-1-(2-furyl)ethanol within 5 minutes with the Rh-diamine catalysts, affording 99% ees at an S:C ratio of 100. The turnover frequency reached as high as 4100 h<sup>-1</sup> with the Rh-3a catalyst (72). (*E*)-Chalcone, an intermediate for a variety of biologically active compounds, was reduced in 2.5 h with Rh-2, affording the fully saturated 1,3-diphenylpropan-1-ol with 93% ee. Gas chromatography (GC) monitoring showed that the C=C bond was first saturated, followed by the carbonyl. While we frequently used an S:C ratio of 100, an S:C ratio of 1000 has been demonstrated to be feasible for many ketones.

**Table II**

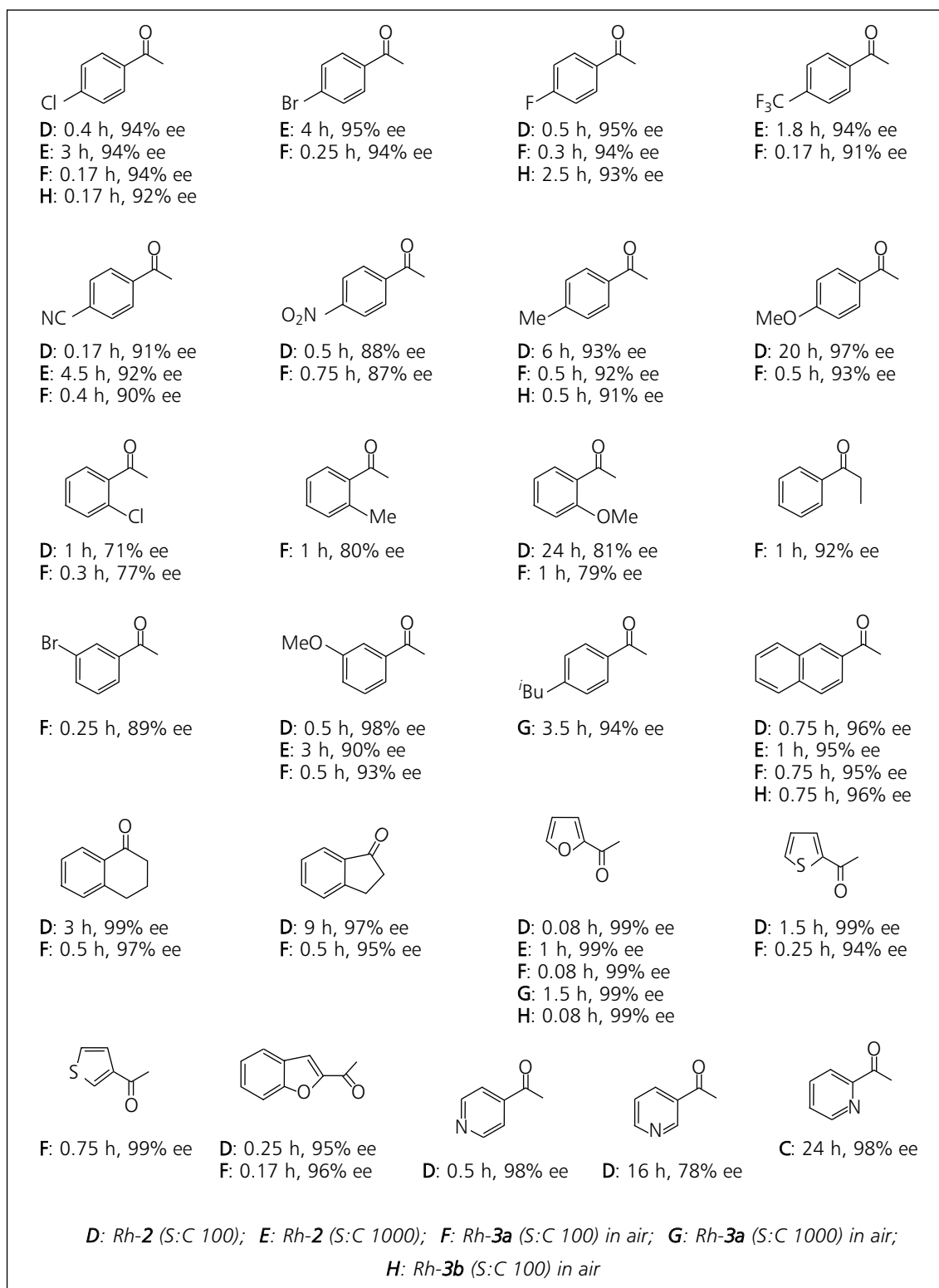
**Comparison of Asymmetric Transfer Hydrogenation of Acetophenone Using Rhodium(III) Catalysts in Water<sup>a</sup>**

Entry	Catalyst	Hydrogen source	S:C	Time, h	Conversion, %	ee, %	Reference
1	Rh-2	HCOONa	100	0.5	99	97	(66)
2	Rh-2	HCOONa <sup>b</sup>	100	0.5	99	97	(66)
3	Rh-2	Azeotrope	100	16	<1	N/A	(66)
4	Rh-2	2-Propanol <sup>c</sup>	100	24	45	89	(66)
5	Rh-2	Azeotrope/H <sub>2</sub> O	100	24	18	64	(66, 68)
6	Rh-2	HCOONa	1,000	3	93	97	(66)
7	Rh-3a	HCOONa <sup>b</sup>	100	0.25	>99	95	(72)
8	Rh-3b	HCOONa	100	0.25	>99	94	(68)
9	Rh-3b	HCOONa <sup>b</sup>	100	0.25	>99	94	(68)
10	Rh-4	HCOONa	100	0.7	99	99	(71)
11	Rh-4	HCOONa	1,000	20	89	99	(71)
12	Rh-5	HCOONa	100	20	92	54	(70)
13	Rh-6	HCOONa	100	20	85	41	(70)
14	Rh-7	HCOONa	100	5	63	31	(70)
15	Rh-8	HCOONa	100	22	77	68	(70)

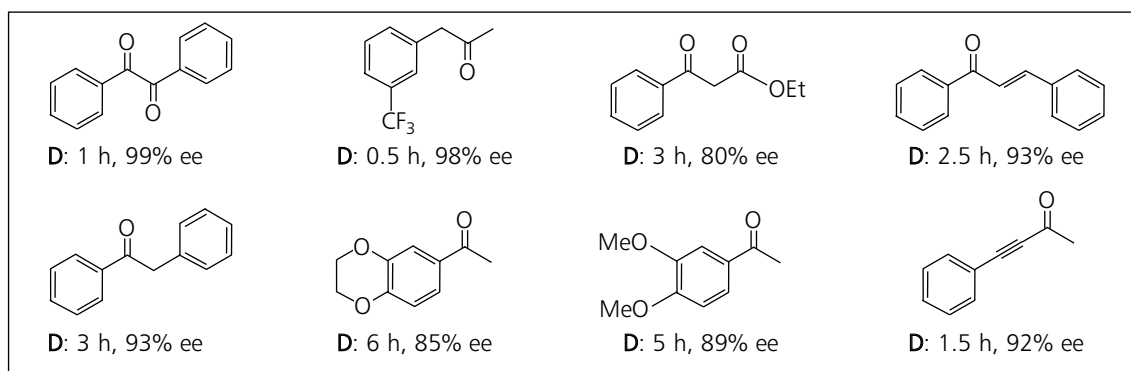
<sup>a</sup> The reaction was carried out at 40°C in 2 ml of water or a mixture of water and azeotrope under inert gas protection unless otherwise specified

<sup>b</sup> No inert gas protection throughout

<sup>c</sup> 0.01 equiv. potassium hydroxide (KOH) was added



Scheme III. Examples of Rhodium-catalysed asymmetric transfer hydrogenation by HCOONa in water at 40°C



Scheme IV. Rhodium-catalysed asymmetric transfer hydrogenation of selected functionalised ketones in water. For conditions see Scheme III. The time to completion (*h*) and enantiomeric excess (*ee*, %) are shown

### 2.3 Iridium-Catalysed ATH in Water

In a similar manner, we have also shown that the analogous Ir catalysts are applicable to the aqueous-phase ATH of ketones (66, 71). Table III summarises the results of ATH of acetophenone with the Ir(III) catalysts. Again the ATH is faster with aqueous HCOONa. Thus, there is no conversion for the reduction with Ir-2 in the HCOOH-NEt<sub>3</sub> azeotrope in 16 h; the same reaction afforded a 39% conversion and 83% ee in 24 h in the presence of water (Entries 2 and 4, Table III). Using 2-propanol as reductant and solvent, the reaction gave a 48% conversion and 87% ee in 24 h (Entry 3, Table III). Compared to the Rh-diamine catalysts, the Ir-diamine tends to show a lower catalytic activity. For instance, Ir-2 afforded virtually full conversion in 3 h with an enantioselectivity of 93% (Entry 1, Table III), while Ru-2 and Rh-2 required reaction times of 1 h (with 95% ee) and 0.5 h (with 97% ee), respectively, to give the same level of conversion under the same conditions (Entry 3, Table I and Entry 1, Table II). However, Ir-4 outperformed Ru-4, Rh-4 and other Ir(III) catalysts in terms of both catalytic activity and enantioselectivity. In particular, acetophenone was reduced with 97% conversion and 98% ee in 2.5 h at an S:C ratio of 1000 (Entry 8, Table III). Furthermore, the Ir-aminoalcohol catalysts displayed faster reduction rates than their Ru(II) and Rh(III) analogues in aqueous HCOONa, although the enantioselectivity remains to be improved (Entries 9–13, Table III).

The Ir catalysts can also be applied to the reduction of other ketones. Selected examples are shown in Scheme V. Most of the ketones were reduced in several hours with Ir-4 by formate in water at an S:C ratio of 1000, affording excellent enantioselectivities. The electronic properties of the substituent on the

ketones impact significantly on the reaction rate, as does the steric effect. Thus, faster reduction was observed for ketones with electron withdrawing groups such as Cl, Br, F, CN or NO<sub>2</sub>; in contrast, electron donating groups such as Me or OMe necessitated longer reaction times (Scheme V).

### 2.4 Iridium-Catalysed Transfer Hydrogenation and Hydrogenation

In a related study, Ir complexes containing tosylated ethylenediamines 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 (69). As shown in Table IV, while the reduction of benzaldehyde with (1,2,3,4,5-pentamethylcyclopentadienyl)iridium(III) chloride dimer ([Cp\*IrCl<sub>2</sub>]<sub>2</sub>) afforded a turnover frequency of only 20 h<sup>-1</sup> (Entry 1, Table IV), introduction of diamine ligands (Scheme VI) led to a dramatic increase in the reaction rate (Entries 2–4 and 7–9, Table IV). In particular, Ir-11, formed *in situ* from [Cp\*IrCl<sub>2</sub>]<sub>2</sub> and 11, afforded turnover frequencies of up to 1.3 × 10<sup>5</sup> h<sup>-1</sup> in the transfer hydrogenation of benzaldehyde (Entry 9, Table IV). Under these conditions, 5.30 g of benzaldehyde was reduced to give phenylmethanol in 98% isolated yield (5.28 g) in 1 h with 0.4 mg of [Cp\*IrCl<sub>2</sub>]<sub>2</sub>, demonstrating the superior activity, robustness and scalability of the aqueous Ir(III) catalytic system. However, using either more electron-rich or electron-deficient diamines as the ligand afforded slower reduction rates (Entries 9 *vs.* 10 and 11, Table IV). By way of contrast, when carried out in 2-propanol or the azeotropic HCOOH-NEt<sub>3</sub> mixture, a much slower reduction resulted (Entries 5 and 6, Table IV).



Table III

Comparison of Asymmetric Transfer Hydrogenation of Acetophenone Using Iridium(III) Catalysts in Water<sup>a</sup>

Entry	Catalyst	Hydrogen source	S:C	Time, h	Conversion, %	ee, %	Reference
1	Ir-2	HCOONa	100	3	99	93	(66)
2	Ir-2	Azeotrope	100	16	None	N/A	(66)
3	Ir-2	2-Propanol	100	24	48	87	(66)
4	Ir-2	Azeotrope/H <sub>2</sub> O	100	24	39	83	(66)
5	Ir-3a	HCOONa <sup>b</sup>	100	1	99	93	(68, 72)
6	Ir-3b	HCOONa	100	1.5	>99	92	(68)
7	Ir-4	HCOONa	100	0.7	98	97	(71)
8	Ir-4	HCOONa	1,000	2.5	97	98	(71)
9	Ir-5	HCOONa	100	5	>99	27	(70)
10	Ir-6	HCOONa	100	1.5	100	27	(70)
11	Ir-6	FA-T/H <sub>2</sub> O <sup>c</sup>	100	1.5	100	55	(70)
12	Ir-7	HCOONa	100	5	61	7	(70)
13	Ir-8	HCOONa	100	2.5	100	54	(70)

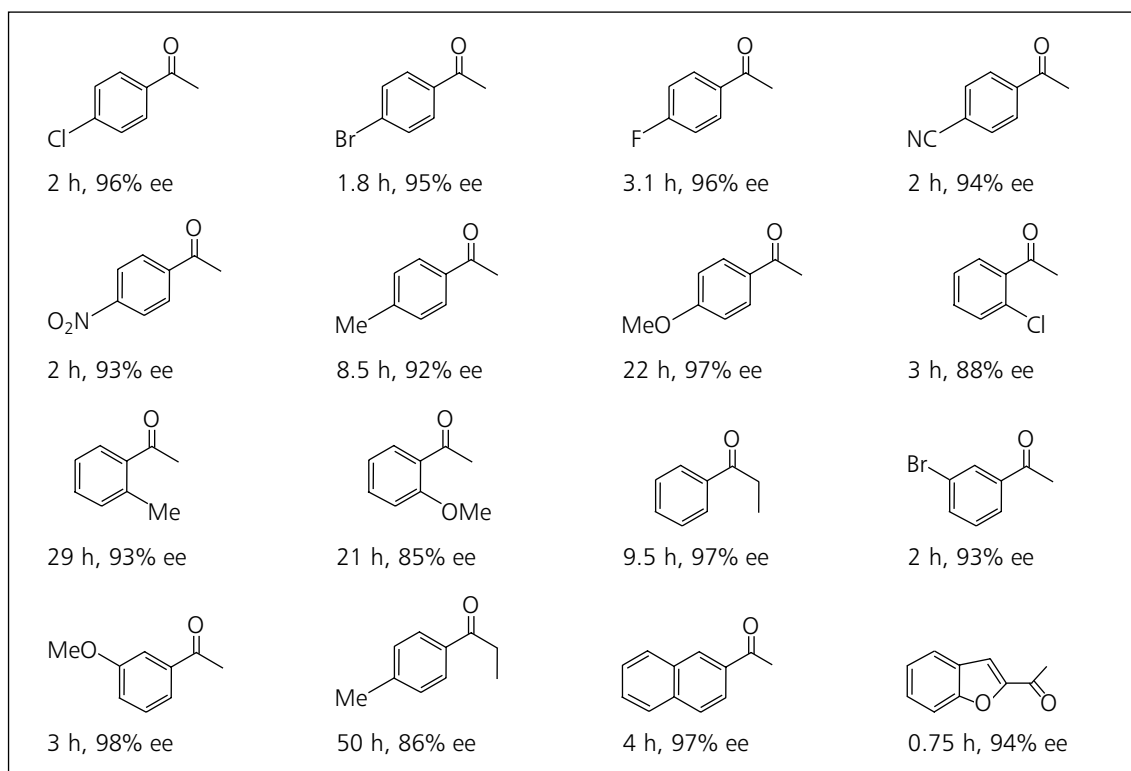
<sup>a</sup> The conditions were the same as in Tables I and II<sup>b</sup> No inert gas protection throughout<sup>c</sup> FA-T = mixture of formic acid and triethylamine (1:1.7 molar ratio)

Table IV

Comparison of Transfer Hydrogenation of Benzaldehyde Using Iridium(III) Catalysts in Water<sup>a</sup>

Entry	Catalyst	Hydrogen source	S:C	Temperature, °C	Time, h	Conversion, %	Turnover frequency, h <sup>-1</sup>
1	Ir	HCOONa	1,000	65	25	70	20
2	Ir-2	HCOONa	1,000	65	0.08	>99	12,000
3	Ir-9	HCOONa	1,000	65	1	99	1,800
4	Ir-10	HCOONa	1,000	65	0.08	>99	12,000
5	Ir-10	2-Propanol	1,000	65	1	2.6	26
6	Ir-10	Azeotrope	1,000	65	1	1.5	15
7	Ir-10	HCOONa	10,000	65	1.5	>99	20,400
8	Ir-10	HCOONa	10,000	80	0.9	>99	28,800
9	Ir-11	HCOONa	50,000	80	1	98	132,000
10	Ir-12	HCOONa	10,000	80	0.5	>99	40,000
11	Ir-13	HCOONa	10,000	80	0.7	99	31,200
12	Ir-14	HCOONa	1,000	65	1	50	4,000

<sup>a</sup> Transfer hydrogenation conditions were 10 ml water and 5 equiv. HCOONa (69)

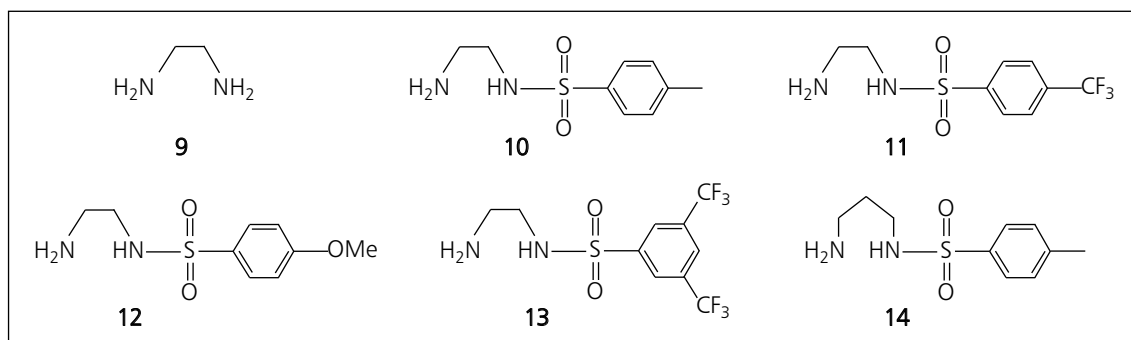


Scheme V. ATH of ketones with Ir-4 by HCOONa in water. Conditions: 5 equiv. HCOONa, 5 ml water, 40°C at an S:C ratio of 1000

These catalysts also catalyse the hydrogenation of aldehydes with hydrogen (H<sub>2</sub>) in water (67). As can be seen, Ir-10 enables the hydrogenation of benzaldehyde under neutral conditions (Entry 1, Table V); but unlike the ATH of ketones, the reduction is faster in the presence of base (Entry 2, Table V). In contrast, introduction of acid led to a significantly lower conversion (Entry 3, Table V). Furthermore, the more electron-deficient Ir-11 and Ir-13 afforded faster reduction, with benzaldehyde being reduced by Ir-11 with

over 99% conversion in 2 h at an S:C ratio of 1000, while the conversion was only 48% with Ir-12 under the same conditions (Entries 4 and 5, Table V). The higher activity of Ir-11 compared to Ir-12 may stem from the higher acidity of its dihydrogen intermediate, which renders the Ir(III)-H hydride easier to form.

The aqueous transfer hydrogenation system works for aromatic,  $\alpha,\beta$ -unsaturated and aliphatic aldehydes and for those bearing functional groups such as halo,



Scheme VI. Selected diamine ligands for reduction of aldehydes in water

Table V

Comparison of Hydrogenation of Benzaldehyde Using Iridium(III) Catalysts in Water<sup>a</sup>

Entry	Catalyst	Hydrogen source	S:C	Temperature, °C	Time, h	Conversion, %
1	Ir-10	H <sub>2</sub>	200	80	2	80
2	Ir-10	H <sub>2</sub> /base	1,000	80	2	88
3	Ir-10	H <sub>2</sub> /CF <sub>3</sub> COOH	1,000	80	2	17
4	Ir-11	H <sub>2</sub> /base	1,000	80	2	>99
5	Ir-12	H <sub>2</sub> /base	1,000	80	2	48
6	Ir-13	H <sub>2</sub> /base	1,000	80	2	99
7	Ir-14	H <sub>2</sub> /base	1,000	80	2	20

<sup>a</sup> Hydrogenation conditions were 10 ml water, 20 bar H<sub>2</sub> and 5 to 20 equiv. (relative to Ir) base (aqueous KOH) (67)

acetyl, alkenyl and nitro groups, and is highly chemoselective towards the formyl group (Scheme VII) (67, 69). For example, 4-acetylbenzaldehyde was reduced only to 4-acetylphenylethanol, and the reduction of 4-acetylcinnamaldehyde took place without affecting the ketone and olefin double bonds. Furthermore, the reduction is highly efficient and can be carried out in air, without inert gas protection throughout. Thus, S:C ratios of 2000 to 10,000 were feasible for both Ir-10 and Ir-11, although the electron-deficient Ir-11 generally displayed a higher catalytic activity than Ir-10.

The same aldehyde substrates have also been reduced with H<sub>2</sub> in water with Ir-11 as the catalyst (Scheme VII). Again, a wide range of aldehydes, including aromatic, aliphatic, heterocyclic and  $\alpha,\beta$ -unsaturated aldehydes, are readily reduced. And, as with the transfer hydrogenation, the hydrogenation is efficient and chemoselective and runs in neat water with no need for an organic cosolvent. In comparison with transfer hydrogenation, however, hydrogenation is less efficient, with a lower S:C ratio of 1000 being feasible under the conditions examined.

### 3. Mechanistic Aspects of ATH in Water

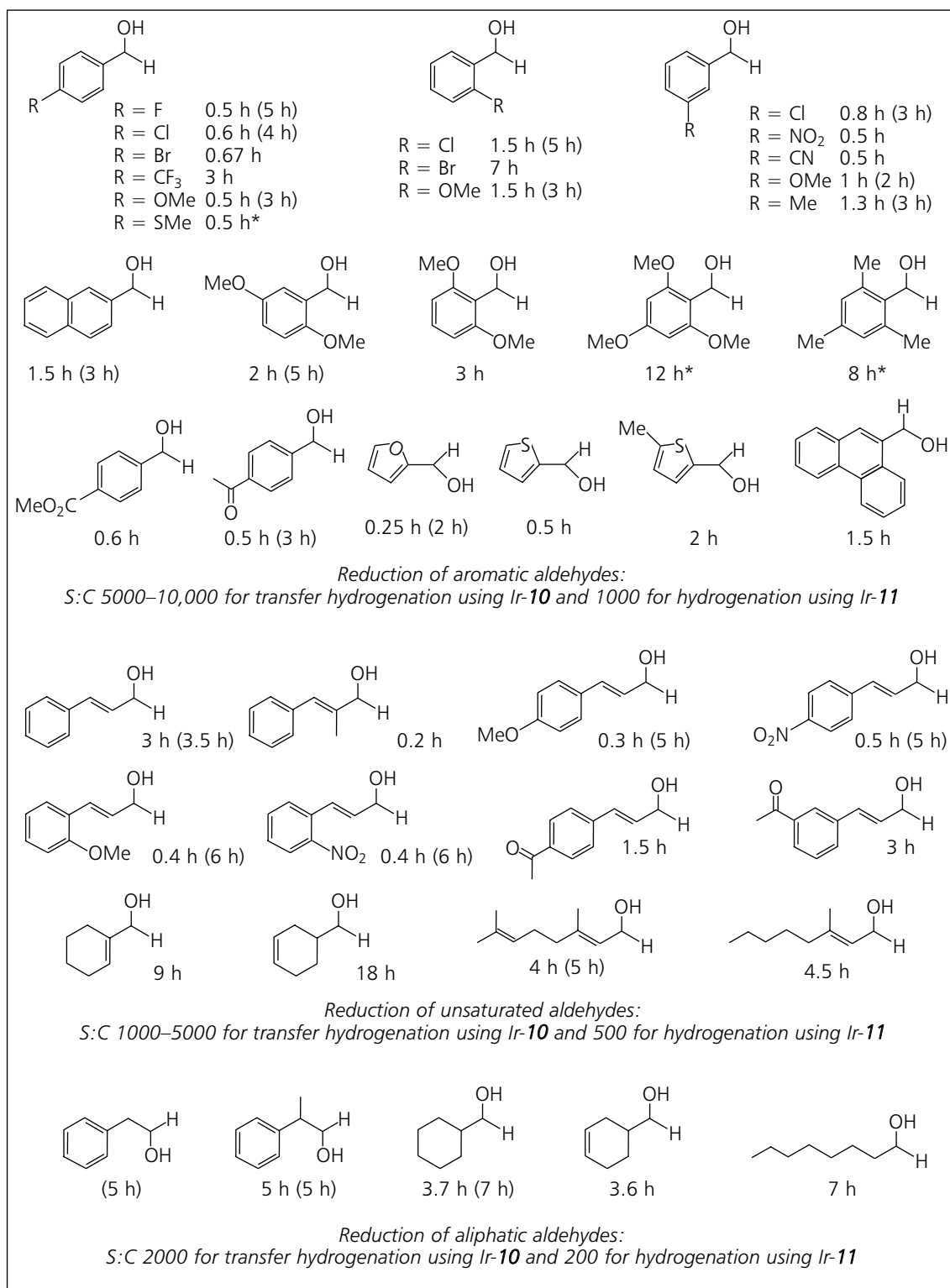
#### 3.1 Effect of Solution pH

As indicated above, a significant feature of the aqueous ATH is that the reaction rates vary with solution pH. We initially demonstrated this in the ATH of acetophenone by formate with Ru-2 in water (73). It was shown that an increase of 1 pH unit at ~pH 3.9 could result in an increase in rate of ~20 times (Figure 1). Little reduction occurred at lower pH, but the pH

increased with time due to the decomposition of HCOOH into carbon dioxide (CO<sub>2</sub>) and H<sub>2</sub> by the catalyst (73). Of particular note is that the enantioselectivity also varied with pH (Figure 1), indicative of competing catalytic pathways (65, 73). Further studies have since revealed that this pH dependence is common for the ATH of ketones in water (65, 66, 69, 70, 73, 85, 92, 95, 98, 107, 111). For example, the Rh-2 and Ir-2 catalysts displayed a window of pH 5.5 to 10 and pH 6.5 to 8.5, respectively, with a turnover frequency of over 50 h<sup>-1</sup> in the ATH of acetophenone in water discussed above (66). And most recently, we showed that quinolines are reduced in high yields and high enantioselectivities with formate in water at pH 5, using a Rh-2 type catalyst (64).

#### 3.2 Mechanism of ATH in Water

The mechanism of the aqueous ATH has recently been investigated (63, 65, 66, 73, 77, 85, 92, 95, 111, 128, 129). In a study into the ATH of acetophenone by formate with Ru-2 using nuclear magnetic resonance (NMR) spectroscopy, kinetic and isotope measurements, and density functional theory (DFT) calculations, we showed that two catalytic cycles are likely to operate in the ATH reaction, depending on the solution pH (Scheme VIII) (65). Cycle 1 describes ATH under neutral conditions and is more efficient, affording fast rates and high enantioselectivity *via* a water-assisted transition state. Under acidic conditions, Cycle 2 dominates, in which protonation occurs at both the hydride and the TsDPEN ligands, leading to lower catalytic activity and lower ees. However,



Scheme VII. Selected examples of reduction of aldehydes to alcohols using iridium catalysts Ir-10 (transfer hydrogenation, TH) and Ir-11 (hydrogenation; time in brackets) in water. \*S:C 1000

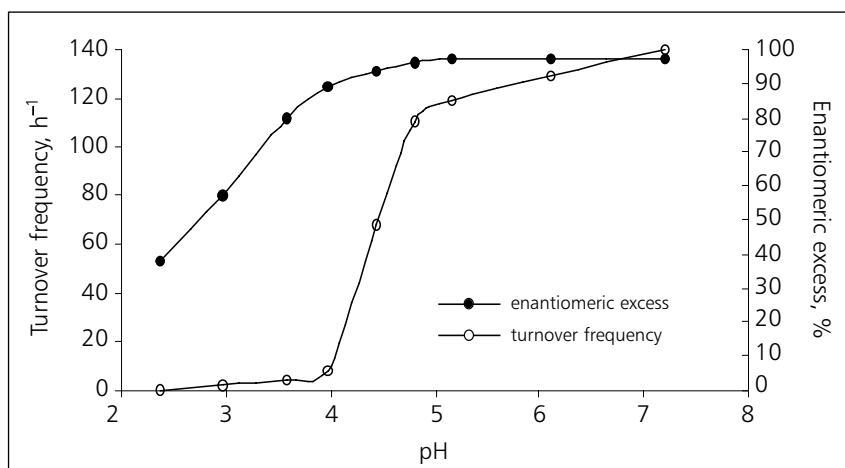


Fig. 1. Initial turnover frequency vs. initial pH values for asymmetric transfer hydrogenation of acetophenone with ruthenium catalyst Ru-2 in water at 40°C

higher pH drives the catalyst into an inactive hydroxyl form shown in Cycle 3, thus decreasing the concentration of active catalyst and so the reduction rates, albeit without affecting the ees.

Further details on Cycle 1 under neutral conditions have also been revealed. The Ru-H species is visible in the NMR spectra; however, the Ru-formate complex could not be detected in either stoichiometric or catalytic reactions. In kinetic studies, it was shown that the ATH is first order in both the catalyst and ketone substrate but is inhibited by CO<sub>2</sub>. This evidence points to the rate-limiting step of the ATH reaction being the hydrogen transfer from Ru to ketone, probably with a transition state similar to that proposed by Noyori for non-aqueous media (19) (Scheme VIII).

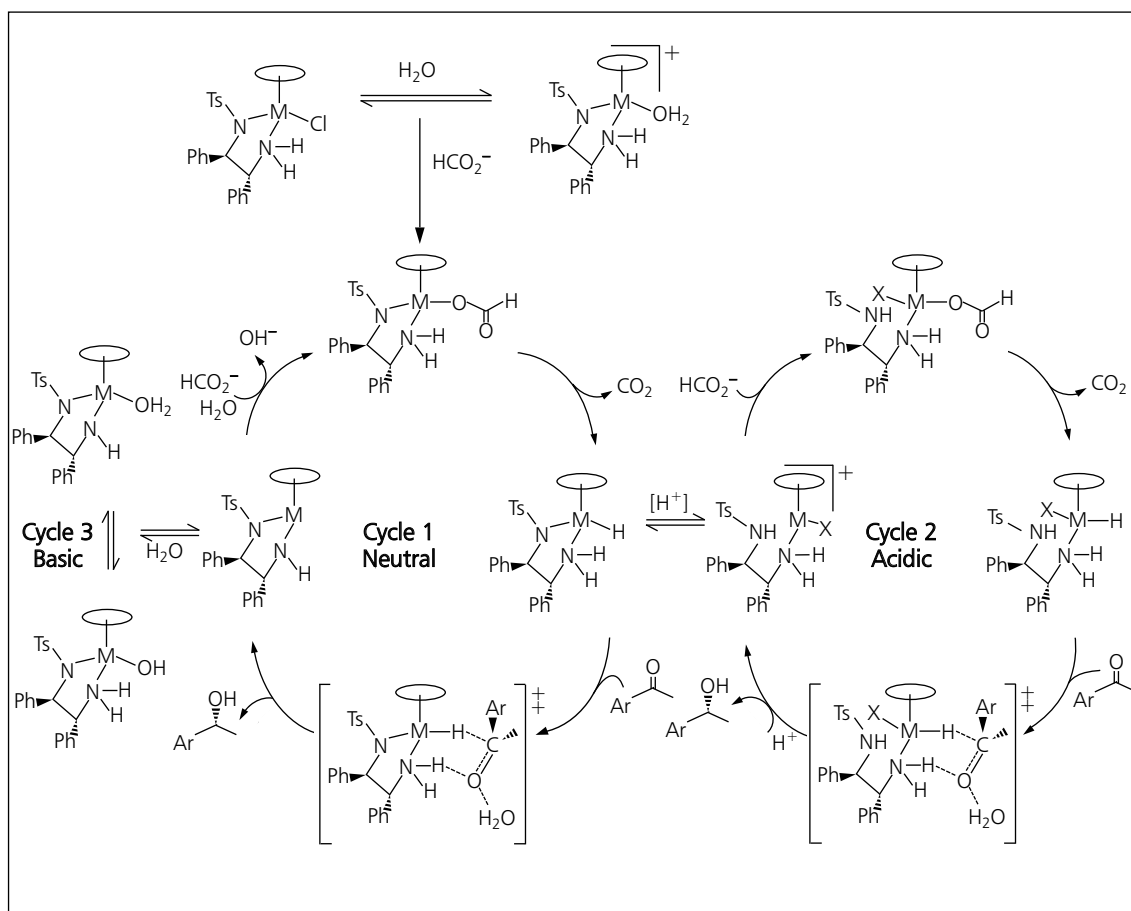
### 3.3 The Role of Water

Water has been demonstrated to accelerate the ATH (65, 74). This acceleration can be at least partly traced to its effect on the rate-limiting step mentioned above. Thus, in the stoichiometric reduction of acetophenone by isolated Ru(II)-H, the rate in wet deuterated dichloromethane (CD<sub>2</sub>Cl<sub>2</sub>) was six times that in dry CD<sub>2</sub>Cl<sub>2</sub>. Further insight was gained from DFT calculations, which showed that water participates in the transition state of hydrogen transfer, stabilising it by ~4 kcal mol<sup>-1</sup> (~17 kJ mol<sup>-1</sup>) through hydrogen bonding with the ketone oxygen. Interestingly, the calculations also suggest that the participation of water renders the hydrogen transfer step-wise, rather than concerted as proposed for ATH in organic solvents (65). A similar solvent effect has been reported in a DFT study of the reduction of formaldehyde in methanol (130).

Water can stabilise the active catalyst species. The lifetime of the Ru catalyst in ATH reactions is remarkably prolonged by water. Thus, in the presence of water, the Ru-2 catalyst was stable for up to a few months; in contrast, the catalyst lifetime was significantly shortened when water was removed from the solution. For instance, the catalyst decomposed in half an hour in diethyl ether. NMR studies indicate that water reacts with the 16-electron species shown in Scheme VIII, affording aqua and hydroxyl species. This would provide a mechanism of stabilising an unstable active species, although the hydroxide will compete with formate for coordination to the metal centre under more basic conditions. Recent work has shown that the M-H hydride can react with oxygen (O<sub>2</sub>) (52, 129, 131–133).

### 4. Concluding Remarks

Asymmetric transfer hydrogenation of ketones with Ru(II), Rh(III) and Ir(III) complexes has been demonstrated to be viable in water. Affording fast reaction rates and excellent enantioselectivities with no organic solvent used, not only is the protocol environmentally appealing, but it is also of significance both practically and fundamentally. Additional advantages include an inexpensive reductant, no modification to ligands, and ease of use. Among the catalysts, the Rh(III) complexes appear to outperform their Ru(II) and Ir(III) analogues for most of the reactions studied, displaying high activity, high enantioselectivity and broad substrate scope. However, the performance of the Rh(III) complexes varies with the ligands used, as in the case of ligand 2 compared to ligand 4, and simple Ir(III)-diamine complexes are excellent



Scheme VIII. Proposed mechanism for the asymmetric transfer hydrogenation of ketones in water.  $M = \text{Ru, Rh or Ir}$  (65)

catalysts for the reduction of aldehydes. Unlike most other air- and/or moisture-sensitive transition metal complexes, the Rh(III)-diamine catalysts are not air-sensitive, allowing the reduction to be performed in air without any inert gas protection. In comparison, the Ru(II) complexes are more sensitive to air.

A common feature of these pgm catalysts is that their ATH rates and enantioselectivities show a strong dependence on the solution pH. Apart from the effect of pH on the concentration of formate, this can be at least partly traced to the protonation of the coordinated diamine ligand at low pH and to the formation of catalytically-inactive M–OH species under basic conditions.

Water has been shown to play a key role in aqueous ATH reactions. It accelerates the reduction, stabilises the catalyst, alters the transition state of hydrogen transfer, and facilitates separation of the catalyst

from the product. We expect that future work will enable aqueous-phase ATH to be applied to a wider range of industrially relevant hydrogenations, while offering unique insight into the chemistry of hydrogen transfer in laboratories and in nature.

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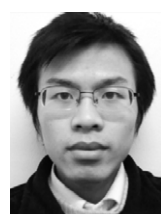


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