



## Transfer hydrogenation in aqueous media



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### ABSTRACT

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

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## 1. Introduction

Transfer hydrogenation (TH), where a non-H<sub>2</sub> hydrogen source is used, has drawn a great deal of attention in the reduction of various polar bonds, finding numerous applications in synthetic chemistry [1–9]. Although enzyme catalysed TH using formate as hydrogen source has been taking place in aqueous media for billions of years [10], most man-made TH catalysts use organic media. The development of aqueous TH reactions is not only fundamentally interesting in terms of understanding enzymatic catalysis, but also offers economic and environmental benefits, as water is cheap and nontoxic. The research for aqueous TH reactions started in ca the 1980s [11,12], and great progress has been made since the 1990s [7,13–15]. In this review, we would like to give an account of our own work on TH in aqueous media.

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

### 2.1. ATH of ketones with HCOONa in water

Due to the importance of chiral compounds, a lot of attention has been paid to developing asymmetric transfer hydrogenation

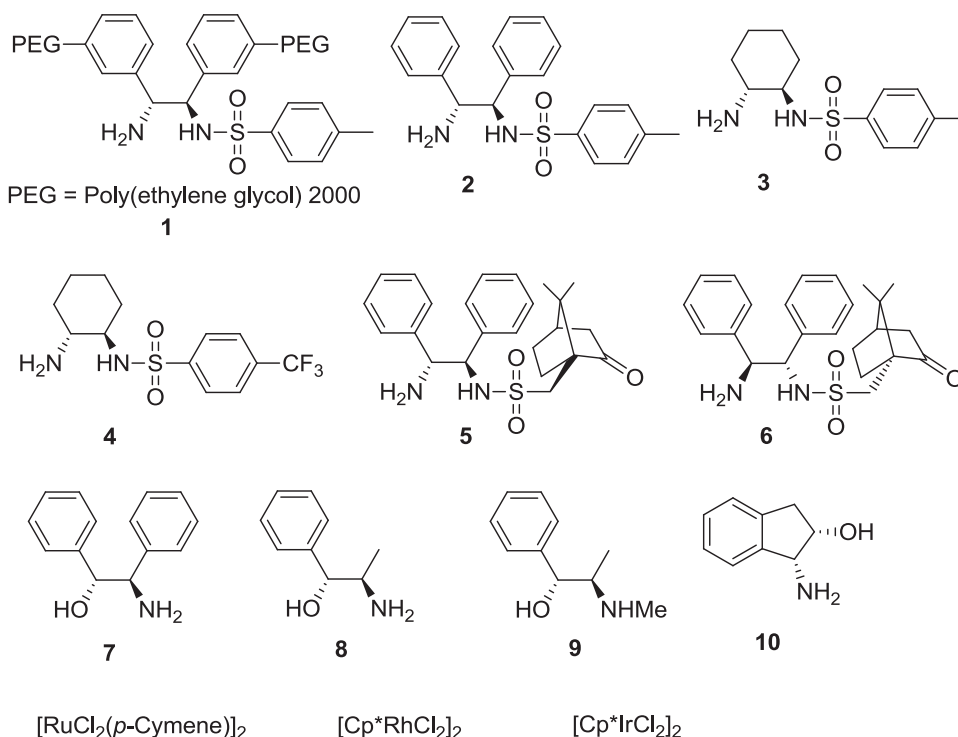
(ATH) systems. One milestone in the history of ATH is the discovery of the Ru-TsDPEN (TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine) catalyst by Noyori, Ikariya, Hashiguchi and co-workers in 1995, which afforded enantiomeric excess (ee) up to 99% for the asymmetric reduction of aromatic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

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

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

a molar substrate-to-catalyst ratio (S/C) of 100, the ketone was fully converted into (*R*)-1-phenylethanol in 95% ee after 1 h reaction time at 40 °C. In comparison, the reaction run in the HCOOH-NEt<sub>3</sub> (F/T) azeotrope afforded a conversion of less than 2% in 1 h, with full conversion requiring more than 10 h (97% ee) at 40 °C. This initial finding has since proven to be quite general, in that other ligands (shown in Scheme 1) which were designed for organic solvents are also effective for ATH in water with no need for modification or organic solvents [29–35]. In Table 1, we summarise the results obtained with various metal catalysts based on Ru, Rh and Ir, in the ATH of the benchmark substrate acp. The catalysts were usually generated from the ligand and a metal precursor at the reaction temperature in water without adding a base, for example Ru-2 from [RuCl<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 [20]. 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” (or in aqueous suspension). As shown in Table 1, the monotosylated diamines 1–6 all served as efficient ligands for the ATH of ketones in water, with almost full conversion and up to 99% ee reached in short reaction times (Entries 2–25, Table 1). Under the given conditions, the ligands 2 and 5/6 afforded the best enantioselectivity. The reaction was frequently carried out at an S/C ratio of 100; however, a high S/C ratio of 10,000 has been demonstrated to be feasible (Entry 7, Table 1).

In comparison with ATH in the azeotropic HCOOH-NEt<sub>3</sub> with or without water, ATH in aqueous HCOONa is much faster (Entries 1 and 2 vs 3 and 4, Table 1). This finding prompted us to explore factors that might lead to these contrasting results [30,34]. The clearest difference between the two systems was found to be the solution pH. Subsequently, the pH value was indeed found to be critical to the reaction rate and enantioselectivity [30]. As a matter of fact, efficient ATH can be performed with HCOOH-Et<sub>3</sub>N in water, provided

the ratio of HCOOH/Et<sub>3</sub>N is controlled such that the solution is close to neutral pH (Entries 4–7, Table 1). Interestingly, while β-aminoalcohol ligands were believed to be incompatible with formic acid as a reductant for ATH of ketones [36], the commercially available simple β-aminoalcohol ligands 7–10 do catalyse the ATH of acetophenone by HCOONa or HCOOH/NEt<sub>3</sub> in water, albeit with slower rates and lower enantioselectivities than those obtained with the diamine ligands (Entries 26–38, Table 1) [32].

We also reported examples of aqueous ATH with catalysts derived from [Cp\*RhCl<sub>2</sub>]<sub>2</sub> and [Cp\*IrCl<sub>2</sub>]<sub>2</sub> [29,31,33,35]. Detailed studies showed that these Rh and Ir catalysts have advantageous features compared with Ru catalysts, e.g. faster reaction rates or higher ees in some cases. Moreover, the reaction with Rh-diamine catalysts can be carried out effectively in the open air without degassing and/or inert gas protection throughout, rendering the reduction much more practical.

The metal-catalysed (M = Ru, Rh, Ir) ATH has since been applied to a wide range of aromatic ketones (Table 2). The reduction is easy to perform, affording the chiral alcohols with high ee's in a short reaction time for most of the substrates at S/C ratios from 100:1 to 1000:1. While the substrate ketones are generally water-insoluble, this does not appear to have a negative effect on the reaction rates. The reduction of most ketones proceeded significantly faster in water than in azeotropic HCOOH/Et<sub>3</sub>N. For example, the reduction of *p*-methoxyacetophenone, which is difficult under normal conditions, gave a conversion of >99% and an ee of 95% with Ru-2 in 1 h at an S/C ratio of 100 and a temperature of 40 °C [28]. With the azeotropic HCOOH/Et<sub>3</sub>N mixture as the reductant, the same catalyst required about 60 h to complete the reduction (97% ee) at 28 °C and an S/C ratio of 200 [17]. In the aqueous phase ATH, there appears to be no clear correlation between the electronic properties of substituents and the enantioselectivity, as shown by the reduction of *para*-OMe- and *para*-CF<sub>3</sub>-acetophenone with Ru-2, with both giving ~95% ee in 2 h.

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

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