



Integration of phase transfer catalysis into aqueous transfer hydrogenation

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ABSTRACT

Aqueous transfer hydrogenation using Noyori's catalyst (η^6 -arene)Ru(H)TsDPEN (TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine) was found to be dependent on the substrate/catalyst ratio. The reaction was suppressed when a large amount of substrate (acetophenone) was used. To relieve this substrate inhibition problem, common phase transfer catalysts were applied to transfer the formate anion from aqueous layer to organic substrate layer. Quaternary ammonium salts with long alkyl chains were shown to enhance the hydrogenation reactivities up to 5 times. The reaction conditions, including formate loading, phase transfer catalyst loading, amount of water, temperature, stirring speed and counterions, were optimized to afford the best catalytic activities.

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1. Introduction

The use of transfer hydrogenation based on metal complex catalysts to reduce alkenes, aldehydes, ketones, or imines has gained increasing attention [1–8]. Transfer hydrogenation in water was relatively unstudied until a few years ago [9–16]. Joo and co-workers [17] first reported aldehydes in aqueous conditions can be reduced to alcohols by HCOONa with Ru(II), Rh(I) and Ir(I) catalysts bearing water-soluble ligand (monosulphonated triphenylphosphine). Subsequently, both the Ogo group [18] and the Suss-Fink group [19,20] reported results on the transfer hydrogenation of using water-soluble half-sandwich Ru catalysts in aqueous HCOONa or HCOOH solutions. These half-sandwich Ru catalysts do not fall into the category of metal-ligand bifunctional catalysis since they lack the NH moiety. In 2001, Williams, Blacker and co-workers [21] first investigated the transfer hydrogenation with water-soluble, Noyori type catalysts. The catalyst was generated in situ by reacting TsDPEN ligand with [RuCl₂(*p*-cymene)]₂ dimer. In the same year, Chung's group [22] also reported a water-soluble arene Ru catalyst containing (*S*)-proline amide ligand. Both of these two bifunctional catalysts introduce hydrophilic ligands to enhance water solubility. The catalysis is biphasic when hydrophobic organic substrates are present, and the catalysts reside in the aqueous phase, thus promoting the solubility of the substrates by using surfactants is needed in most cases. In 2004, Xiao's

group [9] discovered that the unmodified Noyori's catalyst can efficiently perform transfer hydrogenation in aqueous HCOONa solution. Within 1 hour, acetophenone can be fully converted to the product with 1 mol% loading of Noyori's catalyst at 45 °C. In contrast, same reaction in HCOOH/NEt₃ azeotrope requires more than 10 h. Even though Noyori's catalyst has limited solubility in water, it is easily dissolved in warm water (45 °C) at the catalytic loading while insoluble in non-polar solvents such as diethyl ether at the catalytic loading. Thus separation of catalysts and products is easily achieved by simple extraction. Besides the high activity and easy workup operation, Xiao's group [23,24] also found the catalysis can be modulated by pH and the reaction can be carried out in air without degassing.

Although highly efficient hydrogenation can be achieved in the aqueous media, there are some potential concerns to be addressed. The catalyst is partitioned between the organic substrate phase and the aqueous phase, and it resides mostly in the organic phase. This accelerates the hydrogenation step due to the high concentration of catalyst. The regeneration step of the catalyst, however, may become problematic since the hydrogen source formate mostly resides in aqueous layer. Therefore, it is crucial to find solutions to alleviate this problem.

Phase transfer catalysis has proven to be very powerful in organic synthesis [25–28]. Organic-soluble quaternary ammonium or phosphonium cations have been found to be excellent agents for the transport of anions from aqueous phase to organic phase. It was shown the transfer hydrogenation of aromatic aldehydes with RuCl₂(PPh₃)₃ in aqueous HCOONa solution was enhanced by using catalytic amounts of quaternary ammonium salts [11].

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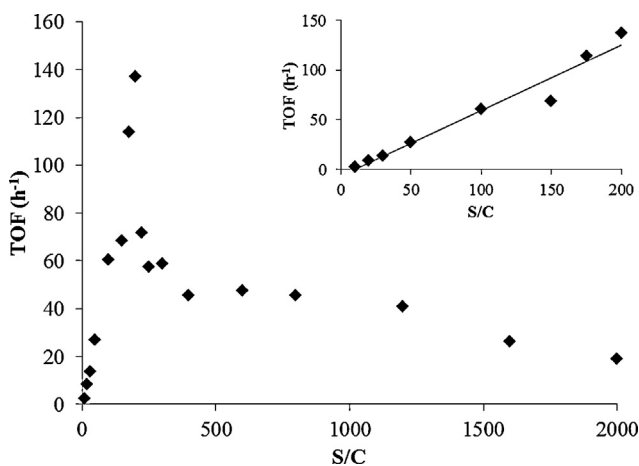


Fig. 1. Dependence of TOF on the S/C ratio (the upper insert shows the expanded S/C region between 0 and 200). Conditions: 0.01 mmol Ru(II) catalyst, 10 mmol HCOONa, $V_{\text{H}_2\text{O}} = 10 \text{ mL}$, 45°C .

A proposal was made that using phase transfer agents could possibly address the abovementioned concerns and might also illuminate more about the mechanism of the biphasic transfer hydrogenation. This paper reports the results of applying phase transfer catalysis into the aqueous transfer hydrogenation based on Noyori's catalyst, as well as the optimization of reaction conditions.

2. Results and discussion

2.1. Observation of substrate inhibition

Acetophenone was used as the model substrate throughout all the experiments. Fig. 1 shows the relationship between TOF (turnover frequency) and S/C (substrate/catalyst) ratio (10–2000). All TOF values were derived from the first hour reactions at different substrate loadings, i.e., $\text{TOF} = (\text{conversion}\%) \times (\text{S/C ratio}) / (\text{time}) \times 100$. A sharp peak is observed around $\text{S/C} = 200$ with the highest TOF ($\sim 140 \text{ h}^{-1}$). Below S/C of 200, TOF shows a reasonably linear relationship against S/C, which might indicate a first order dependence on the concentration of acetophenone, however, TOF dramatically declines to $\sim 60 \text{ h}^{-1}$ when S/C increases from 200 to 300. Beyond S/C of 300, TOF continues to decrease and a 20 h^{-1} TOF is observed at $\text{S/C} = 2000$. The sluggish reaction rates at high S/C ratios suggest the substrate inhibition effect.

Since acetophenone has limited solubility in water and a large amount of acetophenone would separate out from the aqueous phase, it is susceptible that phase separation might occur at $\text{S/C} = 200$ considering the sharp peak. The reaction mixture is homogeneous below this point while becomes heterogeneous beyond this point. This hypothesis, however, is neither in agreement with the solubility of acetophenone nor with the experimental observation. The solubility of acetophenone in water is 5.5 g/L at 25°C and 12.2 g/L at 80°C , therefore the solubility at 45°C is estimated as 7.6 g/L assuming it has linear dependence on the temperature. This corresponds to 76 mg (0.63 mmol) acetophenone in 10 mL water, from which $\text{S/C} = 63$ can be calculated. On the other hand, from the reaction tiny organic droplets were observed to be formed when $\text{S/C} = 100$ while the mixture was homogeneous below this limit.

The following hypothesis might explain the substrate inhibition phenomenon in Fig. 1. It is believed that the biphasic catalysis reaction takes place on the interface between organic substrate and water. Below the substrate solubility, catalysis occurs in a homogeneous solution; above the substrate solubility, organic substrate starts phasing out, however, the organic phase is dispersed to tiny droplets due to the high stirring rate. Since the catalyst has higher

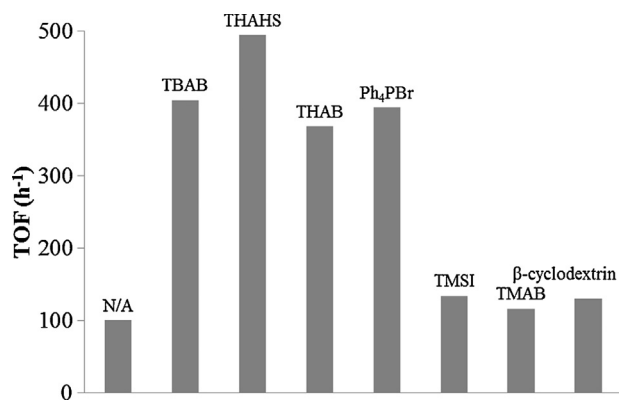


Fig. 2. Screening of different phase transfer catalysts. Conditions: 0.01 mmol Ru(II) catalyst, 50 mmol HCOONa, $V_{\text{H}_2\text{O}} = 10 \text{ mL}$, 45°C , $\text{S/C} = 2000$, phase transfer catalyst loading = 1 mmol, stirring rate = 700 rpm. TBAB: tetrabutylammonium bromide, THAHS: tetrahexylammonium hydrogensulfate, THAB: tetraheptylammonium bromide, Ph_4PBr : tetraphenylphosphonium bromide, TMSI: trimethylsulfonium iodide, TMAB: tetramethylammonium bromide.

solubility in organic substrate than in water, therefore these organic droplets start absorbing the catalyst. The reaction surface area is considerably large on these tiny but numerous droplets, thus the reaction rate continues to increase. However, these small droplets tend to converge together to form big droplets with higher loading of acetophenone. Under these conditions, reaction surface area dramatically decreases, explaining the sharp decrease of TOF. When the organic phase completely becomes the second layer, the concentration of catalyst in organic layer slowly decreases as more substrate is loaded in, explaining the decrease of reaction rates at a slow pace.

At high S/C ratio, the organic layer appears brown while the water layer appears light yellow, indicating most of the catalyst is located in the organic layer since the catalyst is the only colored species in the reaction mixture. The accumulation of the catalyst in the organic layer obviously enhances the hydrogenation step, but it also brings up a severe problem which is the inhibition of the regeneration step. After catalyzing the substrate, catalyst becomes the Ru amido intermediate which needs the hydrogen source formate to be regenerated, however, the formate primarily resides in aqueous layer which inhibits the regeneration step. To alleviate this problem, phase transfer catalyst is proposed to be able to transfer formate to the organic phase to speed up the regeneration step, therefore the catalytic performance can be enhanced.

2.2. Screening phase transfer catalyst

A high S/C ratio (2000) was applied to screen for the best phase transfer catalyst. Excess amount of HCOONa (50 mmol) was loaded to insure its sufficiency to regenerate the catalyst. Six common phase transfer catalysts were screened to study their structural effects on the reaction rates; the results are shown in Fig. 2. The data reveal the reaction rates can be enhanced up to 5 times by using quaternary ammonium or phosphonium salts with longer alkyl or aromatic chains. In comparison, the salts with short chains such as methyl group have almost no effect on the reaction rates. It is well known that longer alkyl chains afford the catalyst more lipophilicity, therefore imparting better ability to the salts for transporting the formate to the organic phase. This finding supports our hypothesis that the formate can be delivered to the organic layer to regenerate the catalysts, therefore alleviating the substrate inhibition problem.

An inverse phase transfer catalyst, β -cyclodextrin, was tested with the assumption that it can increase the solubility of acetophenone in water. β -Cyclodextrin has been shown to increase the

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