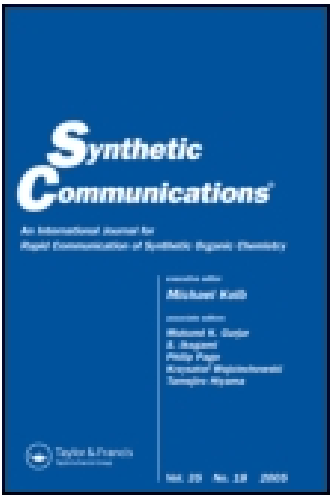

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ASYMMETRIC REDUCTION OF AROMATIC KETONES BY THE BAKER'S YEAST IN ORGANIC SOLVENT SYSTEMS

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ABSTRACT

The reduction of aromatic ketones to optically active alcohols, mediated by dried baker's yeast, proceeded in moderate conversion and good enantioselectivity (82 ~ 91% *e.e.*) in a number of organic solvents, including petroleum ether, toluene, chloroform, and tetrahydrofuran. A small amount of water (0.4 mL: g yeast) was required for the reaction to proceed. The water:yeast ratio and the solvent polarity were found to significantly influence the reactivity of the system.

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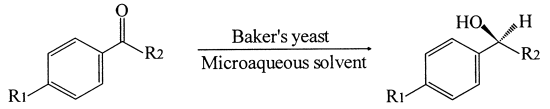

1 **2**

R_1 = -H, $-CH_3$, $-OCH_3$, -Br; R_2 = $-CH_3$, $-C_2H_5$, $-CH_2Br$

Figure 1.

Yeast is often employed as a reducing agent in organic synthesis, such as asymmetric reduction of prochiral β-ketoesters and aromatic ketones.[1,2] One of the major drawbacks associated with yeast-mediated reduction reactions has been the necessity for an aqueous reaction medium that restricts the usefulness of the system for water-insoluble compounds or compounds containing water labile functionality. A number of reports have appeared recently that indicate that the reducing capability of yeast could be preserved in an organic solvent if the yeast is first immobilized.[3–5] Also, it has been reported that free (unimmobilized) yeast is capable of the reduction of α-ketoesters[6] in benzene and β-ketoesters[7] in petroleum ether. Our work was to perform the asymmetric reduction of aromatic ketones **1** by direct use of dried baker's yeast in organic solvent systems (Fig. 1). We have extended our investigation of the yeast-mediated reduction from the medium of petroleum ether to a range of solvents with different polarity. The influence of various water:yeast ratios on the reactivity of the biocatalytic system has also been examined.

EFFECT OF WATER ON REACTIVITY

No reaction was observed when aromatic ketones **1** were stirred in dry petroleum ether in the presence of yeast (1 g:mmol-substrate) at room temperature for 24 h. However, the addition of small amounts of water to the reaction system greatly contributed to the increased reduction of **1**. The most suitable amount of water was 0.4 mL:g-yeast. Perhaps larger amounts of water would improve the substrate conversion. Nevertheless, the amount of 0.5 mL-water/g-yeast resulted in obvious swelling and adhesion of dried baker's yeast. As a result, the reaction proceeded hardly and the conversion went contrary to our expectation. The same effect was also observed when the reaction was carried out in chloroform and toluene (Fig. 2). A water:-yeast ratio (mL:g) of 0.4 was thus considered to be the optimum ratio for the yeast-mediated reduction of aromatic ketones **1** in these solvents.

The yeast-catalyzed reduction of carbonyl groups involves the concomitant oxidation of the coenzyme NAD(P)H to $NAD(P)^+$. In aqueous

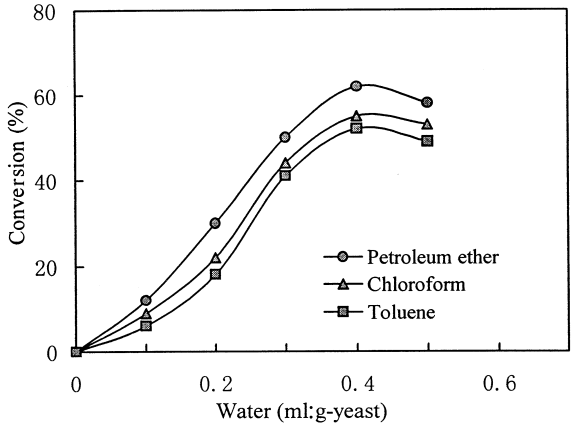

Figure 2. Effect of water on the yeast-mediated reduction of acetophenone. (5 mmol acetophenone, 5 g dried yeast, 100 mL solvent, room temperature, 24 h. Conversion was calculated from GC ratio of substrate to product.)

systems, various metabolic pathways within the yeast continuously recycle the $NAD(P)^+$ back to NAD(P)H, ensuring a continuous supply of the coenzyme. In completely anhydrous organic solvents, however, regeneration of the coenzymes cannot occur and the extent of reduction is limited by the amount of available NAD(P)H in the yeast. The yeast is therefore providing both the catalyst (oxidoreductase enzyme(s)) and the reagent (NAD(P)H) for the reaction. Small amounts of water enabled the recycling of the coenzymes to satisfy the necessity of the reaction process in our organic solvent systems.

From the above results, it is obvious that the water:yeast ratio indeed affects the reaction significantly. It has been shown lately that an enzyme molecule becomes fully hydrated when surrounded by a few layers of water molecules.[8,9] It is thought that this hydration layer acts as a micro-reactor for the enzyme and protects it from any detrimental effects of the bulk organic solvent. It therefore appears that 0.4 mL water:g yeast is the optimum amount of water required to form this protective layer around the yeast enzymes for the reduction of aromatic ketones **1**.

EFFECT OF SOLVENT POLARITY ON REACTION

The extent of interaction between the organic solvent and the essential water surrounding an enzyme depends on the nature of the solvent employed. Hydrophilic solvents usually tend to remove or distort this

Table 1. Effect of Solvents on Conversion and Enantioselectivity[a]

Solvent	log *P*	Conversion[b] (%)	*e.e.*[c] (%)
Petroleum ether	3.5	62	90
Toluene	2.5	52	86
Chloroform	2.0	55	91
Tetrahydrofuran	0.49	50	85
Ethyl acetate	0.68	15	/
Ethanol	−0.24	< 5	/

[a]5 mmol acetophenone, 5 g dried yeast, 100 mL solvent, 2 mL water, room temperature, 24 h;
[b]calculated from GC ratio of substrate to product;
[c]determined by chiral HPLC analysis using a Daicel chiralcel OD column.

protective water layer and cause inactivation of the enzyme. While hydrophobic solvents are less able to interfere with the water and thus are expected to be the most suitable nonaqueous media for enzymatic reactions. Our results have also lead to the same conclusion (Table 1).

The partition coefficient of a solvent between water and *n*-octanol has been proposed as a measure of the polarity of the solvent.[10] The logarithm of the partition coefficient (log *P*) has been shown to correlate reasonably well with the reactivity of a variety of enzymes in organic solvents.[8,11] As expected, enzymes were more active in nonpolar solvents (log $P > 2$) and the results from the yeast-mediated reduction of acetophenone in variety of solvents followed this trend (Table 1). In fact, the reaction proceeded smoothly in the nonpolar solvents such as petroleum, ether, toluene, and chloroform, while product of the reaction was hardly detected in solvents of higher polarity. However, the activity of yeast in tetrahydrofuran was rather surprising, given the low log *P*value of this solvent. The higher-than-expected activity of enzymes in diethyl ether has been previously noted.[10] Tetrahydrofuran is similar to diethyl ether in many ways.

CONVERSION AND ENANTIOSELECTIVITY

In aqueous solvents, the yeast-mediated reduction of substituted acetophenones afforded (S)-1-arylethanols in moderate yields and *e.e.* values between 82% and 96%.[1] In our organic solvent systems, the yeast-mediated reduction of acetophenone proceeded in moderate conversion and also resulted in the formation (> 85% *e.e.* of (*S*)-1-phenylethanol (Table 1). The other aromatic ketones had similar results (Table 2). No influence on the

Table 2. The Results of Asymmetric Reduction of Several Aromatic Ketones

Entry	R_1	R_2	Conversion[b] (%)	*e.e.*[c] (%)	Configuration
1	−H	$-CH_3$	62	90	S
2	−H	$-C_2H_5$	59	88	S
3	$-CH_3$	$-CH_3$	62	89	S
4	$-OCH_3$	$-CH_3$	54	82	S
5	−Br	$-CH_3$	63	90	S
6	−H	$-CH_2Br$	51	85	R

[a]See also Fig. 1. Conditions: 5 mmol substrate, 5 g dried yeast, 100 mL petroleum ether, 2 mL water; room temperature, 24 h;
[b]calculated from GC ratio of substrate to product;
[c]determined by chiral HPLC analysis using a Daicel chiralcel OD column.

steric course of the reduction was observed when the group R_1 and R_2 of aromatic ketones **1** were changed, but there were some changes in the conversion ratios of substrates and enantiomeric excesses of products. The reduction of α-bromoacetophenone also had the same steric course as the reduction of the other ketones although (R)-1-phenyl-2-bromoethanol was obtained (Table 2, Entry 6).

GENERAL PROCEDURE FOR REDUCTION OF AROMATIC KETONES[12]

In a 250-mL round-bottom flask was placed 0.60 g (5 mmol) acetophenone, 100 mL petroleum ether, 2.5 mL water, and 5 g yeast, and the reaction was stirred at room temperature. After 24 h, the reaction mixture was filtered to remove the yeast. Being dried over anhydrous magnesium sulfate, the filtrate was concentrated with a rotary evaporator under reduced pressure. The oily residue was refined by silica gel column chromatography using chloroform as an eluant. 1-Phenylethanol was finally obtained. Enantiomeric excess of (*S*)-1-phenylethanol was 90%, determined by chiral HPLC analysis using a Daicel chiracel OD column. Conversion, calculated from GC ratio of substrate to product, was 62%.

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12. Baker's yeast was purchased from Oriental Yeast Co., Ltd., Japan. Chemicals such as acetophenone and petroleum ether were purchased from Shanghai Chemical Reagent Co., P.R. China. The enantiomeric excesses of the products were determined by chiral HPLC analysis using a chiralcel OD column (Daicel Chemical Industry, Ltd., Japan) with hexane/propane-2-ol (98:2 ~ 95:5) as a mobile phase. Gas chromatography was performed with a 25-m PEG-30M bonded column at 90°C.

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