



# Use of surfactants in water-soluble ruthenium(II) complex-catalyzed asymmetric hydrogen-transfer reduction of aromatic ketones

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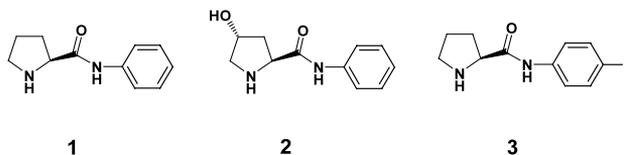
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**Abstract**—The introduction of surfactants to the water-soluble Ru(II)-catalyzed asymmetric transfer hydrogenation of ketones led to an increase of the catalytic activity and reusability compared to the catalytic systems without surfactants © 2002 Elsevier Science Ltd. All rights reserved.

Catalytic asymmetric hydrogenation using a chiral ruthenium complex is a powerful method for producing chiral alcohols and chiral amines with excellent enantioselectivity.<sup>1</sup> Recently, the use of homogeneous catalysts in aqueous solution and on liquid supports has become feasible, representing a tremendous opportunity for the practice of green chemistry.<sup>2</sup> As a consequence, there has arisen considerable interest in the development of water-soluble catalytic systems which allow catalytic reactions to occur in water.<sup>3</sup> However, novel catalytic systems that enable the use of water as a solvent in the asymmetric transfer hydrogenation, are not well developed.<sup>4</sup> The catalytic reaction occurs at the interface between water and the organic layer because of the insolubility of organic substrates in water. Thus, the catalytic activity and/or enantioselectivity in aqueous solution were usually low compared to those of the homogeneous catalytic system.<sup>5</sup> In order to overcome this drawback, phase-transfer catalysts or surfactants, or modified cyclodextrins<sup>6</sup> were added to the reaction mixture. Recently, we were successful in carrying out asymmetric hydride transfer reduction of ketones in aqueous solution using ruthenium complexes with chiral amino amide ligands.<sup>7</sup> However, the catalytic activity and reusability were not satisfactory. Thus, the catalytic reaction was reexamined more closely by screening surfactants, chiral ligands, and substrates. Herein we report our new findings, especially the effect of surfactants on the catalytic activity.

The asymmetric transfer hydrogenation reactions of ketones were carried out by using amino amides **1–3** (Chart 1),  $[\text{RuCl}_2(p\text{-cymene})]_2$ , and  $\text{HCOONa}$  in water. In order to confirm the effect of surfactants on the catalytic activity, we introduced several surfactants to the ruthenium-catalyzed asymmetric hydrogen-transfer reduction of 2'-methoxy acetophenone. We screened surfactants, chiral ligands, and the reaction temperature to optimize the reaction conditions (Table 1). When the substrate to catalyst (S/C) ratio was 10, the reaction without surfactants proceeded smoothly at 30°C. The addition of sodium dodecyl sulfate (SDS) to the reaction mixture shortened the reaction time from 4 to 1.5 h but did not affect the e.e. value. When the chiral ligands **1–3** were screened with S/C of 100 at 30 and 40°C, the best result was obtained with ligand **3**. Thus, ligand **3** was chosen as a ligand. The increase of the reaction temperature from 30 to 40°C dramatically shortened the reaction time from 24 to 5.5 h. When the surfactant was altered to cetyltrimethylammonium bromide (CTAB) and tetrabutylphosphonium bromide (TBPB), the best result was obtained with SDS. Using SDS and ligand **3** at 40°C, the amount of  $\text{HCOONa}$  used was screened. When the amount of  $\text{HCOONa}$  was changed from 10 to 5 equiv., no noticeable differences were observed. However, when the amount of



**Chart 1.** Proline aromatic amide ligands.

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**Table 1.** Optimization of asymmetric hydrogenation of 2'-methoxyacetophenone by using surfactants<sup>a</sup>

Entry	L*	S/C	HCOONa (equiv.)	Surfactant	T (°C)	t (h)	Conv. (%)	E.e. (%)
1	1	10	10		30	4	99.8	95
2	1	10	10	SDS	30	1.5	97	95.8
3	2	10	10	SDS	30	1.5	99	95.7
4	3	10	10	SDS	30	1.5	99	95.8
5	1	100	10	SDS	30	24	12.7	93.1
6	3	100	10	SDS	30	24	93.4	93.6
7	1	100	10	SDS	40	5.5	92.4	91.8
8	2	100	10	SDS	40	5.5	87.5	94.3
9	3	100	10	SDS	40	5.5	99.5	93.9
10	3	100	10	CTAB	40	6	13	93.3
11	3	100	10	TBPB	40	6.5	75	93.3
12	3	100	5	SDS	40	5.5	98.5	93.9
13	3	100	2	SDS	40	7	41	86.9
14	3	100	5	SDS	50	3	70	91.6
15	3	100	5	–	40	5.5	39.5	93
16	3	1000	5	SDS	40	24	43.4	93.6
17 <sup>b</sup>	3	1000	–	–	40	24	34	94.5
18	3	400	5	–	40	24	20.5	92
19	3	400	5	SDS	40	16	99.7	94.1

<sup>a</sup> M/L\* = 1 and surfactant 2 mol%. Conv. (%) and e.e. (%) were determined by a chiral column CP Chirasil DEX CB 25 m×0.32 μm and the configuration *R* was determined by the retention time.

<sup>b</sup> In dichloromethane, a mixture of HCOOH/Et<sub>3</sub>N (5/2 azeotrope distilled) was used as a hydrogen source.

HCOONa was lowered to 2 equiv., the catalytic activity and the enantioselectivity were considerably reduced. Thus, the amount of HCOONa must be over 5 equiv. When the reaction temperature was increased to 50°C under the same reaction conditions, the catalytic species changed to turbid and acquired a brownish color. After 3 h of the reaction, the conversion rate was 70%. Increasing the reaction time did not improve the reaction yield. Thus, the reaction temperature was fixed at 40°C. The optimum reaction conditions were as follows: ligand **3**, SDS, 5 equiv. HCOONa, and at 40°C. In order to calculate the maximum turnover number under the optimum reaction conditions, the S/C was raised to 1000. After the reaction, 43.4% of the conversion yield and 93.6% of the e.e. value were obtained. A prolonged reaction time (3 days) did not result in increasing the conversion yield. When the reaction (S/C = 100) was carried out without using surfactants under the optimum reaction conditions, the conversion yield and e.e. were 39.5 and 93%, respectively. When S/C was 400, the conversion yield and e.e. were 20.5 and 92%, respectively. Thus, the conversion yield was highly dependent upon the presence of surfactants, but the e.e. value was invariant. When the reaction (S/C = 1000) was carried out by using the homogeneous catalyst in dichloromethane, the conversion yield was 34% and the e.e. was 94.5%. A prolonged reaction time (3 days) did not improve the conversion yield. Thus, the introduction of the surfactant to the catalytic system improved the conversion yield with even better results than for the homogeneous reaction.

Heterogeneous catalysts often suffer extensive leaching of active metal species during reactions and eventually lose their catalytic activity.<sup>8</sup> Many organic substances are insoluble and many reactive substrates and catalysts are decomposed or deactivated by water. Thus, recov-

ery and reusability of the catalytic system were tested by carrying out consecutive cycles with the same catalyst (S/C = 400) in aqueous solution, carefully separated from the organic phase at the end of each run (Table 2). At the end of each run, substrates and 1.0 equiv. HCOOH were added. Interestingly, the reusability of the catalytic system was quite dependent upon the use of formic acid. When pure formic acid was used as a hydrogen source, in the second run the conversion yield (99%) and the e.e. (94.2%) were quite good, as in the first run (99.7% and 94.1% e.e.). But, in the third run, the conversion yield was only 8% and the e.e. was not determined. However, when 0.5 equiv. of 1.0 M HCOOH was used, the catalytic system could be used in the fourth run even though the conversion yield was lowered to 35.8% and the e.e. was 89%. Thus, the overall turnover number could be increased to 1270.

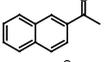
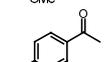
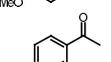
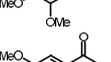
**Table 2.** Recycling test<sup>a</sup>

Recycle no.	Additive <sup>b</sup>	t (h)	Conv. (%)	E.e. (%)
1		16	99.7	94.1
2	99% HCOOH	30	99	94.2
3	99% HCOOH	48	8	N.D.
1		15.5	99.7	94.2
2	1 M HCOOH	23	99.7	94.6
3	1 M HCOOH	25	82	94.3
4	1 M HCOOH	39	35.8	89

<sup>a</sup> The reaction conditions were the same as used in entry 19 of Table 1.

<sup>b</sup> 1 equiv. of 99% HCOOH or 0.5 equiv. 1 M HCOOH was added.

**Table 3.** Asymmetric transfer hydrogenation of some aromatic ketones<sup>a</sup>

Entry	Substrate	t (hr)	Conv. (%)	E.e. (%)
1		18	98.3	68.6
2		18	62.9	53.7
3		18	85.3	89.4
4		18	44	90.6
5		15	67	89
6		18	69	88
7		17	75.4	58.8
8		16	95	60
9 <sup>b</sup>		20	96.2	41.1
10 <sup>b</sup>		19	99	94.1

<sup>a</sup> Chiral ligand **3**, M/L<sup>\*</sup>=1, S/C=400, HCOONa 5eq. SDS 2mol%, and 40°C. Conv. (%) and e.e. (%) were determined by a chiral column CP Chirasil DEX CB 25m x 0.32µm. The configuration (R) was determined by the retention time. <sup>b</sup> The configuration was not determined.

We have also examined the hydrogen-transfer reaction of other aromatic ketones (Table 3). For the hydrogen-transfer reaction of acetophenone (entry 1), the conversion yield (98.3%) was good but the e.e. (68.6%) was poor. For the hydrogen-transfer reaction of propiophenone (entry 2), the conversion yield (63%) and the e.e. (53.7%) were not comparable to those of 2'-acetophenone. Thus, as the steric bulkiness increased, the conversion yield and the enantioselectivities decreased. For the hydrogen-transfer reaction of 2'-acetonaphthone (entry 3), the conversion yield was 85.3% and the e.e. was 89.4%. The enantioselectivity was highly improved. For the hydrogen-transfer reaction of 2'-substituted acetophenones (entries 4–6), the conversion yields were poor but the e.e. values were quite high, ca 90%. Thus, the *ortho*-substitution by Me, Cl, and Br decreased the conversion yield, but increased the enantioselectivity. For the hydrogen-transfer reaction of 3'-methoxyacetophenone and 4'-methoxyacetophenone (entries 7 and 8), the conversion yields (75 and 95%, respectively) were quite different from each other but the e.e. values were quite similar (59–60%). When the hydrogen-transfer reaction of 3',4'-dimethoxyacetophenone (entry 9) was compared to that of 2',5'-dimethoxyacetophenone (entry 10), the conversion yields were virtually the same but the enantioselectivities (41 and 94%, respectively)

were quite different from each other. Thus, the methoxy group on the *ortho* position dramatically improved the enantioselectivity. The order of enantioselectivities for acetophenone derivatives is 2'-methoxy > 2'-Me ~ 2'-Br ~ 2'-Cl ≫ H. This observation is quite similar to that for the homogeneous system although the details differ.<sup>9</sup> When (1*S*,2*S*)-DPEN-Ts was used as a ligand in the homogeneous catalytic system, quite a low conversion yield and poor enantioselectivity were obtained for *ortho*-substituted aromatic ketones.<sup>10</sup>

This work shows that the introduction of surfactants to the water-soluble ruthenium-catalyzed system improves the catalytic activity and reusability and the resulting catalytic system is quite effective for the asymmetric hydrogen transfer of *ortho*-substituted aromatic ketones.

### A typical procedure for catalytic reactions

Ruthenium complex [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (3.1 mg) and chiral ligand **3** (2.1 mg) were dissolved in 10 ml of water. After the solution was stirred at 40°C for 1 h, 5 equiv. HCOONa was added to the solution. After the solution was stirred for 10 min, 2'-methoxyacetophenone (4.0 mmol) and SDS (23 mg, 2 mol%) were added to the solution. The resulting solution was allowed to react for the predetermined reaction time. After reaction, a mixture solvent (3×5 ml) of *n*-hexane and diethyl ether (v/v, 10:1) was added to extract organic materials. GC analysis of a sample aliquot then determined the conversion rate and the enantioselectivity.

### Recycling test

After the organic materials were extracted, substrate, surfactant, and HCOOH were added to the aqueous solution. The solution was allowed to react for the predetermined reaction time.

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