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Chiral Surfactant-Type Catalyst for Asymmetric Reduction of Aliphatic Ketones in Water

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Supporting Information

ABSTRACT: A novel chiral surfactant-type catalyst is developed. Micelles formed in water by association of the catalysts themselves, and this was confirmed by TEM analyses. Asymmetric transfer hydrogenation of aliphatic ketones catalyzed by the chiral metallomicellar catalyst gave good to excellent conversions and remarkable stereoselectivities (up to 95% ee). Synergistic effects between the metal-catalyzed center and the hydrophobic microenvironment of the core in the metallomicelle led to high enantioselectivities.

As the demand for environmentally friendly methods increases, water as a solvent is of great interest. Although water has the advantages of being safe, nontoxic, environmentally benign, and inexpensive, the insolubility of many organic compounds in water limits its application in various chemical transformations. An efficient way to address this matter is to introduce surfactant additives or use surfactant-like catalysts. Generally, amphiphilic surfactants can form micelles in water as microreactors[1] to increase not only the solubility of nonpolar substrates and catalysts but also the reactivity and stereoselectivity of reactions due to the hydrophobic interaction and the preorganizing function of micelles.[2] Thus, the use of micellar surfactants as additives or catalysts has attracted considerable attention in aqueous reactions in recent years.[2−8] However, there are few reports of successful asymmetric synthesis with high enantioselectivity in chiral micellar systems,[2,4−6] especially metallomicellar catalysts with chiral surfactants as the ligands.[2,5b] Actually, lower enantioselectivity was usually observed with chiral metallomicellar catalysts compared to the corresponding chiral molecular catalysts in micelles.[5,6]

Asymmetric reduction of ketones catalyzed by transition-metal complexes is a key and practical technology for synthesis of optically active alcohols. Although asymmetric catalyzed reduction of aromatic ketones is well documented, the development of efficient catalytic systems for asymmetric reduction of aliphatic ketones with high enantioselectivities and wide-ranging substrates is a challenge.[9−11] Recently, asymmetric transfer hydrogenation (ATH) of ketones has attracted increasing attention due to its safety and easy operation.[12] Among the catalysts explored so far, the Noyori−Ikariya catalysts (Ru, Rh, and Ir complexes of TsDPEN (**1**, Figure 1))[12d,e] and their modifications have been found to be highly efficient for ATH of aromatic ketones,[12a−c] but limitations arise in the case of aliphatic ketones.[11a−d] Herein, we report a novel chiral surfactant-type metal catalyst with ligand **4** for efficient ATH of aliphatic ketones in neat water in air.

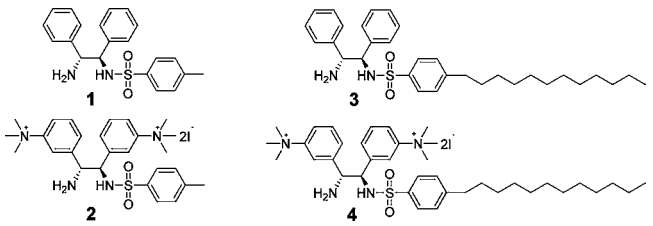

Figure 1. Chiral diamine ligands.

In our previous work, we found that the reactivity and selectivity for ATH of aromatic ketones and imines catalyzed by lipophilic[7] and hydrophilic[8] catalysts, respectively, could be improved by adding cationic surfactant CTAB to form micelles in water, around which positive charges of the surfactants elevated the concentration of formate ions via the electrostatic attraction between them. Moreover, our preliminary experiments indicated that, in the presence of surfactant CTAB or SDS, the selectivy (54% ee with either surfactant) of ATH of octan-2-one (**7b**) was markedly improved with a cationic water-soluble ligand **2** (Figure 1) in water (Table 1, entries 4 and 5). Anionic surfactant SDS provided lower conversion (60% vs 94%), although in the absence of surfactant the reduction was sluggish (15% conv) and 35% ee was obtained (entry 3), similar to the results obtained with lipophilic ligands **1** (37% ee, entry 1) and **3** (39% ee).[11c] However, only a small increase in ee was observed with CTAB as surfactant using **1** or **3** as ligand (42% ee with either) in ATH of **7b** (entries 2 and 6). These observations inspired us to develop amphiphilic surfactant-type ligand **4** (Figure 1) based on chiral and cationic **2** as the

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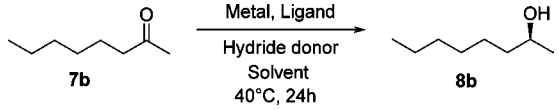
Table 1. ATH of Octan-2-one with Different Metal Precursors and Ligands in Different Solvents



entry	ligand	metal	solvent	conv.[b] (%)	ee[c] (%)
1	**1**	Rh	H_2O	93	37 *S*
2[d]	**1**	Rh	H_2O	97	42 *S*
3	**2**	Rh	H_2O	15	35 *S*
4[d]	**2**	Rh	H_2O	94	54 *S*
5[e]	**2**	Rh	H_2O	60	54 *S*
6[d]	**3**	Rh	H_2O	99	42 *S*
7	**4**	Ru	H_2O	72	40 *S*
8	**4**	Ir	H_2O	98	82 *S*
9	**4**	Rh	H_2O	94	84 *S*
10[d]	**4**	Rh	H_2O	98	75 *S*
11	**4**	Rh	CH_2Cl_2	5	7 *S*
12	**4**	Rh	*i*-PrOH	22	33 *S*

[a]Reaction conditions: see Supporting Information. [b]Conversion was determined by GC analysis using decane as internal standard. [c]Enantiomeric excess was determined by GC analysis. The absolute configuration was assigned by comparing the retention time (GC) with (*S*)-octan-2-ol. [d]10 mol% CTAB was added. [e]10 mol% SDS was used.

hydrophilic headgroup, of which metal complexes might form chiral metallomicelles in water by self-association.

Precatalyst **5** (Figure 2) was prepared by mixing **4** and $[Cp^*RhCl_2]_2$ in water at 40 °C for 2 h, and then it was applied

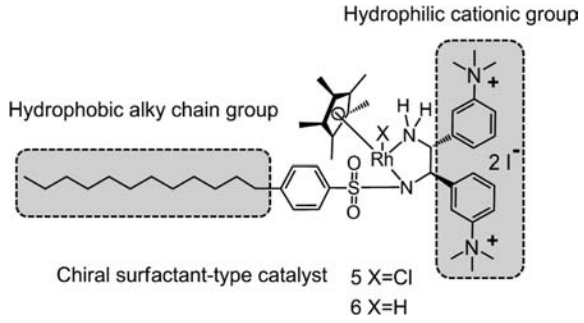


Figure 2. Structures of precatalyst **5** and catalyst **6**.

to catalyze ATH of **7b** with HCO_2Na as hydrogen source in water. To our surprise, excellent conversion (94%) and high enantiomeric excess (84%) were obtained in 24 h with catalyst **6** (Figure 2) produced *in situ* (entry 9). Different metal precursors, $[RuCl_2(p\text{-cymene})]_2$, $[Cp^*IrCl_2]_2$, and $[Cp^*RhCl_2]_2$, were tested using **4** as a ligand, and the Rh complex turned out to be the most selective (84% ee, entry 9 vs entries 7 and 8). It is interesting that the ee decreased (75%) with catalyst **6** when CTAB was added to the reaction mixture (entry 10). In organic media, very low conversion (5%) and ee value (7%) were obtained in dichloromethane (entry 11), and 22% conversion and 33% ee were obtained in isopropanol (entry 12).

Furthermore, the reaction was strongly dependent on reaction temperature (Figure 3). With increasing temperature, the ee value gradiently decreased. The highest ee value (90%) was obtained at 0 and 5 °C; however, the conversion was low (42%) at 0 °C. The conversion increased when the temperature

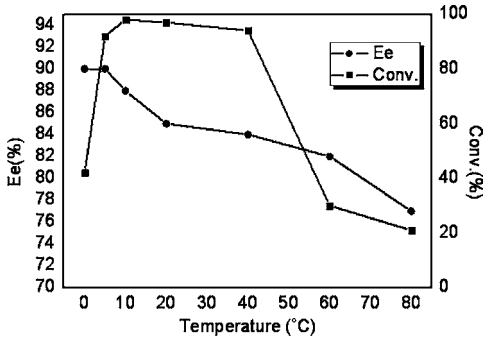


Figure 3. Effect of temperature on ATH of octan-2-one catalyzed by Rh−**4** complex.

was promoted from 0 to 10 °C and then decreased. A dramatic drop in conversion was observed on going from 40 to 60 °C. It was possible that increasing the reaction temperature disfavored micelle formation.[13]

The above results showed that the reaction may proceed in chiral metallomicelles only formed from surfactant-type Rh−**4** complexes in water (Figure S1). In fact, spherical micelle particles were observed during the reaction by TEM analyses. Figure 4 shows TEM micrographs of precatalyst **5**, catalyst **6**,

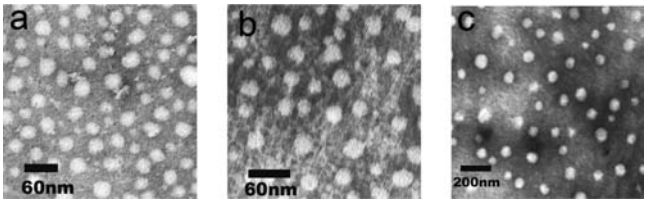


Figure 4. TEM images of micelles of (a) precatalysts, (b) catalysts, (c) and reaction mixture.

and the reaction mixture.[14] The micelle size in the reaction mixture, with an average diameter of 66.8 ± 15.6 nm, was bigger than in both precatalyst **5** (20.9 ± 2.5 nm) and catalyst **6** (22.3 ± 5.7 nm) because **7b** was incorporated into the metallomicelles.

We also found that the alkyl length of aliphatic ketones greatly influenced the reactivity and enantioselectivity (Table 2). For linear alkyl methyl ketones (**7a**−**7f**), the enantioselectivity increased with the length of the alkyl chain from 76% to 94% ee (entries 1−5), but the ee did not increase from **7e** to **7f**. These results show that there may be a hydrophobic interaction between the long alkyl group of aliphatic ketones and the long chain of **6** in the metallomicelle (Figure 5). When the methyl group of **7c** was substituted with ethyl and propyl groups, the reactivities were very low, and the reaction proceeded at a lower molar ratio of substrate to catalyst (s/c = 50), in 74% conversion with 81% ee for **7g** and in 45% conversion with 72% ee for **7h** after 48 h (entries 7 and 8). For the alkyl methyl ketones with terminal branch chains **7i** and **7j**, **7i** gave better results than the corresponding linear ketone **7a**, and even **7j** was comparable to **7b** in both rate and selectivity (entries 9 and 10 vs entries 1 and 2). A wider range of aliphatic ketones (**7k**−**7q**), even bearing functional groups, has successfully given 80−95% ee (entries 11−17). **7m**, with a cyclic hexyl group, was reduced in 95% ee, which was higher than that of **7b** (90% ee) with a linear hexyl group (entry 13 vs 2). **7o** was hydrogenated in 92% ee to give *tert*-butyl 3-

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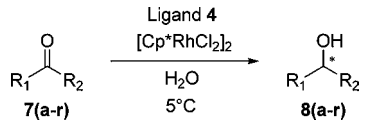
Table 2. ATH of Ketones with Surfactant-Type Catalyst[a]



entry	substrate	time (h)	conv.[b] (%)	ee[c] (%)
1	7a	37	98	76 *S*
2	7b	24	92	90 *S*
3	7c	24	97	92 *S*
4[d]	7d	48	97	92 *S*
5[d]	7e	48	93	94 *S*
6[d]	7f	48	74	94 *S*
7[e]	7g	48	75	81 *S*
8[e]	7h	48	45	72 *S*
9	7i	24	95	84 *S*
10	7j	24	97	91 *S*
11	7k	37	96	80 *S*
12[f]	7l	72	99	90(*Z*) 87(*E*)
13	7m	24 24[g]	93 94[g]	95 *S* 92 *S*[g]
14	7n	48	99	90 *S*
15	7o	48 24[h]	91 87[h]	92 *R* 92 *R*[h]
16	7p	37	90	86 +
17	7q	24	96	83 *S*
18	7r	48 24[g]	97 99[g]	97 *R* 96 *R*[g]

[a]Reaction conditions: 0.004 mmol of ligand **4**, 0.002 mmol of $[Cp^*RhCl_2]_2$, 1 mL of H_2O, 2 mmol of HCOONa, 0.4 mmol of ketone, 5 °C, s/c = 100. [b]Conversion was determined by GC analysis using decane as internal standard. [c]Enantiomeric excess was determined by GC analysis. Absolute configurations: see Supporting Information. [d]2 mL of H_2O was used for the solid substrate. [e]s/c = 50. [f]*Z*/*E* ratio was 38.8:61.2 for both **7l** and **8l**, and the configuration of both *E*- and *Z*-isomers was (*S*)-form. [g]At 40 °C. [h]At 10 °C.

hydroxylpyrrolidine-1-carboxylate (**8o**) as a key intermediate of factor Xa inhibitor DX-9065a (entry 15).[15] Acetophenone (**7r**) was also tested for the reaction scope, and 97% ee was obtained (entry 18). These results indicated that catalyst **6** was effective for the reduction of not only aliphatic ketones but also aromatic ketones.

The absolute configuration of 1-phenylethanol (**8r**) was opposite to those of aliphatic alcohols except for **8o** (Table 2). For comparison, the Rh complex of (*R*,*R*)-TsDPEN (**1**) was also used for reduction of **7r** and **7m**, to give (*R*)-**8r** in 97% ee and (*S*)-**8m** in 82% ee, which was much higher than the 37% ee of (*S*)-**8b** (Table 1, entry 1) in water at 40 °C. The identical

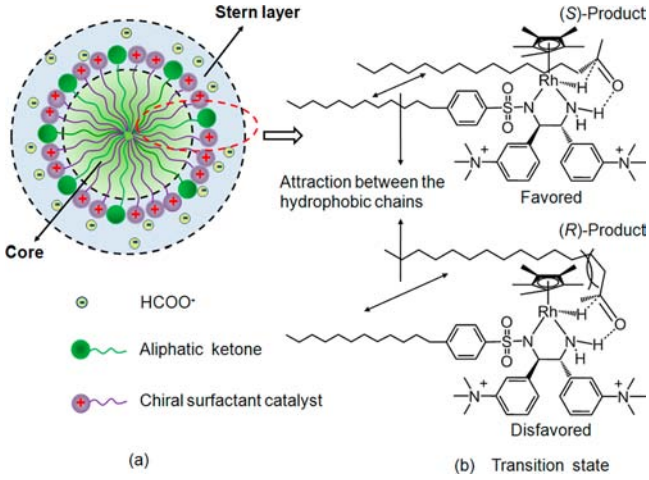


Figure 5. Proposed mechanism of reduction of aliphatic ketones in the metallomicelle formed from catalyst **6**. (a) Schematic representation of the metallomicelle. (b) Probable transition states of the reaction.

stereochemistry implies that the reaction mechanism of metallomicellar catalyst **6** resembles the concerted process suggested by Noyori and co-workers.[16] In contrast to aryl alkyl ketones, for which a transition state was stabilized by CH−π interaction between the substrate and the catalyst (Figure S7),[17] we propose that in this transition state, the large alkyl group of the aliphatic ketone is far away from the Cp* (1,2,3,4,5-pentamethylcyclopentadiene) ligand of the catalyst, due to steric hindrance between them,[17c] leading to (*S*)-aliphatic alcohols (Figure 5). Furthermore, the steric interaction allows the large alkyl group to be orientated toward the long-chain sulfonylamino group of the catalyst and thereby the core of the self-assembled metallomicelle.[16a] On the other hand, amphiphilic catalyst **6**, bearing a large hydrophilic headgroup with two positive charges, may favor the formation of metallomicelles, leading to strongly hydrophobic interaction between the chain of the catalyst and the alkyl chain of the substrate in the core. Therefore, synergistic effects between the metal-catalyzed center and the hydrophobic microenvironment of the metallomicelle core facilicate the reduction, proceeding with higher stereochemical induction compared to the catalysts formed from the corresponding ligands **1**−**3** (Table 1),[11c] which is an important feature of enzyme catalysis.[2b]

In conclusion, a novel surfactant-type ligand was designed and synthesized. A rhodium complex with this ligand was successfully applied in asymmetric transfer hydrogenation of a broad range of aliphatic ketones, especially those bearing functional groups that might form key intermediates of bioactive compounds[15] and natural products.[18] Good to excellent conversions and remarkable enantioselectivities (up to 95%) were obtained, with substrate-to-catalyst ratios as high as 100. The reactivity and enantioselectivity depended on the solvent, the temperature, and the chain length of the aliphatic ketones. Furthermore, TEM analyses showed that the precatalyst and catalyst formed metallomicelles in water, and the reaction proceeded in micelles. A probable transition state was proposed on the basis of the absolute configuration of the products, in which the stereochemistry was controlled by the steric interaction between the alkyl groups of the aliphatic ketone and the Cp* ligand of the amphiphilic catalyst. Hydrophobic interactions between the alkyl chains of aliphatic ketones and the catalyst in the metallomicelle may lead to high

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enantioselectivity in the reduction of aliphatic ketones. This work will reveals a new aspect of asymmetric synthesis in chiral micelles. Further research to find new metallomicellar catalysts to improve the reaction efficiency is under way.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experiment procedures; spectral data of ligands. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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