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Asymmetric Transfer Hydrogenation of Ketones Catalyzed by Hydrophobic Metal−Amido Complexes in Aqueous Micelles and Vesicles

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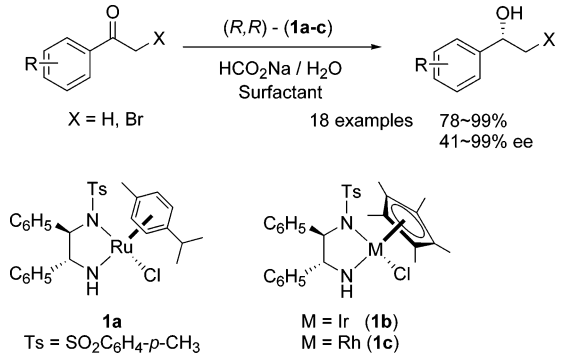

Asymmetric transfer hydrogenation of ketones, especially α-bromomethyl aromatic ketones, catalyzed by unmodified, hydrophobic transition metal−amido complexes (TsDPEN−M), was performed successfully with significant enhancement of activity, chemoselectivity, and enantioselectivity (up to 99% ee) in aqueous media containing micelles and vesicles. The hydrophobic catalyst, embedded in micelles constructed from the surfactant cetyltrimethylammonium bromide (CTAB), could be separated from the organic phase along with the products and was recycled for at least six times.

Introduction

Presently there is an intense interest in developing "greener" chemistry for both laboratory and industrial applications. Although as a solvent water has the advantage of being safe, benign, nontoxic, inexpensive, environmentally friendly, and easily separable, the insolubility of many organic compounds in water limits its application in various chemical transformations.[1] One strategy to address this problem involves the use of water-soluble ligands that have been successfully applied in many catalytic systems in aqueous media. However, the applications of most of these ligands are limited by their rather difficult preparation and the requirement of a reasonable water solubility for their efficient application.[2] These limitations of organic ligands may be overcome by using surfactants as cosolvents, which can solubilize organic reactants, products, and organometallic catalysts. Indeed, this approach has been successfully applied in many reactions such as asymmetric hydrogenation[2b,3] and transfer hydrogenation,[4] Suzuki coupling,[3d,5] aldol reactions,[6] Diels−Alder reaction,[7] and alkylation.[8]

Developed initially by Noyori and co-workers,[9] the enantioselective transfer hydrogenation of prochiral ketones was achieved with ruthenium complexes by using chiral mono-*N*-tosylated vicinal diamine as the ligand. Recently, supported[10] and water-soluble[11] Noyori−Ikariya catalysts received widespread attention because of their application in asymmetric transfer hydrogenation in

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aqueous media. We reported a novel chiral water-soluble catalyst based on the Noyori−Ikariya system, which was successfully used in the asymmetric transfer hydrogenation of α-bromomethyl aromatic ketones in aqueous media.[12] To the best of our knowledge, few reports[13] involving asymmetric reduction of α-bromomethyl ketones catalyzed by transition metal complexes are known, which is possibly due to catalyzed dehalogenation. In this paper, we report our recent results which reveal that the unmodified catalyst can increase the rate of the asymmetric transfer hydrogenation of acetophenone in aqueous media.[14] Moreover, the unmodified hydrophobic catalyst could be separated from the organic phase with the products and were reused in the presence of micelle-forming surfactants in water. We discuss herein the influence of surfactants on the asymmetric transfer hydrogenation of prochiral ketones, especially α-bromomethyl aromatic ketones. Our approach should provide an alternative method for the synthesis of β-adrenergic receptor agonists.[15,16]

Results and Discussion

It is well-known that the nature of surfactant plays a very important role in catalytic reactions involving micelles. The charge of the constituent surfactant molecules is particularly important in catalysis involving micelles.[17] Noyori−Ikariya catalyst, (*R,R*)-TsDPEN-[RuCl(cymene)] (**1a**), and most ketone substrates are generally hydrophobic and neutral and tend to locate within the micelles. Unfortunately, the hydrogen source used in this reaction, sodium formate ($HCOO^-$), is an anion and is readily soluble in water. Thus the cationic surfactant, CTAB, was initially applied to accelerate the asymmetric transfer hydrogenation of acetophenone (**2a**) in aqueous media, on the basis of the consideration that $HCOO^-$ ions should be attracted by cationic charge around the micelle surface. Besides, CTAB was chosen as the surfactant due to its low critical micelle concentration (cmc).[3d]

It was found that even in the absence of any surfactant molecules, the reduction of **2a** proceeded quickly in water, leading to (*R*)-1-phenylethanol (**3a**) with 94% enantiomeric excess (ee) and 99% isolated yield within 7 h.[9b] In this case, higher turn over frequency (TOF, 52 h^{-1}) was observed than that of the reaction using formic acid−triethylamine (azeotrope) as the hydrogen source and solvent[18] (Table 1, entry 1), since the hydrophobic catalyst was soluble in liquid acetophenone. Interestingly, marked increase of reaction activity (TOF, 69 h^{-1}) was observed by employing cationic CTAB as a surfactant (entry 2). As expected, reactions involving neutral and anionic surfactants resulted in lower reactivities as compared to the control without surfactant (entries 3 and 4 vs entry 1). The lowest TOF value was obtained when the anionic surfactant, SDS, was used, which was most likely due to the repulsion between the negatively charged formates and the micelles formed from the anionic surfactants. Zwitterionic surfactant DDAPS led to higher reactivity (entry 5). Because vesicles were used as microreactors[19b] and could be formed by mixing simple single-tailed cationic and anionic surfactants,[19] mixtures of SDS and CTAB of different ratios were therefore tested in the transfer hydrogenation of **2a.** The highest TOF value (76 h^{-1}) was obtained in 95% ee with a 2:1 molar ratio of SDS and CTAB (entry 6).

Furthermore, the asymmetric transfer hydrogenation of **2a** could be completed in the presence of aqueous micelles within 4 h with a 95% ee (entry 7). The pH value of the reaction medium changed from 7.9 to 9.0 at the end of the reaction. A decrease of reactivity was observed

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TABLE 1. Influence of Different Surfactants on the Conversion and Enantioselectivity of Ketones[a]

entry	sub	surfactant	S/C	time (h)	conv (%)[b]	TOF (h^{-1})[c]	ee (%)[b]
1	**2a**	none in water	100	1	52	52	94
2	**2a**	CTAB	100	1	69	69	95
3	**2a**	SDS	100	1	42	42	93
4	**2a**	Triton X-100	100	1	50	50	95
5	**2a**	DDAPS	100	1	73	73	94
6	**2a**	SDS:CTAB = 2:1	100	1	76	76	95
7	**2a**	CTAB	100	4	>99	99[d]	95
8[e]	**2a**	CTAB	100	4	14		94
9[f]	**2a**	CTAB	100	4	>99	67[c]	95
10	**2a**	CTAB	500	30	55	52[d]	94
11[g]	**2a**	CTAB	500	20	>99	98[d]	95
12[g]	**2a**	CTAB	1000	45	>99	99[d]	95
13[g]	**2a**	CTAB	1500	70	93	91[d]	95
14	**4**	none in water	100	28	>99	99[d]	96
15	**4**	CTAB	100	4	>99	98[d]	98

[a] [TsDPEN−Ru] = 0.004 M; [TsDPEN−Ru]:[Surfactant]:[substrate]:[HCO_2Na] = 1:10:100:500; 0.5 mL of water at 28 °C. CTAB = cetyltrimethylammonium bromide; SDS = sodium dodecyl sulfate; Triton X-100 = poly(ethylene glycol) mono[4-(1,1,3,3-tetramethylbutyl)phenyl] ether; DDAPS = dodecyldimethylammonio propanesulfonate. [b] The conversion and ee were determined by GC analysis (CP-cyclodex B-236 M). [c] The average TOFs were calculated over the 1 h reaction time. [d] Isolated yields. [e] Both 2.5 equiv of HCO_2Na and HCO_2H were used as hydrogen source. [f] 1.25 equiv of Na_2CO_3 was added. [g] The reactions were performed in degassed water under an argon atmosphere.

when HCO_2Na−HCO_2H (1:1 molar ratio, pH 3.8−4.1) was used as the hydrogen source (entry 8) during the reaction.[20] No product was observed by employing HCOOH as the hydrogen donor. However, high conversion (>99%) and TOF value (67 h^{-1}) were obtained in a more basic range (pH 9.6−10.2) when 1.25 equiv of Na_2CO_3 was added (entry 9 vs entries 2 and 7).

When the ratio of substrate and catalyst (S/C) was increased to 500, a conversion rate of 55% was obtained with 94% ee in 30 h. Interestingly, complete conversion was achieved with 98% yield and 95% ee in 20 h by using degassed water as the solvent and carrying out the reaction under an argon atmosphere (entry 10 vs 11). Moreover, quantitative conversion was obtained along with high enantioselectivity of 95% and an S/C ratio of 1000 (entry 12). A conversion rate of 93% was achieved in 70 h while the S/C ratio increased to 1500 (entry 13).

Meanwhile, solid 1-indanone (**4**) was selected to study the effect of substrate state on this reaction in aqueous micelle. It is notable that the mixture of **4** and catalyst (**1a**) formed a separate liquid phase in aqueous media in the absence of surfactants, in which the transfer hydrogenation reaction was completed with a 96% ee in 28 h (entry 14). In contrast, the corresponding reaction took 40 h to complete when the azeotrope was used as the hydrogen source and solvent.[9b] Impressively, quantitative conversion with increased enantioselectivity (98%) was obtained in only 4 h in the presence of 10 mol % CTAB (entry 15). Interestingly, under this condition (0.04 M of CTAB), colloidal dispersion systems formed in the aqueous solution and the reaction resulted in the highest TOF value (31 h^{-1}).

Influence of the CTAB concentration was also investigated for asymmetric transfer hydrogenation of both **2a** and **4** (Figure 1). Initially, reactivities increased significantly as the concentrations of the surfactant increased. The highest TOF values were obtained at 0.04 M of CTAB for both ketones. The TOF values declined as the CTAB concentration further increased. The declined reactivity was probably due to increase in the viscosity of the solution,[8a] which may interfere with the impingement of reactant molecules. For **2a**, the colloidal dispersion systems formed when CTAB was increased to 0.08 M in the aqueous reaction media. An interesting phenomenon was observed in the reduction of **2a**. When the concentration of CTAB was higher than 0.08 M, the hydrophobic organometallic catalyst (**1a**) remained as colloidal dispersion even after the aqueous media were extracted with *n*-hexane. The concentration of ruthenium was determined in both organic and aqueous layers by ICP-MS analysis to be 0.25 and 322.5 mg/L, respectively, with the concentration in the aqueous layer being 1290 times higher than that in the organic layer. The recycling of **1a** was tested on **2a** employing 0.12 M of CTAB. After each catalytic cycle, formic acid (1.1 equiv) was added to regenerate sodium formate. High conversion (90%) and enantioselectivity (95%) were obtained even on the seventh run (Table 2). To the best of our knowledge, the reuse of hydrophobic catalyst embedded in micelles in aqueous media was not reported before.[21]

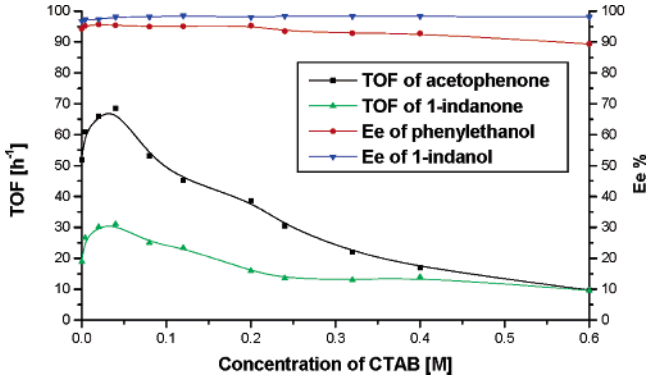

FIGURE 1. Influence of concentration of CTAB. The average TOFs were calculated over 1 h for **2a** and 2 h for **4**.

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TABLE 2. Results of Catalyst Recycling of Asymmetric Transfer Hydrogenation of Acetophenone[a]

	run								
param	1	2	3	4	5	6	7	8	9
time (h)	6	6	9	11	12	13	24	24	24
conv (%)[b]	>99	>99	>99	>99	>99	>99	90	38	15
ee (%)[b]	95	94	95	95	95	95	95	94	94

[a] [TsDPEN−Ru] = 0.004 M; [TsDPEN−Ru]:[CTAB]:[**2a**]:[HCO_2Na] = 1:30:100:500; 0.5 mL of degassed water; under an argon atmosphere at 28 °C; 1.1 equiv of HCO_2H used to regenerate HCO_2Na. [b] The conversion and ee were determined by GC analysis (CP-cyclodex B-236 M).

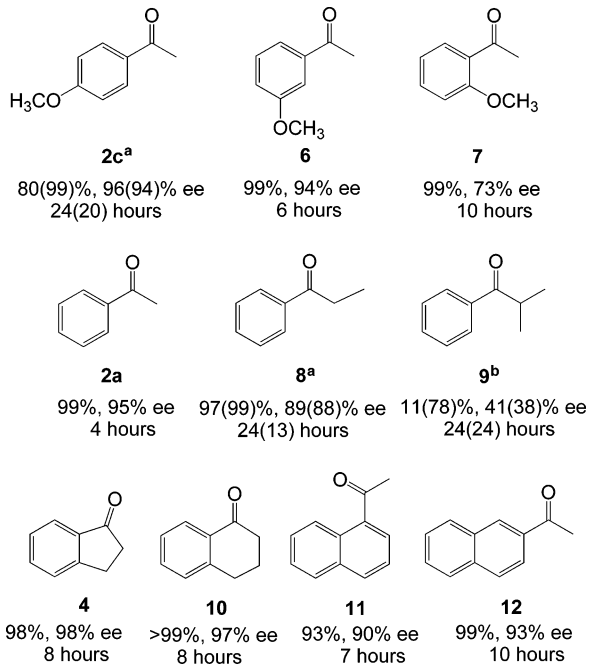

FIGURE 2. Asymmetric transfer hydrogenation of aromatic ketones in aqueous media. [TsDPEN−Ru] = 0.004 M, [TsDPEN−Ru]:[CTAB]:[substrate]:[HCO_2Na] = 1:10:100:500, 0.5 mL of degassed water, under an argon atmosphere at 28 °C, yield was isolated yield and ee determined by GC analysis (CP-cyclodex B-236 M). (a) Data in parentheses were obtained with 50 mol % CTAB. (b) Data in parentheses were obtained with 10 mol % SDS and CTAB (2:1 molar ratio).

Micelles have been considered as microreactors that provide hydrophobic reaction sites for the acceleration of reactions. In some cases the stereoselectivity of the corresponding reaction was altered due to the preorganizational function of micelles.[3d,17,19b] Thus, we tested the asymmetric transfer hydrogenation of a variety of aromatic ketones, **2**, **4**, and **6**−**12**, in micelles consisting of CTAB. As shown in Figure 2, high yields and satisfactory enantioselectivities were obtained. Most reactions proceeded quickly and was completed in a few hours except for substrates **2c**, **8**, and **9**, whose solubilities were found to be poor in aqueous media. Nevertheless, by an increase of the concentration of CTAB or using vesicle system, the reactions proceeded satisfactorily. For different position-substituted acetophenones **2c**, **6**, and **7**, high enantioselectivities were obtained for the reduced products, **3c** and **13**, with the *ortho*-methoxyphenylethanol **14** being the exception (73% ee). The enantioselectivities of the reduced products, **3a**, **15**, and **16**, decreased as the bulk of substituents on the substrates (**2a**, **8**, and **9**) increased. It is known that the bulk of the ketone substrates can influence the chirality-determining diastereomeric transition state.[22] For substrates **4** and **10**−**12**, excellent activities and enantioselectivities were demonstrated by the reduced products **5** and **17**−**19**. Particularly noteworthy was product **18**, which was obtained in 93% yield and 90% ee in 7 h. However, the same reaction gave only 83% ee when formic acid−triethylamine (azeotrope) was used as the hydrogen source and solvent.[9b]

Optically pure 2-bromo-1-arylethanols (**21**) were the key intermediates for preparing β-adrenergic receptor agonists, which were usually obtained from the corresponding α-bromomethyl aromatic ketones by reduction by employing CBS oxazaborolidine[23] or biocatalysts.[24] As reported previously,[25] asymmetric transfer hydrogenation of α-bromoacetophenone (**20a**) cannot be performed in the azeotrope system due to the formate displacement reaction. We recently found that **20a** could be reduced by employing **1a** as the catalyst in a two-phase system, resulting in the expected 2-bromo-1-phenylethanol (**21a**) with 75% yield and 94% ee.[12] We decided to extend this methodology to the asymmetric transfer hydrogenation of a variety of α-bromomethyl aromatic ketones[26] in aqueous media without using any organic solvents. This method offers a green synthesis of β-adrenergic receptor agonists. Initially, **20a** was reduced by using **1a** as the catalyst and HCO_2Na as the hydrogen source in aqueous media. After careful examination of the products by ^1H NMR analysis, the reaction resulted in a mixture of **2a**, **3a**, and **21a**−**23a**, which was produced via three possible ways (Scheme 1).

When the reaction was performed in water without any additives, only 63% of **21a** was obtained in 24 h (Table 3, entry 1). In contrast, when CTAB was applied, the reaction was completed with a yield of 73% and a slightly increased ee (96%) in only 2 h. However, in this case, the formate product **23a**, was detected by ^1H NMR analysis to be present in 18% (entry 2). When phase-transfer catalyst tetrabutylammonium bromide (TBAB) was used, 29% of **23a** with lower ee of 90% and other byproducts were detected by ^1H NMR analysis (entry 3). The effects of CTAB and TBAB on the reaction were then compared in the absence of any catalyst. It was found that compound **20a** was completely converted to **23a** in

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TABLE 3. Asymmetric Transfer Hydrogenation of α-Bromoacetophenone in Aqueous Media[a]

entry	metal	surfactant	*T* (h)	**23a** (%)[b]	**21a** (%)[b,c]	ee (%)[d]	**22a** (%)[b,c]	**2a** (%)[b]	**3a** (%)[b]	tot. (%)[b,e]
1	Ru		24		63 (59)	93	7	3		73 (26)
2	Ru	CTAB	2	18	73 (71)	96	7	2		100
3	Ru	TBAB	2	29	35 (30)	90	7			71[f]
4		CTAB	5	95						95
5		TBAB	5	93						93
6[g]	Ru	Triton X-100	6		77 (75)	95	8		7	92
7	Ru	SDS	10		88 (86)	95	8		4	100
8	Ru	SDS:CTAB = 2:1	7		91 (90)	96	5		4	100
9	Ir	SDS	2		93 (92)	96		3	5	101
10	Ir	SDS:CTAB = 2:1	2		87 (85)	97	5	3	6	101
11	Rh	SDS	2		96 (95)	98			2	98
12	Rh	SDS:CTAB = 2:1	1		98 (97)	98			3	101
13[h]	Rh	SDS:CTAB = 2:1	15		(88)	99	(9)			97
14[i]	Rh	SDS:CTAB = 2:1	24		(86)	98	(11)			97
15[j]	Rh	SDS:CTAB = 2:1	48		(54)	99	(9)			63 (35)

[a] [TsDPEN−M] = 0.004 M; [TsDPEN−M]:[surfactant]:[**20a**]:[HCO_2Na] = 1:10:100:500; 1.0 mL of degassed water; under an argon atmosphere at 28 °C. [b] Yield was determined by ^1H NMR analysis. [c] The data in parentheses were isolated yields. [d] Ee values were determined by GC analysis (CP-cyclodex B-236 M). [e] The data in parentheses were recovered yields of substrates. [f] The products were complex and some compounds could not be identified by ^1H NMR analysis. [g] 2.0 mL of water and 1.0 equiv of Triton X-100 were used. [h] S/C = 2000. [i] S/C = 3000. [j] S/C = 5000.

TABLE 4. Asymmetric Transfer Hydrogenation of α-Bromomethyl Aromatic Ketones[a]

entry	sub	S/C	time (h)	**21** (%)[b,c]	ee (%)[d]	**2** + **3** (%)[b]	tot. (%)[b]
1	**20b**	100	2	77 (75)	95	18	95
2	**20c**	100	1	82 (80)	98	18	100
3	**20d**	100	3	96 (95)	90	2	98
4[e]	**20e**	100	6	(87)	93		
5	**20f**	100	2.5	93 (90)	97	4	97
6	**20g**	100	5	95 (93)	94	2	97
7[f]	**20**g	500	22	(92)	94		

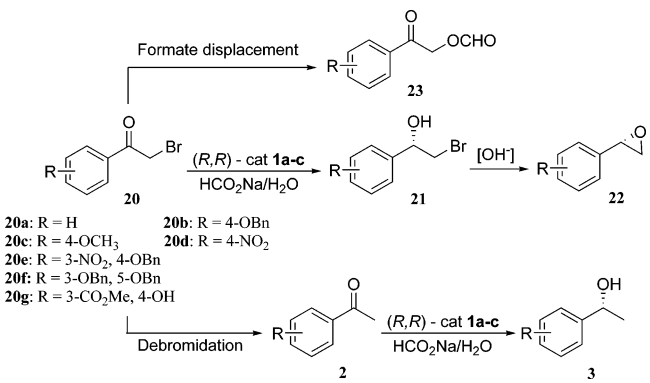
[a] [TsDPEN−Rh] = 0.004 M; [TsDPEN−Rh]:[SDS:CTAB = 2:1]:[**20b**−**g**]:[HCO_2Na] = 1:10:100:500; 1.0 mL of degassed water; under an argon atmosphere at 28 °C. [b] Yields were determined by ^1H NMR analysis. [c] The data in parentheses were isolated yields. [d] Ee values were determined by GC or HPLC analysis with chiral columns. [e] 2.0 mL of water and 1.0 equiv of Triton X-100 were used, and 7% **22e** was isolated. [f] [TsDPEN−Rh] = 0.0008 M; 10 mL of degassed water; 1.09 g (4.0 mmol) of **20g** was used.

5 h (entries 4 and 5). These results showed that the cationic charge in aqueous media accelerated the formate displacement. Surprisingly, when the anionic surfactant (SDS) was used, the reduction product, **21a**, was obtained in high yield (88%) and enantioselectivity (95% ee) in 10 h. Byproduct **23a** was not detected by ^1H NMR in this case. Meanwhile, oxetane (**22a**, 8%), which was formed via cyclization of the corresponding **21a**, and phenylethanol (**3a**, 4%), which was produced by reduction of the debromidation product (**2a**), were also observed in the ^1H NMR spectrum (entry 7). In the presence of vesicles, an increased yield (91%) was obtained with 96% ee in 7 h (entry 8).

To improve chemoselectivity, $[IrCl_2(cp^*)]_2$ and $[RhCl_2(cp^*)]_2$ were used to replace $[RuCl_2(cymene)]$ (entries 9−12).[27] Increased yield (98%), enantioselectivity (98% ee), and chemoselectivity were obtained with the catalyst (**1c**) in 1 h (entry 12). When the reaction time was extended to 15 h, the S/C ratio increased to 2000, along with an 88% isolated yield and 99% ee (entry 13). Although the isolated yield slightly dropped to 86% if the reaction was allowed to proceed for 24 h, similar enantioselectivity (98% ee) were obtained along with 11% oxetane (97% ee), with a significant increase of the S/C ratio to 3000 (entry 14).

In aqueous media, α-bromomethyl aromatic ketones (**20b**−**g**) can also be converted to the corresponding chiral 2-bromo alcohols (**21b**−**g**) by using **1c** as the catalyst. Compounds **21e**−**g** are the key intermediates for preparing the antiasthma drugs fermoterol, terbutaline,[16] and salbutamol (Table 4). For substrates **20b**,**c**, which bear electron-donating groups on their benzene rings, good yields (77% for **20b** and 82% for **20c**) and high enantioselectivities (95% ee for **20b** and 98% ee for **20c**) were obtained within 2 h. However, for these two substrates, increased yields of dehalogenated products and their corresponding reduced products (18% for both **20b**,**c**) were observed on the basis of ^1H NMR analysis (entries 1 and 2). For substrate **20d** with its electron-withdrawing group, higher yield (96%) but lower enantioselectivity (90%) were obtained in 3 h with little dehalogenated product (2%) (entry 3). These results implied that the

SCHEME 1



(27) (a) Mashima, K.; Abe, T.; Tani, K. *Chem. Lett.* **1998**, 1199. (b) Murata, K.; Ikariya, T.; Noyori, R. *J. Org. Chem.* **1999**, *64*, 2186.

electron densities of benzene rings played an important role in the dehalogenation step. In contrast, for **20e**, the product was obtained in a yield of only 42% in 8 h. This reaction could not proceed satisfactorily even with high concentrations of vesicles due to the poor solubility of substrate in aqueous media. To deal with this problem, 1 equiv of Triton X-100 was used to replace the mixture of SDS and CTAB (2:1 molar ratio), which resulted in a good isolated yield (87%) and high enantioselectivity (93% ee) of **21e** in 6 h, along with 7% oxetane (**22e**) (entry 4). On the contrary, the reaction proceeded smoothly for **20f**, with 93% yield and 97% ee in 2.5 h, and for **20g**, with 95% yield and 94% ee in 5 h (entries 5 and 6). It is noteworthy that an isolated yield of 92% and an ee value of 94% for **21g** were obtained while the S/C ratio increased to 500. Furthermore, optically pure **21g** (99% ee) was obtained with satisfactory yield (53%) after recrystallization from a mixed solvent containing petroleum ether and ethyl acetate (10:1 v/v, entry 7).

In conclusion, the asymmetric transfer hydrogenation of ketones, particularly α-bromomethyl aromatic ketones, was successfully performed by employing the unmodified and hydrophobic metal−amido complexes (TsDPEN−Ru, −Ir, −Rh) in aqueous micelles and vesicles with HCOONa as the hydrogen donor. Significant enhancement of activity, chemoselectivity, and enantioselectivity was observed in the presence of surfactants and vesicles (2:1 molar ratio of SDS and CTAB). It is notable that the hydrophobic catalyst (**1a**), which was embedded in the micelles, could be separated from the organic phase containing the product and could be reused. High activity and enantioselectivity remained for at least six cycles of asymmetric transfer hydrogenation of acetophenone in aqueous media. To the best of our knowledge, this is the first report describing the recycling of this hydrophobic catalyst in aqueous media. High isolated yields (up to 97%) and excellent enantioselectivities (up to 99%) of 2-bromo alcohols and oxetanes were obtained in aqueous vesicles by employing (*R,R*)-TsDPEN−Rh (**1c**) as the catalyst, which has provided an environmentally compatible method for the synthesis of *β*-adrenergic receptor agonists.

Experimental Section

General Procedure for Asymmetric Transfer Hydrogenation of α-Bromomethyl Aromatic Ketones. The mixture of (*R,R*)-TsDPEN (1.6 mg, 0.004 mmol) and $[RhCl_2(cp^*)]_2$ (1.3 mg, 0.002 mmol) was added to a flask and degassed for three times. Methylene chloride (0.5 mL) was added to dissolve the mixture, and the solution was stirred at 40 °C for 1 h. After removal of CH_2Cl_2 under reduced pressure, α-bromomethyl aromatic ketones (0.4 mmol), surfactant (0.04 mmol), $HCO_2Na\cdot 2H_2O$ (208 mg, 2 mmol), and 1 mL of water were added. After being degassed for three times, the reaction mixture was stirred at 28 °C under an argon atmosphere with 800 r/min. After the reaction was completed (monitored by TLC), the reaction mixture was extracted with CH_2Cl_2 (5 mL) for three times. The combined organic phases were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was dissolved in 2 mL of $CDCl_3$, and the yield was determined by ^1H NMR analysis using 1,3,5-trimethylbenzene as an internal standard. Isolated yield was obtained by purifying the products using flash chromatography.

2-Bromo-1-(3,5-bis(benzyloxy)phenyl)ethanol (21f): white solid; mp 85−86 °C; $[\alpha]_D^{23}$ +20.9° (*c* 1.00, $CHCl_3$); 96.9% ee; ^1H NMR ($CDCl_3$, 300 MHz) *δ* 7.44−7.33 (m, 10H), 6.65−6.64 (m, 2H), 6.59−6.57 (m, 1H), 5.04 (s, 4H), 4.87−4.84 (m, 1H), 3.65−3.60 (m, 1H), 3.51−3.49 (m, 1H), 2.60 (br, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) *δ* 160.2, 142.7, 136.6, 128.6, 128.1, 127.5, 105.1, 102.0, 73.8, 70.2, 40.1 ppm; IR (KBr) *ν* 3362, 1596, 1438, 1167, 1061, 1042, 731, 693 cm^{-1}. Anal. Calcd for $C_{22}H_{21}BrO_3$: C, 63.93; H, 5.12; Br, 19.33. Found: C, 64.22; H, 5.35; Br, 19.13.

Methyl 5-(2-bromo-1-hydroxyethyl)-2-hydroxybenzoate (21g): white solid; mp 73−74 °C; $[\alpha]_D^{23}$ + 42.1° (*c* 1.16, $CHCl_3$); 99.3% ee; ^1H NMR ($CDCl_3$, 300 MHz) *δ* 10.7 (s, 1H), 7.82 (d, *J* = 2.3 Hz, 1H), 7.43 (dd, *J* = 2.3, 8.6 Hz, 1H), 6.95 (d, *J* = 8.6 Hz, 1H), 4.83 (dd, *J* = 3.6, 8.6 Hz, 1H), 3.93 (s, 3H), 3.56 (dd, *J* = 3.7, 10.5 Hz, 1H), 3.48 (dd, *J* = 8.6, 10.4 Hz, 1H), 2.94 (br, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) *δ* 170.2, 161.5, 133.3, 131.1, 127.5, 118.0, 112.3, 73.0, 52.4, 40.0 ppm; IR (KBr) *ν* 3507, 2953, 1675, 1615, 1492, 1444, 1330, 1208, 1090, 794 cm^{-1}. Anal. Calcd for $C_{10}H_{11}BrO_4$: C, 43.66; H, 4.03; Br, 29.05. Found: C, 43.42; H, 4.02; Br, 28.85.

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Supporting Information Available: General procedure for asymmetric transfer hydrogenation and recycle experiment of ketones in aqueous media, influence of the CTAB concentration, optical rotation, NMR data, and GC or HPLC conditions for the reduced products (**3a**,**c**, **5**, **13**−**19**, and **21a**−**g**), epoxide (**22a**), and formate product (**23a**). This material is available free of charge via the Internet at http://pubs.acs.org.

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