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Highly efficient and recyclable heterogeneous asymmetric transfer hydrogenation of ketones in water†

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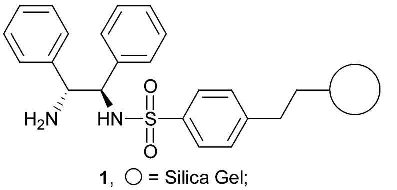
A highly efficient heterogeneous asymmetric transfer hydrogenation of ketones in water was developed for the first time, which exhibited excellent enantioselectivities, distinct acceleration effect and remarkably high recyclabilities.

The heterogeneous asymmetric catalytic reactions[1] performed in water[2] using the supported chiral catalysts, are attracting great interest[3,4] as they provide risk-free and environmentally friendly processes, as well as easy work-up and efficient catalyst recycling. Recently, we reported the accessible and highly recyclable Ru–TsDPEN catalysts immobilized on amorphous silica gel or mesopores of MCM-41 and SBA-15 for asymmetric transfer hydrogenation of ketones.[5] Herein, we wish to report the first heterogeneous asymmetric transfer hydrogenation in water using the supported catalysts, where the advantages of both aqueous and heterogeneous switching were combined in one system.

Ligands **1–3** supported respectively on silica gel, mesopores of MCM-41 and SBA-15 (Fig. 1) were readily synthesized by the methods we described,[5] and the ruthenium complexes Ru–**1**–Ru–**3** were prepared *in situ* by mixing the corresponding ligands with $[RuCl_2(p\text{-cymene})]_2$ (ligand:Ru = 1.7:1) in water and heating at 80 °C for 1 h. The organic solvent free transfer hydrogenation in water was then carried out at 40 °C using acetophenone as the model substrate and HCO_2Na (5 equiv.) as the hydrogen source, in the presence of Ru–**1** (1% mol); affording 91% ee and >99% yield after 9 h. The subsequent reactions using the recovered catalyst gave a little higher enantioselectivies and high yields with prolonged reaction time (entries 1, 2 in Table 1). Encouraged by this initial observation, we screened a series of additives (4% mol) for this catalytic system with the hope of better results as shown in Table 1. Firstly, we looked at the usage of the surfactants such as SDS (sodium dodecyl sulfate), SDBS (sodiumdodecylbenzenesulfonate) and tween 60. We were pleased that the enantioselectivities and reactivities of the transfer hydrogenation were enhanced and the recovered catalyst worked more efficiently with the surfactants (entries 3–7). We also attempted to apply methyl triglycol[6] to the system but the results were undesirable (entries 8, 9). When PEG-1000 was used as the additive, the reaction afforded excellent enantioselectivity (95% ee), remarkably high reactivity and very good recycling performance as the catalyst could be used 6 runs with the ultimately same ee values and very high yields (entries 10–11). The following screens were focused on the phase transfer catalysts (PTC) as quaternary ammonium halides. CATB (cetyltrimethylammonium bromide) with a very long chain group and TEAB (tetraethylammonium bromide) with the short chain groups could promote the reactions and the ee values were as high as those obtained with the other surfactants (entries 12–15).

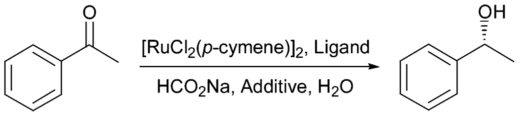


1, ○ = Silica Gel;
2, ○ = MCM-41;
3, ○ = SBA-15.

Fig. 1 The supported TsDPEN ligands.

When TBAB (tetrabutylammonium bromide) was added to the catalytic system, the transfer hydrogenation of acetophenone in water demonstrated the best enantioselectivity (96% ee) and highest reactivity (>99% yield after 2 h in 1–3 runs). Moreover, the

Table 1 Heterogeneous asymmetric transfer hydrogenation of acetophenone in water.[a]



Entry	Additives	Run	Time/h	Conv. (%)[b]	ee (%)[c]
1	None	1	9	>99	91
2		2–3	21–79	>99–98	92
3	SDS	1–2	9–36	>99–97	94
4	SDBS	1	10	>99	92
5		2–4	12–21	83–64	93
6	Tween 60	1–2	5–10	>99	94
7		3–4	13–27	>99–88	95
8	Methyl triglycol	1	10	>99	93
9		2–3	12–40	68–56	92–91
10	PEG-1000	1–2	2–5	>99	95
11		3–6	3.5–35	>99–95	95
12	CTAB	1–3	3–8	>99–99	93–94
13		4–5	9–46	77–82	94
14	TEAB	1–3	7–12	>99–98	92–94
15		4	58	87	93
16	TBAB	1–3	2	>99	96
17		4–6	3.5–12	>99–99	96
18		7	60	66	96
19[d]	TBAB	1–3	8–13	>99	96
20[d]		4–5	30–69	98–76	96
21[e]	TBAB	1	52	88	96
22[f]	TBAB	1–3	5	>99	93
23[f]		4–5	6–37	87–89	93
24[g]	TBAB	1–5	6–28	>99–99	94–95
25[g]		6	90	92	95

[a] The reactions were carried out using 0.4 mmol of acetophenone with 0.004 mmol Ru–**1** (Ru:ligand:ketone = 1:1.7:100) in 0.4 mL water containing 2.0 mmol $HCO_2Na.2H_2O$ and 0.016 mmol additives unless noted. [b] Based on GC analysis. [c] Determined by GC with a CP-Chirasil-DEX CB column (25 m × 0.32 mm) unless noted and the configuration *R* was determined by retention time. [d] The reactions were carried out at S/C = 200. [e] The reactions were carried out at S/C = 500. [f] Ru–**2** was used at S/C = 100. [g] Ru–**3** was used at S/C = 100.

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† Electronic supplementary information (ESI) available: Experimental procedure for the transfer hydrogenation of ketones in water and the analytical data for the obtained chiral aromatic alcohols. See http://www.rsc.org/suppdata/cc/b4/b408533g/

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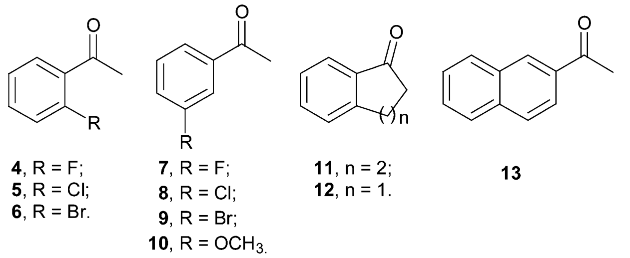
Table 2 Immobilized ruthenium(II) complex Ru–**1** catalyzed heterogeneous asymmetric transfer hydrogenation of ketones in water.[a]



Entry	Ketone	Run	Time/h	Conv. (%)[b]	ee (%)[c,d]
1	**4**	1–7	2–16	>99	90
2		8	58	91	90
3	**5**	1–5	2–12	>99	92
4		6–7	10–58	98	92
5	**6**	1–10	2.5–11	>99–98	92
6	**7**	1–7	2–11	>99–99	93
7		8–10	9–87	98–95	93
8	**8**	1–7	3–11	>99–99	94
9		8	58	99	94
10	**9**	1–9	5–35	>99	93
11		10–11	47–93	95–88	93
12	**10**	1–4	5–35	>99–98	95
13		5–6	48–58	98–85	95
14	**11**	1–4	6–16	>99–99	98[e]
15		5–7	16–64	97–91	98[e]
16[g]	**12**	1–3	6–35	>99–99	>99[e]
17[g]		4	72	73	>99[e]
18[g]	**13**	1–5	8–27	>99	95–96[f]

[a] The reactions were carried out using 0.4 mmol of ketones with 0.004 mmol Ru–**1** in 0.4 mL water containing 2.0 mmol $HCO_2Na.2H_2O$ and 0.016 mmol Bu_4NBr. [b] Based on GC analysis. [c] Determined by GC with a CP-Chirasil-DEX CB column (25 m × 0.32 mm) unless noted. [d] The configurations of the products were all determined *R* by the retention time. [e] Determined by HPLC on Chiralcel OB column. [f] Determined by HPLC on Chiralcel OJ column. [g] Extra 0.4 mL CH_2Cl_2 was added.

catalyst could be used for 6 runs with completely maintained enantioselectivities and quantitative yields (entries 16–17). It is particularly noteworthy that the unusual distinct "acceleration effect" of this catalytic system in water was observed since its reactivity was much higher than that in organic solvent (formic acid–triethylamine azeotrope) which needed 6 h to achieve >99% yield;[5] and the TOF (turnover frequency) of this aqueous reaction determined at 0.5 h was 109, while the TOF in organic solvent was just 10. We presumed that in the aqueous media, the liquid organic substrate as acetophenone diffused into the silica gel matrix to form a highly concentrated reaction sphere, which could be observed in the experiments, and the ketone might react with formate anion with the efficient promotion of appropriate PTC as TBAB through the interfacial silica gel region[7] and thus exhibit much higher reactivity than that in organic solvent.[4] In addition, the catalyst in aqueous solution could be used more runs than that in organic solvent.[5] When S/C (substrate/catalyst in mol) of the reaction was increased to 200 or 500, the same 96% ee could still be obtained but the reactivities and the recycling use of the catalyst were affected undesirably (entries 19–21). The catalysts Ru–**2** and Ru–**3** supported in mesopores of MCM-41 and SBA-15, were also examined for the transfer hydrogenation of acetophenone and the results proved that mesopores of MCM-41 and SBA-15 were worse supports in comparison with the cheap amorphous silica gel in this asymmetric catalytic reaction (entries 22–25).

Moreover, as shown in Table 2, a variety of aromatic ketones **4–13** could be reduced to the corresponding chiral alcohols under the optimum conditions with much higher reactivities, enantioselectivities or recyclabilities in most cases compared with the former catalytic systems for asymmetric transfer hydrogenation in water.[8] The reduction of liquid substrates **4–11** was performed well without any organic solvent. The transfer hydrogenation of *ortho*-halogen substituted acetophenones **4–6** and *meta*-halogen substituted acetophenones **7–9** demonstrated high enantioselectivities (90–94% ee), high reactivities (all >99% yields after 2–5 h) and remarkably high recyclabilities (up to 11 runs without any loss of the enantioselectivities!). The results also revealed that the enantioselectivities of the reduction of *meta*-halogen substituted acetophenones were higher than those of *ortho*-halogen substituted ones (entries 1–11). For 3′-methoxy-acetophenone **10**, excellent enantioselectivity (95% ee), high reactivity and good recycling performance of the catalyst were obtained (entries 12–13). The reduction of 1-tetralone **11** with the rigid structure afforded very excellent 98% ee and much higher reactivity compared with the reaction in organic solvent which needed 16 h to achieve >99% yield.[5] In addition, the catalyst could be used 7 runs without any loss of enantioselectivity. For the solid substrates, 1-indanone **12** and 2′-naphthanone **13**, the cosolvent as CH_2Cl_2 was necessary for the smooth proceeding of the reactions. Ketone **12** with a more rigid ring gave the extremely high enantioselectivity (>99% ee) and quantitative yield after 6 h, and the catalyst could be used 4 runs with the same >99% ee. For ketone **13**, the transfer hydrogenation achieved 95–96% ee and >99% yield in all 5 runs.

In summary, we have developed a highly efficient heterogeneous asymmetric transfer hydrogenation in water for the first time using the silica gel supported Ru-TsDPEN catalyst, which demonstrated excellent enantioselectivities (up to >99% ee) and very high reactivities (all >99% yield within 2–8 h) for various aromatic ketones. Particularly, the catalyst could be readily recovered and reused in multiple consecutive catalytic runs (up to 11 runs without recharging Ru) without any loss of the high enantioselectivities. Another unique feature of this catalytic system in aqueous media was its distinct "acceleration effect" (109 TOF) in comparison with the reaction in organic solvent (10 TOF). To the best of our knowledge, this catalytic system is the first successful work on recyclable asymmetric catalysis in water using the covalently immobilized catalyst on silica.

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