Green Chemistry

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View Article Online
DOI: 10.1039/C7GC01639E

Journal Name

COMMUNICATION

Asymmetric transfer hydrogenation of aryl ketoesters with chiral double-chain surfactant-type catalyst in water

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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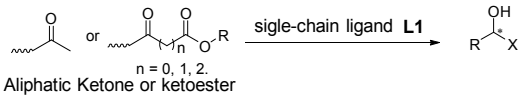
A chiral double-chain surfactant-type ligand was designed and synthesized. The rhodium catalyst formed from the ligand can self-assemble into chiral vesicular aggregates in water, which was applied to ATH of broad range of aromatic ketoesters in neat water and gave up to 99% yield and 99% ee. In addition, this double-chain surfactant-type catalyst could also be applied to the dynamic kinetic resolution (DKR) of bicyclic *β*-ketoesters in water.

Amphiphilic surfactants, commonly used as additives or catalysts, can form aggregates in water as nano- or micro-reactors, such as micelle, vesicle. These microreactors can not only increase the solubility of nonpolar substrates and catalysts, but also accelerate the reaction rates and stereoselectivities due to the effect of aggregate formation, such as the hydrophobic interaction and the preorganizational function of micelles.[1-5] Thus, the use of micellar surfactants as additives or catalysts is attracting considerable attention in aqueous reactions in recent years,[1, 3-4, 6-7] among which surfactant-type catalysts attract our interesting, especially. However, most works in chiral surfactants-type catalyst systems with high enantioselectivity used single chain surfactant-type catalyst[8-15] and there have been a few successful reports on using double-chain amphiphilic surfactant as asymmetric catalyst[16-17]. Moreover, compared to the single-chain catalyst, the double-chain catalyst geneally aggregates to vesicles rather than micelles in water.[18-21] The excellent catalytic performance of surfactant-type catalysts for specific reaction lies not only in their catalytic functional group, but also in the structure and morphology of their aggregates as reaction medium formed by associating surfactant-type catalysts themselves in water.[10, 22-25] The hydrophobic and hydrophilic region of the surfactant-type catalyst play an significant role in the formation of aggregates, which can be easily changed by modifying the hydrophobic chain or the polar head according to specific substrates. Sometimes a little change of hydrophobic or hydrophilic region of amphiphilic catalyst may make a great difference of its catalytic performance, with the catalytic site unchanged.[8, 11]

Our Previous Works:



This Work:

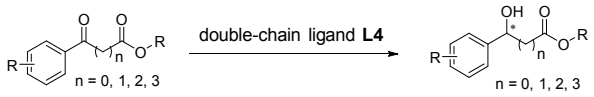


Figure 1

In our previous work,[8, 11] we have developed one kind of chiral single-chain surfactant-type catalyst **L1**-Rh, which may self-assembles to micelles in water to form aqueous-micelles as reaction media. And different kinds of aliphatic ketones and ketoesters have been reduced with high yield and enantioselectivities (Figure 1) using this kind of surfactant-type catalyst. However, it takes a long time to complete those reactions. Considering the activity of surfactant-type catalysts strongly depend not only on the structure of the catalyst itself but also on the structure and morphology of the nanoaggregate, we designed and synthesized a novel double-chain ligand **L4** derived from Noyori's diamine ligand TsDPEN and hoped to develop a catalytic system with a different state of aggregation from our previous micelle system. Herein, we report the results of a study of accelerating reaction and increasing stereoselectivities with surfactant-type catalysts bearing two polar hydrophilic heads and two chains as hydrophobic tail in asymmetric transfer hydrogenation (ATH) of aromatic ketones.

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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DOI: 10.1039/C7GC01639E

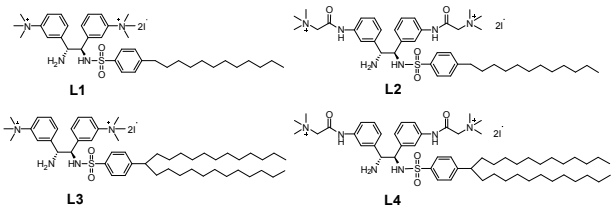
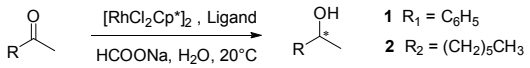


Figure 2. Chiral Surfactant-type Diamine Ligands.

Firstly, we examined the catalytic activity of four kinds of surfactant-type ligands **L1**, **L2**, **L3**, **L4** (Figure 2) at the same conditions (Table 1). We were impressed by the fact that the ATH of acetophenone (acp) with double-chain ligand **L4** afforded a conversion of 94% in 10 min at 40°C, which was faster than single-chain ligands **L1** and **L2** (entry 4 *vs* 1-2). while the ATH of aliphatic ketone **2,** single-chain ligand **L1** showed the best results among the four ligands (entry 5 *vs* 6-8), with 80% conversion and 88% ee in 120 min.[11] Ligand **L2** and **L3** only offered moderate results in the ATH of both aromatic ketone **1** (entries 2, 3 *vs* 4) and aliphatic ketone **2** (entry 6, 7 *vs* 5) compared with **L4** and **L1**. It's worth mentioning that the conversion in the ATH of **1** with **L4** is 94% in 3h, when the S/C ratio is as high as 1000 (entry **9**), which is one of the fastest ligands for the ATH of acp in the Noyori's diamine ATH system.[26-27]

Table 1. The activities of different ligands in the ATH of aromatic ketone and aliphatic ketones.



entry	ligand	ketone	T (min)	T (^{o}C)	conv. [b](%)	Ee [c](%)
1	**L1**	**1**	10	40	43	96
2	**L2**	**1**	10	40	61	97
3	**L3**	**1**	10	40	41	95
4	**L4**	**1**	10	40	94	97
5	**L1**	**2**	120	20	80	88
6	**L2**	**2**	120	20	71	80
7	**L3**	**2**	120	20	61	82
8	**L4**	**2**	120	20	63	79
9[d]	**L4**	**1**	180	40	94	97

[a] reaction conditions: 0.004 mmol of ligand, 0.002 mmol of metal precursor, 5.0 mL of H_2O, 2 mmol of HCOONa, 0.4 mmol of ketones, S/C = 100. [b] Conversion was determined by GC analysis using decane as internal standard. [c] Enantiomeric excess was determined by GC analysis. [d] S/C = 1000.

We speculated that the noticeable difference of experimental result between ligands **L1** and **L4** may own to the fact that the difference of structure and morphology of aggregates assembled from catalysts **L1**-Rh and **L4**-Rh in water, respectively. Thus, we did TEM research of the aggregates of **L4**-Rh-H in water. As shown in Figure 3, a simplified interrelation between the structure and the morphology of aggregates formed from the two surfactant-type catalysts, respectively, are given. Actually, the one chain catalyst **L1**-Rh-H can self-assemble into spherical nanoscale micelle particles, in which favours the hydrophobic interaction between the chain of catalyst and the alkyl chain of organic substrate (Figure 3, c and d).[11] However, the nano aggregate of double-chain catalyst **L4**-Rh-H has the structure of branch chain or bilayer and a hollow core (Figure 3, a and b), which is nearly ten times of the diameter compared to that of the micelle of **L1**-Rh-H. The bilayer formed from vesicular **L4**-Rh-H, may significantly enlarge the interfacial area of catalyst layer. For the ATH in aqueous medium, the hydrogen source HCOONa may solubilize in the internal and external aqueous phases of the bilayer in vesicular catalyst (Figure 2, b), and the substrates may be incorporated into the hydrophobic interior of the bilayer (SI, Figure S2). Moreover, the presence of lipophilic double chains in **L4**-R4-H leads to formation of a more hydrophobic microenvironment in the vesicular bilayers, which can enhance the solubility of organic substrates in water. Thus, it is not only increase the concentration of substrates but also the rate of reactions in the vesicle.

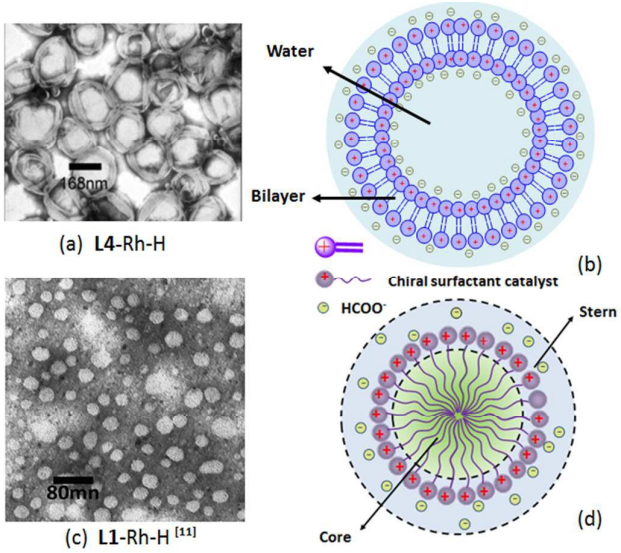


Figure 3. TEM images of nano-aggregates of catalyst in water.

After investigating the ATH of acp, we studied the effect of hollow nano-vesicle on the ATH of aromatic ketoesters, compared to what have been test with the micellar ligand **L1** in our previous work. [8] We tested the aryl α, β, γ, δ ketoesters **3**, **4**, **5**, and **6**, respectively. The ATH of these four substrates (Figure 4) shows that the ligand **L4** has the advantages of higher reaction speed, higher yield than that of ligand **L1**, and has comparative enantioselectivites with **L1**. Especially, ehyl β-oxo-β-phenylpropanoate **4** was completely converted to the β-hydroxy ester in 2 h with excellent ee value (97%).

Optical active β-hydroxyacids and their derivatives are versatile chiral building blocks for many key structural elements in pharmaceuticals and natural products.[28-31] The reaction conditions were optimized in detail for the ATH of **4** (SI, Table **S1**-**S5**). Three metal precursors, $[RuCl_2(p\text{-cymene})]_2$, $[Cp^*IrCl_2]_2$ and $[Cp^*RhCl_2]_2$, which are commonly used in the

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ATH, were tested using **L4** as a ligand and the Rh-complex turned out to show the best reactivity and enantioselectivity, with 84% yield and 96% ee (Table S4, entry 4) at 30 °C. The influence of temperature of the reaction was also investigated. To our delight, the enantioselectivity of ATH of **4** exhibited only a slight decrease as the temperature increased (SI, Table S5), 96% ee was obtained at 40 °C. It is noticeable that unmodified Rh-TsDPEN catalyst only gave 80% ee at the same conditions[32] but similar results were obtained in emulsions[33] and also in organic solvents[34] with Ru-TsDPEN as a catalyst. Furthermore, 94% ee was obtained even at 50°C, and the reaction rate was significantly elevated to 99% conversion in 30min. For the micellar catalyst **L1**-Rh-H, at the temperature above 40°C, the activity was sharply decreased and the aggregates were disrupted.[11] These results indicate that the vesicular aggregates of the catalyst **L4**-Rh-H are remarkably thermostable and can be used as a nanoreactor for the ATH, in which there is a more hydrophobic microenvironment.

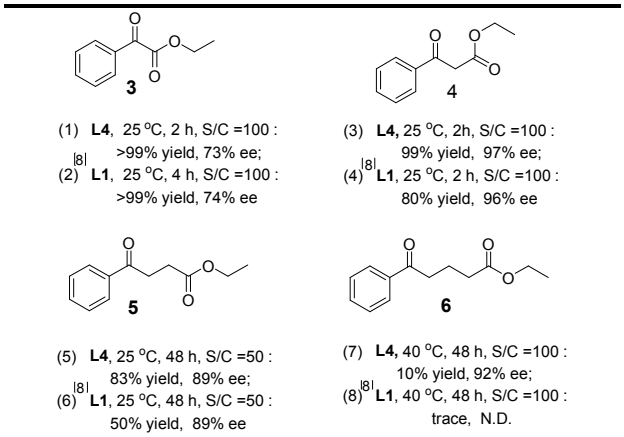
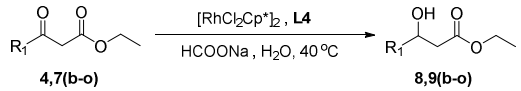


Figure 4. The ATH of aromatic ketoesters with ligand **L4** and **L1**.

With the optimal catalyst and conditions in hand, the *β*-aryl *β*-ketoester substrate scope was investigated at 40°C. As shown in Table 2, for most of the ketoester substrates, regardless of bearing electron-donating or -withdrawing substituents at the para- or meta-position, high yields and good to excellent enantioselectivities were obtained (entries 1-9). Though, the enantioselectivities of other 2-substituted ketoesters **7d** and **7h** showed the lowest ee values 86% and 74% respectively (entries 4 and 8). However, in Carreira's catalyst system,[35] comparable enantioselectivities were observed in longer reaction time with higher catalyst load (S/C = 50) at low temperature (4 °C). To our delight, the ATH of heteroaromatic ketoesters **7l** and **7m** shows the best result, with 98% and 97% ee respectively (entries 12 and 13). Noticeably, the product of **7m** has also been used in the enantioselective synthesis of duloxetine which is a dual inhibitor of serotonin, norepinephrine re-uptake and an antidepressant drug.[31]

Table 2. ATH of *β*-ketoesters with double-chain surfactant-type catalyst.



entry	substrate	time (h)	yield.[b] (%)	d.r.[c]	e.e.[d] (%)
1	**4**	1.5	99	-	96 ***R***
2	**7b**	1.5	98	-	83 ***R***
3	**7c**	1.5	99	-	94 ***R***
4	**7d**	3	91	-	86 ***R***
5	**7e**	1.5	98	-	94 ***R***
6	**7f**	3	96	-	93 ***R***
7	**7g**	6	52	-	97 ***R***
8	**7h**	6	81	-	74 ***R***
9	**7i**	6	94	-	96 ***R***
10	**7j**	6	77	-	95 ***R***
11	**7k**	6	85	-	93 ***R***
12	**7l**	1.5	98	-	98 ***R***
13	**7m**	3	91	-	97 ***R***
14	**7n**	24	95	99:1	98 ***1R,2R***
15	**7o**	30	51	97:3	99 ***1R,2R***

[a] reaction conditions: 0.004 mmol of ligand L4, 0.002 mmol of $[Cp^*RhCl_2]_2$, 5 mL of H_2O, HCOONa (2 mmol), 0.4 mmol of ketoesters 40 ℃, S/C=100. [b] isolated yield. [c] Diastereomeric ratio was determined by ^{1}HNMR analysis. [d] Enantiomeric excess was determined by HPLC analysis.

Moreover, the catalyst Rh-**L4**-H has also realized the dynamic kinetic resolution (DKR) of bicyclic β-ketoesters **7n** and **7o** in water.[36-37] The ATH of bicyclic β-ketoester **7n** afforded the product **9n** with 95% yield, 98% ee and 99:1 of dr (Table 2, entry 14), and the product **9o** provided a result with 99% ee and 97:3 of dr (entry 15). The absolute configurations of the products **9n** and **9o** were (1*R*, 2*R*) speculated by the 2D-nuclear overhauser effect spectroscopy (NOESY).

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Conclusions

In conclusion, we have developed a new type of efficient chiral double-chain surfactant-type ligand **L4**, and the rhodium complexes **L4**-Rh-H formed from the surfactant-type ligand has been applied in ATH of aromatic ketoesters with high to excellent activities and enantioselectivities. The catalyst **L4**-Rh-H can self-assemble to vesicular aggregates in water as was evidenced by TEM analysis, which may serve as a nanoreactor in aqueous reaction. Compared to the micellar catalyst **L1**-Rh-H derived from single-chain surfactant-type ligand **L1**, the vesicular catalyst **L4**-Rh-H has the advantages of thermostability and more hydrophobic environment, which may contribute to its higher activity. In addition, the Rh-**L4** system was also applied to the dynamic kinetic resolution (DKR) of bicyclic *β*-ketoesters in water, giving excellent enantioselectivities and diastereoselectivities. Therefore, enhancing activities and enantioslectivities in asymmetric catalytic reactions, using vesicular nanoreactors formed from double-chain surfactant-type catalyst, were reasonably obtained. Undoubtedly, this strategy is promising and will gain more and more future achievement. In a word, double-chain surfactant-type catalyst can greatly enhance the reaction rate and enantioselectivity in water via the formation of vesicular nanoreactors, which should be highly promising for green synthesis in water and will gain more and more future achievement.

We thank National Natural Science Foundation of China (Grant No. 20972154), National Natural Science Foundation of China (Grant No. 21372161), National Basic Research Program of China (973 Program, No. 2010CB833300), the Fundamental Research Funds for the Central Universities (A0920502051722-86), and Sichuan University for financial support.

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