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First example of asymmetric transfer hydrogenation in water induced by a chiral amino alcohol hydrochloride

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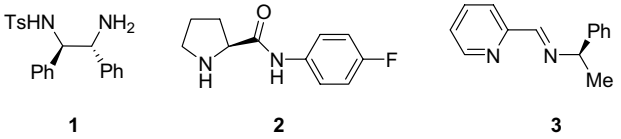
Abstract—The low-cost and commercially available (−)-ephedrine hydrochloride was firstly employed in the $[RuCl_2(p\text{-cymene})]_2$-catalyzed asymmetric transfer hydrogenation of prochiral ketones in water. The reaction could be performed in the open air at rt, affording excellent yields (up to 99%) and good enantioselectivities (up to 83% ee). It provided a further step toward the discovery of simplified catalyst systems for eventual availability.

Asymmetric transfer hydrogenation of prochiral ketones has emerged as an attractive alternative to asymmetric hydrogenation for the production of chiral alcohols, due to its operational simplicity and easy availability of hydrogen sources. Over the past few years, many effective chiral ligands have been developed,[1,2] notably the TsDPEN **1** reported by Noyori and co-workers.[3] Ru-**1** catalyst showed excellent catalytic performance in 2-PrOH and the HCOOH–Et_3N azeotropic mixture.[3a,b] However, with the increasing demand for atom economy and environmentally friendly methods,[4] the asymmetric transfer hydrogenation performed in water is now of great interest.[5] Consequently, many efficient asymmetric catalysts containing **1**-type ligands have been developed for this reaction performed in water, including water-soluble aminosulfonamides[6] and **1** immobilized on the polymer or inorganic support by chemical grafting.[7,8] More recently, Ru-**1**[9], Ru-**2**[10] and Rh-**3**[11] were directly employed in catalyzing enantioselective transfer hydrogenation of prochiral ketones in aqueous media (Fig. 1). It can be seen that till now these ligands are uniformly N,N-types. On the other hand, recent analyses show that the application of asymmetric catalysis for the industrial production is limited.[12] Two major factors that hamper its use are the cost and availability of the catalysts, in particular of the ligand that is often prepared in a tedious multistep synthesis. For this reason, we have embarked on a program aimed at the development of enantiopure ligands that are cost effective and easily prepared in short synthetic steps. A recent breakthrough is the finding of chiral sulfamide–amine alcohol ligands for the highly enantioselective reactions.[13] In the procedure of extending these ligands, we accidentally found that (−)-ephedrine hydrochloride was effective in asymmetric transfer hydrogenation of ketones, which was the first N, O-type ligand in this aqueous reaction. In this letter, we present our preliminary results in these aspects: (1) the low-cost and commercially available (−)-ephedrine hydrochloride was an efficient ligand for asymmetric transfer hydrogenation of ketones performed in water; (2) the asymmetric reduction reaction could be conducted in the open air at room temperature; (3) the destined products could be easily separated from the catalytic system by addition of ether in the reaction mixture.

The commercially available chiral amino alcohols (**4**–**13**) (Scheme 1) were applied to the $[RuCl_2(p\text{-cymene})]_2$-catalyzed[14] asymmetric transfer hydrogenation of acetophenone in water at rt.[15] The results are summarized in Table 1. It was indicated that different amino alcohol ligands showed significant difference in catalytic activity and enantioselectivity. Using **6** and **7**, the reactions



1 **2** **3**

Figure 1.

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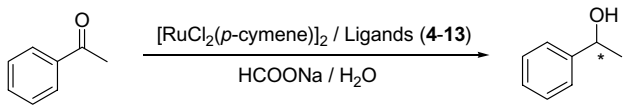
Table 1. Asymmetric transfer hydrogenation of acetophenone catalyzed by ligands **4**–**13**[a]



Entry	Ligand (mol%)	Conv.[b] (%)	Ee[c] (%)	Conf.[d]
1	**4** (3)	19.6	27	*R*
2	**5** (3)	22.5	3	*R*
3	**6** (3)	<1	—	—
4	**7** (3)	—	—	—
5	**8** (3)	76.5	54	*R*
6	**9** (3)	2.7	56	*S*
7	**10** (3)	100	76	*R*
8[e]	**11** (3)	100	53	*S*
9[e]	**10** (3)	20.4	30	*R*
10	**11** (3)	33.6	31	*S*
11	**12** (3)	99.3	75	*R*
12	**13** (3)	99.5	49	*S*
13	**12** (1.2)	81.1	78	*R*
14	**12** (5)	99.4	74	*R*
15	**12** (8)	96.9	71	*R*

[a] Reactions were performed at room temperature, using 1 mmol acetophenone, 5 equiv of HCOONa, and S/C ratio of 40 in 2 ml of water.
[b] Determined by GC.
[c] Determined by HPLC with chiralcel OD-H column.
[d] Absolute configuration determined by comparison with reported optical rotations.
[e] Solvent = 2-propanol, traditional ^{i}PrOH/KOH system was employed.

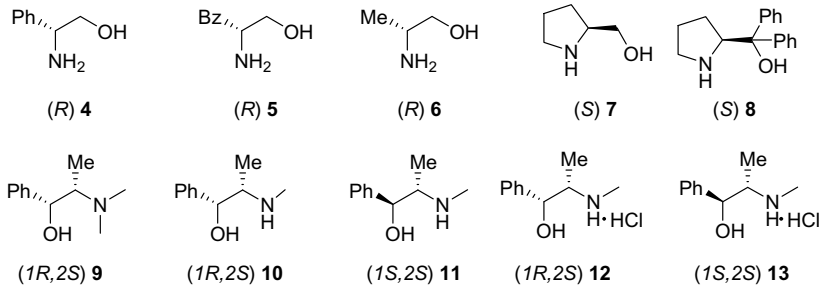
could hardly proceed (Table 1, entries 3 and 4). However, proline-based **8** with the same backbone as **7** afforded 54% ee with 76.5% conversion (entry 5). Interestingly, although *N*-methylephedrine **9** afforded very low conversion, the enantioselectivity was 54% ee (entry 6), quantitative conversions with significant enantioselectivities were observed using ephedrine ligands **10** and **11** (entries 7 and 8). These results indicated that ephedrines were promising candidates for this reaction. When the reactions were performed in the ^{i}PrOH/KOH system, low conversions were obtained unexpectedly (entries 9 and 10). It showed that the ketone reduction was drastically accelerated in water.

As ephedrine hydrochloride is more stable, cost-effective and accessible comparing with ephedrine, we thus examined the catalytic characteristics of the corresponding ephedrine hydrochlorides (**12** and **13**). With the expectation that ephedrine hydrochlorides could dissolve in water very well, the product could easily be separated from the catalyst system by addition of organic solvent. In this way, the sample could be easily taken for analytical determination. To our delight, high conversions and moderate enantioselectivities were obtained using **12** and **13** (entries 11 and 12). Considering the simple work-up, we chose **12** as the optimal ligand for this reaction. Subsequently, a brief survey of ligand loading was carried out. Decreasing the ligand loading led to enhanced enantioselectivity but lower conversion (entry 13). Increasing the ligand loading resulted in a lower enantioselectivity (entries 14 and 15).

Under the conditions optimized for acetophenone, **12** was further extended to the asymmetric transfer hydrogenation of other ketones in water at rt (Table 2). Excellent yields and moderate to good enantioselectivities were obtained. The configurations of the products were constantly *R* as determined by comparing with the literatures.[16] For the substrates, aromatic ketones gave better results than aliphatic ketones. On the other hand, asymmetric transfer hydrogenation of aromatic ketones possessing substituents in *para*- or *meta*-position proceeded with higher enantioselectivity than those in *ortho*-position (Table 2, entries 2–10).

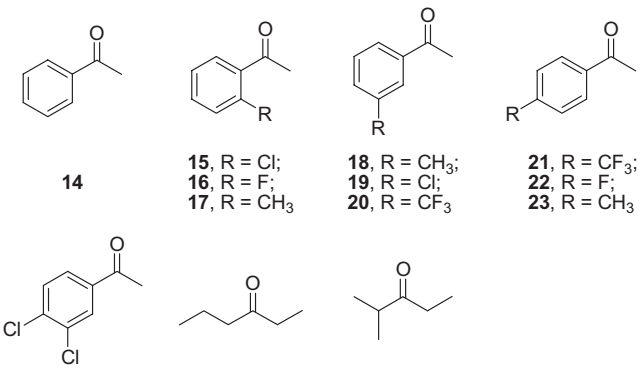
The results indicated that the low-cost and commercially available (−)-ephedrine hydrochloride with [$RuCl_2$-(*p*-cymene)]$_2$ was indeed an effective catalyst system for this reaction. After the reaction was stirred for the predetermined period of time, by adding some ether in the reaction mixture, the chiral product was transferred to the organic phase and the catalytic system was remained in the aqueous phase. Thus, the work-up of the reaction became very easy and practical, which provided a potential possibility for reusing catalysts in the similar reactions. The analysis of the results obtained revealed that both catalytic activity and enantioselectivity were greatly influenced by the structures of the chiral amino alcohols. As the further extending work, the other commercially available or readily prepared enantiopure amino alcohols could be directly converted into a very large library of enantiopure amino alcohol hydrochlorides in situ.[17] It provided an advance toward the discovery of simplified catalyst systems for eventual availability.

In summary, we have demonstrated that a combination of the low cost and commercially available (−)-eph-



Scheme 1. The evaluated ligands in this paper.

Table 2. Asymmetric transfer hydrogenation of prochiral ketones employing **12**[a]



Entry	Ketone	Yield[b] (%)	Ee[c] (%)	Conf.[d]
1	**14**	99	75	*R*
2	**15**	99	43	*R*
3	**16**	99	50	*R*
4	**17**	94	48	*R*
5	**18**	93	79	*R*
6	**19**	95	83	*R*
7	**20**	91	81	*R*
8	**21**	96	83	*R*
9	**22**	95	76	*R*
10	**23**	92	75	*R*
11	**24**	57[e]	65	Nd[f]
12	**25**	97[e]	50	Nd[f]
13	**26**	96[e]	62	Nd[f]

[a] Reactions were performed at room temperature, using 1 mmol ketone, 5 equiv of HCOONa, and S/C ratio of 40 in 2 ml of water.
[b] Isolated yield.
[c] Determined by HPLC or GC.
[d] Absolute configuration determined by comparison with reported optical rotations.
[e] Conversion of ketone was determined by GC.
[f] Not determined.

rine hydrochloride with $[RuCl_2(p\text{-cymene})]_2$ is an effective catalyst system for the asymmetric transfer hydrogenation of prochiral ketones in water, providing excellent yields up to 99% and good enantioselectivities up to 83% ee. The asymmetric reduction reaction could be performed in the open air at rt. The destined chiral secondary alcohols were easily separated from the catalytic system by adding some ether to the reaction mixture. The use of the stable, easily accessible, operationally simple and low-cost ligand for this reaction performed in water is practical and could be amenable to scale-up.[18] Further work is in progress in this laboratory with the aim of reusing the catalytic system and examining the scope of this catalyst.

Acknowledgements

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15. The representative procedure of asymmetric transfer hydrogenation of acetophenone. A suspension of $[RuCl_2(p\text{-cymene})]_2$ (0.0125 mmol, 7.5 mg) and the ligand (0.03 mmol) in H_2O (2 mL) was stirred at room temperature for 2 h. HCOONa (5 mmol, 340 mg) and acetophenone (1.0 mmol) were then added. After the mixture was stirred for 24 h, Et_2O (6 mL × 3) was added. The resulting mixture was stirred for 3 min and separated. The combined organic phase was concentrated under vacuum to give the crude product. The residue was purified by flash chromatography to give *R*-phenylethanol (0.604 g, 99%) as a clear liquid, which was analyzed by GC analysis with a HP-CHIRAL-20β, 30 m × 0.248 m × 0.25 μm capillary column or HPLC analysis with a Daicel Chiralcel OD-H column on an Agilent HP-1100 HPLC instrument (Solvent, 97:3 hexane/isopropanol; Flow rate 1 mL min^{-1}; 254 nm UV detection, $t_R = 12.11$ min and $t_S = 15.30$ min) gave the results. 1-Phenylethanol: ^1H NMR (400 MHz, $CDCl_3$): δ 1.34 (d, $J = 6.4$ Hz, 3H), 3.45 (s, 1H), 4.66–4.69 (m, 1H), 7.16–7.25 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 25.06, 69.96, 125.41, 127.16, 128.05, 128.29, 145.91.
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