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Asymmetric hydrogenation of simple ketones with planar chiral ruthenocenyl phosphinooxazoline ligands

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ABSTRACT

Ruthenocenyl phosphinooxazoline ligands have been shown to be highly efficient catalysts in the asymmetric hydrogenation. Both simple aromatic and heteroaromatic ketones were examined and excellent conversions and enantioselectivities were achieved.

1. Introduction

Enantiomerically pure alcohols have a wide range of applications, for example, key building intermediates for the manufacture of pharmaceuticals and advanced materials in organic synthesis.[1] Due to its high atom economy and activity, the metal-catalyzed asymmetric hydrogenation of ketones is one of the simplest and most powerful ways to produce chiral alcohols and as a core technology has attracted much attention not only in academics but also in industry.[2] Among them, the asymmetric Ru(II)-catalyzed hydrogenation of various ketones using chiral phosphine-oxazoline ferrocenes as chiral ligands have been widely studied with excellent catalytic behaviors.[3] However, ruthenocene-based chiral ligands, especially the chiral phosphine-oxazoline ruthenocenes have received much less attention so far.

It is known that the distances between the two cyclopentadienyl rings in ferrocene and ruthenocene are 3.32 and 3.68 Å, respectively.[4] A longer distance by about 10% in ruthenocene compared to their ferrocene analogues would be expected to present different enantioselectivity and catalytic activity in catalyzed asymmetric synthesis. In our previous reports, planar chiral ruthenocenes were shown to be more efficient ligands in comparison to the corresponding ferrocene ligands, much higher stability, catalytic activity, and comparable excellent enantioselectivity were observed in many kinds of asymmetric synthesis.[5] Recently, we reported the novel planar chiral ruthenocenyl phosphinooxazoline ligands and their application in the enantioselective transfer hydrogenation of simple aromatic ketones, which afforded excellent yields and enantioselectivities (>99% ee).[6] Encouraged by the excellent catalytic abilities of the planar chiral ruthenocenyl phosphinooxazoline ligands, we wondered whether these high effective ligands would also offer excellent catalytic behavior in the asymmetric hydrogenation with H_2 as a hydrogen source. Herein, we report a highly efficient enantioselective hydrogenation of a wide range of simple aromatic and heteroaromatic ketones using these planar chiral ruthenocenyl phosphinooxazolines **1**–**4** as chiral ligands with H_2 as the hydrogen source (Fig. 1).

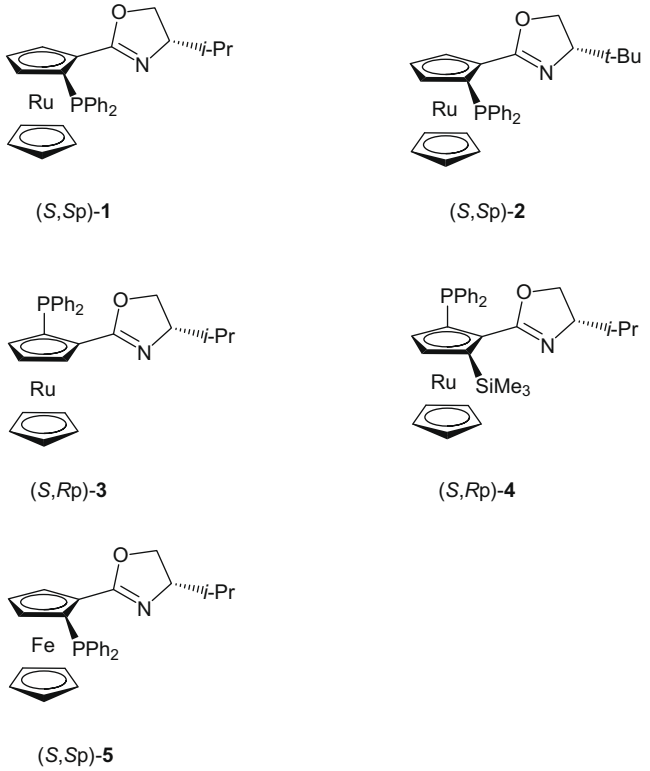

Figure 1.

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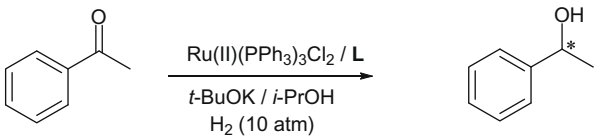
2. Results and discussion

Our initial efforts focused on screening a variety of ruthenocenyl phosphinooxazoline ligands **1**–**4** in order to ascertain their effect on the asymmetric hydrogenation reaction (Table 1).

Firstly, the chiral ruthenocenyl ligands **1** and **2**, which have the same chiral elements were applied in this Ru(II)-catalyzed hydrogenation of acetophenone. Thus, the catalyst was first prepared in situ by the addition of *i*-PrOH to a mixture of **1** or **2** with $Ru(II)(PPh_3)_3Cl_2$ under Ar gas followed by heating the solution at reflux for 1 h. Then the hydrogenation was conducted at the relatively low pressure of 10 atm H_2 at room temperature for 24 h. Excellent enantioselectivities were obtained with quantitative conversions (Table 1, entries 1 and 2). It was evident that the planar chiral ruthenocenyl phosphinooxazoline ligands were also efficient ones here, compared to the reactions with *i*-PrOH as a hydrogen source. The effect of planar chirality was also examined.[8] Ligand **3** with the identical central but opposite planar chirality was applied and a somewhat lower ee value was obtained with the same configuration of product (Table 1, entry 3). This demonstrates that the central chirality on the oxazoline plays an important role in the construction of the absolute configuration of the product. Meanwhile the matching of the planar chirality and the central chirality is essential for the ee values of the product. Ligand **4**, with a bulky TMS group at another *ortho*-position of the oxazoline, was also used as a chiral ligand in this asymmetric hydrogenation. The ee value was closer to that of ligand **3** since the TMS group is far away from the reaction center (Table 1, entry 4). For the sake of comparison, ligand **5**, the ferrocene analogue of the ligand **1**, was also used as a chiral ligand in this asymmetric hydrogenation. It was found that the ruthenocene ligand **1** showed a slightly higher enantioselectivity for this asymmetric catalysis under the identical reaction conditions (Table 1, entries 1 and 5).

Table 1
Asymmetric hydrogenation of acetophenone with planar chiral ruthenocenyl phosphinooxazoline ligands[a]



Ligands	Conv.[b] (%)	ee[c] (%) (config.)[d]
1	100	97 (*S*)
2	100	96 (*S*)
3	100	83 (*S*)
4	100	85 (*S*)
5	100	96 (*S*)

[a] Reactions were conducted using 0.4 mmol of acetophenone in *i*-PrOH (5 ml) containing 1.3 mol % of the ligands, 1 mol % of $Ru(II)(PPh_3)_3Cl_2$, and 10 mol % of *t*-BuOK/*i*-PrOH (0.2 M), under H_2 atmosphere (10 atm) at 25 °C for 24 h.
[b] The conversions were determined by ^1H NMR.
[c] Determined by GC using CP-Chirasil-Dex CB column.
[d] The absolute configuration of product was assigned through comparison of the sign of specific rotations with the literature data.[7,3d,e]

Since the reaction conditions here were almost identical to those in the transfer hydrogenation except the presence of H_2 and the difference of the reaction temperature, we wanted to determine whether the reaction was carried out via transfer hydrogenation or a combination of transfer hydrogenation and H_2 hydrogenation. Thus, the reaction was conducted under the same reaction conditions in the absence of H_2. No reaction was observed at room temperature, although it could proceed smoothly and quickly at reflux. This phenomenon explained that it was H_2 rather than *i*-PrOH providing the hydrogen resource in the asymmetric hydrogenation reaction.

In order to examine the steric and/or electric effect of the substituent in the phenyl group of the substrate, several substituted ketones were examined (Table 2). Compound **1** was selected as the chiral ligand according to its catalytic activity and enantioselectivity. It was shown that electronic effects of the aromatic ring substituents played an important role in determining the degree of the enantioselectivity of the reaction. High enantioselectivities were obtained when an electron-donating group, such as Ph, CH_3, and CH_3O, was located in the benzene ring (Table 2, entries 2–7). However, when the substituent on the benzene ring was changed to an electron-withdrawing group, such as F, Cl, and Br, the value of an enantiomeric excess was slightly decreased (Table 2, entries 8–12). On the other hand, the steric hindrance of the aromatic ring substituents also seemed to have an influence in this case: *meta*-substituted acetophenone gave a higher enantiomeric excess than their *ortho*- and *para*-substituted analogues due to the combination of the steric and electric effects (Table 2, entries 3–11). In total, all aromatic substrates including the β-acetonaphthone showed high catalytic activity and had been hydrogenated with consistently high enantioselectivity (Table 2, entries 1–13). In addition, this method also allowed the asymmetric hydrogenation of heteroaromatic ketones in excellent conversion and enantioselectivity (Table 2, entries 14 and 15).[9]

Table 2
Asymmetric hydrogenation of aromatic and heteroaromatic ketones catalyzed by planar chiral ruthenocenyl phosphinooxazoline ligand **1**[a]

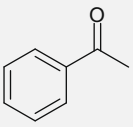
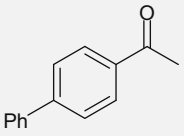
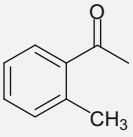
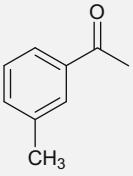
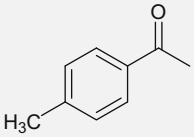
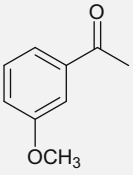
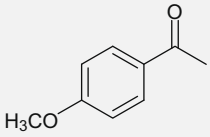
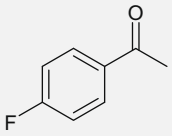
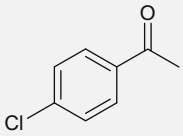
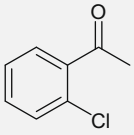
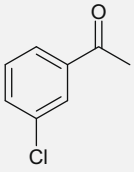
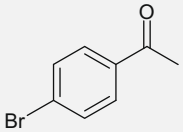
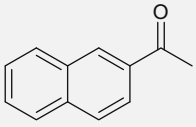
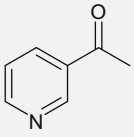
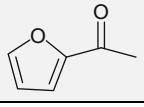
Entry	Substrate	Conv.[b] (%)	ee[c] (%)
1		100	97
2		94	97
3		100	97
4		100	98
5		100	97
6		100	98

Table 2 (*continued*)

Entry	Substrate	Conv.[b] (%)	ee[c] (%)
7		98	96
8		100	96
9		100	91
10		100	90
11		100	96
12		99	92
13		94	95
14		99	89
15		99	95

[a] All reactions were conducted in *i*-PrOH (5 ml) using 1.3 mol % of the ligands, 1 mol % of Ru(II)$(PPh_3)_3Cl_2$, 10 mol % of *t*-BuOK/*i*-PrOH (0.2 M), under a H_2 atmosphere (10 atm) at 25 °C for 24 h.

[b] The conversions were determined by ^1H NMR.

[c] Determined by GC using a CP-Chirasil-Dex CB column.

3. Conclusion

In conclusion, ruthenocenyl phosphinooxazoline ligands were shown to be highly efficient in the asymmetric hydrogenation. Various ketones including both aromatic and heteroaromatic ketones were examined and the reaction proceeded with consistently high enantioselectivity. Comparative enantioselectivity and catalytic activity were obtained by using ruthenocenyl phosphinooxazoline ligands compared to the corresponding ferrocenyl phosphinooxazolines. All the results greatly broaden the scope and utility of the planar chiral ruthenocenyl phosphinooxazoline ligands and the Ru-catalyzed asymmetric hydrogenation.

4. Experimental

4.1. General procedure for the asymmetric hydrogenation of acetophenone

Under an argon atmosphere, 1 mol % of $[RuCl_2(PPh_3)_3]$ and 1.3 mol % of chiral ligand were dissolved by heating at reflux in degassed dry 2-propanol (3 mL) for 60 min. After quickly cooling to rt, a solution of the acetophenone (0.4 mmol) in degassed dry 2-propanol (2 mL) was added. Then a solution of *t*-BuOK in degassed dry 2-propanol (0.2 M, 0.2 mL) was added to the mixture. The above reaction mixture was stirred under a H_2 atmosphere (10 atm) at 25 °C for 24 h in an autoclave. The residue was determined by ^1H NMR directly to give the percent conversion and purified on silica gel column chromatography with ethyl acetate–petrol ether (1:4) to afford pure product for the determination of the ee value by GC using CP-Chirasil-Dex CB column.

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