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Asymmetric transfer hydrogenation of alkyl/aryl or alkyl/methyl ketones catalyzed by known C_2-symmetric ferrocenyl-based chiral bis(phosphinite)-Ru(II), Rh(I) and Ir(III) complexes

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ABSTRACT

Known Ru(II), Rh(I) and Ir(III) complexes of C_2-symmetric ferrocenyl based chiral bis(phoshinite) ligands were catalyzed the asymmetric transfer hydrogenation of alkyl/aryl or alkyl methyl ketones. Corresponding secondary alcohols were obtained with high enantioselectivities up to 98% ee and reactivities using *iso*-propanol as the hydrogen source.

1. Introduction

Extensive researches have been carried out in the field of asymmetric synthesis, not only to synthesis of new chiral compounds, but also to improve catalyst that can give higher enantioselectivity and catalytic activity. The enantioselective reduction of ketones by molecular hydrogenation is one of the most important methods for preparing chiral secondary alcohols. From an economic and environmental point of view, the transfer hydrogenation is a powerful alternative for their synthesis [1,2]. Traditionally, an asymmetric catalyst most often consists of a transition metal ion in combination with chiral ligands. Choosing a ligand plays a key role in the performance of chiral ligand-based catalysts toward both high enantioselectivity and high activity. Phosphorus donor ligands have been shown to be indispensable for the asymmetric transfer hydrogenation (ATH) reactions [3–8].

Ru(II), Rh(I) and Ir(III) metals have received wide attention due to their exclusive applications in asymmetric catalysis, especially in asymmetric transfer hydrogenation. Ruthenium catalysts are most widely used in transfer hydrogenation reactions [9]. Ru complexes of phosphinite ligands have been more explored than Rh- and Ir-phosphinite complexes in asymmetric transfer hydrogenation reactions. Chiral Rh(I) C_2-symmetric ferrocenyl phosphinites complexes were used as catalysts in asymmetric transfer hydrogenation of ketones for the first time by our research group [10]. One of the first reports on the iridium-based ATH of ketones was carried out by Grazani and co-workers [11] who used dihlorobis(1,5-cyclooctadiene)diiridium as a precatalyst in the presence of the chiral phosphines (CHIRAPHOS, PROPHOS). In addition, contemporarily, Bakos et al. found that in-situ prepared iridium complexes of phosphinites (BDPOP, BDPODP) could also catalyze the ATH of aromatic ketones [12].

Following our interest in C_2-symmetric ferrocenyl-phosphinites as a highly modular chiral source for preparing Ru(II) [13], Rh(I) [10] or Ir(III) [14] complexes and encouraged by the results of these complexes in asymmetric transfer hydrogenation of aromatic ketones, we have applied C_2-symmetric ferrocenyl-phosphinite ligands in the Ru-, Rh- and Ir-catalyzed enantioselective transfer hydrogenation of alkyl aryl or alkyl methyl ketones.

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2. Results and discussion

2.1. Synthesis of the C_2-symmetric ferrocenyl-phosphinite ligands and their ruthenium(II), rhodium(I) and iridium(III) complexes

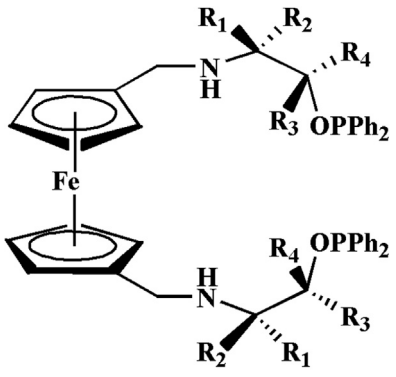
To synthesize chiral ligands with ferrocenyl backbones, we became interested in chiral phosphinite ligands from chiral diols having ferrocenyl backbones. For this aim, C_2-symmetric ferrocenyl-phosphinite ligands **1-3** (Scheme 1) were prepared according to the literature procedures [10]. The ^{31}P-{^1H} NMR spectra of compounds, **1-3** show single resonances due to phosphinite ranging from δ 107–112 ppm in line with the values previously observed for similar compounds [7,8,15–17].

Ru(II), Rh(I) or Ir(III) complexes(Scheme 2) were prepared by the reaction of corresponding ligands (1 equiv.) with [Ru(η^6-*p*-cymene)(μ-Cl)Cl]$_2$ (1 equiv.), [Rh(cod)Cl]$_2$ (1 equiv.) or [Ir(η^5-C_5Me_5)(μ-Cl)Cl]$_2$ (1 equiv.), respectively, in CH_2Cl_2 [10,13,14]. The ^{31}P NMR spectra of ruthenium(II) complexes **4-6** show singlets ranging from δ 109–114 ppm, rhodium(I) complexes **7-9** show doublets (d, $^1J_{RhP}$: 178–180 Hz) at approximately δ 120 ppm, iridium(III) complexes **10-12** show singlets ranging from δ 72–74 ppm.

2.2. Catalytic studies

The ruthenium(II), rhodium(I) or iridium(III) catalyzed asymmetric transfer hydrogenation reactions have received increasing attention in the last decade, as they are selective method to form new chiral secondary alcohols in a single operational step [9,18]. The activity of ruthenium(II), rhodium(I) or iridium(III) complexes containing different chiral ligands bearing phosphorus moiety is well known in this catalytic reaction. In the asymmetric transfer hydrogenation reactions different hydrogen sources such as *iso*-propanol/base [19–21] and formic acid/triethylamine system [22,23] have long been used.

According to our knowledge, there are not many reports on asymmetric transfer hydrogenation of ketones by using chiral metal C_2-symmetric ferrocenyl phosphinites as catalyst in the literatures. In the beginning we have reported some studies on monodedendate and bidendate phosphinite ligands with Rh(I), Ir(III) and Ru(II) complexes [24–26]. Although the catalytic results for asymmetric transfer hydrogenation were not perfect, they are not so bad, so these results prompted us to develop these types of catalysts. Furthermore, we found that the monodendate ferrocenyl-phosphinite ligands gave better enantioselectivity than other phosphinite ligands [6,7,27]. It is well known that the C_2-symmetric catalysts enhance the enantioselectivity of the reaction by reducing the number of the competing diastereomeric pathways due to the homotopic nature of the ring coordination sites of the complexes formed by the catalysts [28]. So, it is expected that phosphinites based on C_2-symmetric ferrocenyl ligands may result in unique properties suitable for catalytic reactions. Finally, considering advantage of both C_2-symmetrical ligands and phosphinites often give high levels of enantioselectivity in asymmetric reactions [29]. Inspired by the prompted results obtained by several chiral phosphinite ligands, we have developed a new class of C_2-symmetric ferrocenyl phosphinite ligands that allow good control of enantioselectivities via facile structural manipulation [10,13,14]. Finally, encouraged by the enantioselectivities obtained in these studies with aromatic ketones, we next extended our investigations to include asymmetric hydrogenation of various ketones. In this study, we preferred to investigate the asymmetric transfer hydrogenation of alkyl/aryl or alkyl methyl ketones by using a *iso*-propanol/base system in the presence of a catalytic amount of ferrocenyl-phosphinite based ruthenium(II), rhodium(I) or iridium(III) complexes. For this aim, complexes **4-12** were evaluated as precursors for the catalytic asymmetric transfer hydrogenation of methyl ethyl ketone (2-butanone) by *iso*-propanol and the results were summarized in Table 1. Catalytic experiments were carried out under argon atmosphere using standard Schlenk-line techniques. To an *iso*-propanol solution of complex **4-12**, an appropriate amount of methyl ethyl ketone and KOH/*iso*-propanol solutions were added, at room temperature. The solution was stirred, and the reaction was monitored by GC. At room temperature, transfer hydrogenation of methyl ethyl ketone occurred very slowly, with low conversion (up to 35%, 72 h, entries 1-9) and moderate to high enantioselectivity (up to 90% ee). As a result of reversibility of the reaction, prolonging the reaction time (144 h) at room temperature led to a decreasing of enantioselectivity, as indicated in the catalytic results of **4-12** (Table 1). In addition, the choice of base, such as KOH and NaOH, had little influence on the conversion and enantioselectivity. Furthermore, the complexes **4-12** are very active leading to quantitative conversions of the methyl ethyl ketone with a catalyst/KOH ratio of 1/5 in reflux conditions (Table 1, entries 19-27). The chiral (*R*)- or (*S*)-2-butanol was obtained in high yield with moderate-to-good enantiomeric excess. The best enantioselectivity (95% ee) was obtained by use of ligand **2** among the three ferrocenyl-phosphinites (entries 20, 23 and 26), while the use of ligand **1** in Ru(II), Rh(I)- and Ir(III)-catalyzed transfer hydrogenation of methyl ethyl ketone gave the lowest enantioselectivity (entries 19, 22 and 25).



R$_1$: H,	**R$_2$**: H,	**R$_3$:** H,	**R$_4$**: CH_3,	**1**
R$_1$: H,	**R$_2$**: H,	**R$_3$:** phenyl,	**R$_4$**: H,	**2**
R$_1$: phenyl,	**R$_2$**: H,	**R$_3$:** phenyl,	**R$_4$**: H,	**3**

Scheme 1. C_2-symmetric ferrocene based bis(phosphinite) ligands **1-3**.

Following investigation of the optimum conditions, Ru(II), Rh(I) and Ir(III) complexes were evaluated for their catalytic activity toward transfer hydrogenation of alkyl/aryl or alkyl/aryl methyl ketones using *iso*-propanol both as the hydrogen source and solvent in the presence of KOH as the base. First, we applied these Ru(II), Rh(I) and Ir(III)-catalyzed reaction systems to variety of alkyl aryl ketones (Table 2 for Ru(II), Table 3 for Rh(I), Table 4 for Ir(III)). The ATH of 1′-acetonaphthone was particularly efficient yielding a virtually perfect enantioselectivities (Tables 2–4, entry 11) with high conversion in 2 h for Ru(II), in 3 h for Rh(I) and Ir(III) at 82 °C. The reduction of the cyclohexyl phenyl ketone was also successful using the complexes **4-12** culminating at 82 °C in 55–74% ee (Tables 2–4, entries 19-21). It was found that the product yield was much dependent on the nature of the alkyl and aryl groups [18]. Next, we applied these catalytic systems to a variety of alkyl methyl ketones. ATH of alkyl methyl ketones has been known to be more difficult to achieve higher enantioselectivity than those of alkyl aryl ketones [30]. The results are summarized in Table 2 for Ru(II),