



Enantioselective transfer hydrogenation of various ketones with novel efficient iridium(III) ferrocenyl-phosphinite catalysts



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ABSTRACT

The asymmetric reduction of prochiral ketones is a pivotal reaction for the preparation of chiral alcohols which form an extremely important class of intermediates for fine chemicals and pharmaceuticals. Especially, iridium-based asymmetric reduction of ketones to enantiomerically enriched alcohols has recently attracted important attention by a number of research groups and interest in this area is growing. Therefore, a series of novel neutral mononuclear iridium(III) ferrocenyl-phosphinite complexes have been prepared and applied in the iridium(III)-catalyzed asymmetric transfer hydrogenation (ATH) of ketones to give corresponding secondary alcohols with outstanding enantioselectivities and reactivities using 2-propanol as the hydrogen source (up to 99% ee and 99% conversion). It was seen that the substituents on the backbone of the ligands resulted in a significant effect on both the activity and % enantioselectivity. Furthermore, the structural elucidation of the complexes was carried out by elemental analysis, IR and multi-nuclear NMR spectroscopic data.

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1. Introduction

The development of new asymmetric catalytic systems is still a major challenge because of its importance in synthetic organic chemistry and manufacturing fine chemicals [1,2]. An increasing number of chiral compounds and enantiomerically pure drugs are prepared through transition metal-catalyzed asymmetric reactions [3–6]. Since the reactivity and stereoselectivity of an asymmetric transformation are highly dependent on the structure of the chiral ligand coordinated to the transition metal, the design and synthesis of efficient chiral ligands are important in this area and have attracted a great deal of attention from both academia and industry [7,8]. In particular, asymmetric transfer hydrogenation of prochiral ketones to provide chiral alcohols has received a great deal of attention in the last decade or so [9,10]. For that reason, among several applications such as polymers [11] to bioorganometallic chemistry [12–14], the use of ferrocene-based chiral ligands in asymmetric synthesis is the most prominent [15,16]. The ferrocene moiety has been extensively explored as a backbone of chiral phosphine ligands due to its easy modifiability and highly electron

donating property [17]. Furthermore, their distinctive structure allows one to design a variety of chiral ferrocenyl phosphine ligands, which are useful tools in metal-catalyzed asymmetric hydrogenation reactions [18,19].

In spite of the encouraging performance of many ferrocene based bidentate phosphorus-chelate ligands [20–25], the past few years have witnessed a renewed interest in the development of chiral monodendate phosphorus ligands for use in asymmetric hydrogenation reactions [26–29]. This resurgence in monodendate ligands is due to the ready accessibility of a range of diverse ligand structures, and often their lower cost compared to bidentate ones [30]. Following the studies from the groups of Pringle [31], Reetz [32], Feringa [33] and more recently Chan [34] and Zhao [35] a large number of chiral monodendate phosphonite, phosphite, and phosphoramidite ligands have been found to induce good to excellent enantioselectivities in asymmetric hydrogenation reactions, comparable to or exceeding those obtained with bidentate ligands [36,37]. Furthermore, the most important advantage of chiral phosphinite ligands over the corresponding phosphine ligands is the easiness of preparation, which leads to a substantial interest to develop highly effective chiral monodendate phosphinite ligands for asymmetric catalysis [38–41].

Lately, the synthesis and applications of efficient rhodium-based catalysts have been reported in the literature [42]. However the

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interest in iridium catalysts [43], which have been successfully used for the asymmetric transfer hydrogenation, is rapidly growing in recent years. Iridium has the advantage to be much less expensive than rhodium [44]. Since the pioneering work of Mestroni et al. on the use of iridium complexes in the transfer hydrogenation of ketones [45], numerous iridium-based catalytic systems have been studied [46]. The different catalytic systems will be presented according to the coordination pattern of the ligands involved. One of the first reports on the iridium-based ATH of ketones was by Grazani and co-workers [47]. Dichlorobis(1,4-cyclooctadiene)diiridium was used as a precatalyst in the presence of the chiral phosphines for the asymmetric transfer reduction of ketones. In addition, contemporarily, Bakos et al. found that in-situ prepared iridium complexes of phosphinites could also catalyze the ATH of aromatic ketones [48,49]. Comparable studies were carried out by numerous P-based ligands by many researchers. Even though ferrocenyl-phosphine ligands have found widespread applications in transition metal catalyzed asymmetric transformations [50–52], the analogous phosphinites provide different chemical, electronic and structural advantages compared to phosphines. For instance, the metal-phosphorus bond is often stronger in phosphinites compared to the related phosphines due to the presence of electron-withdrawing P-OR group. In addition, the empty σ^* -orbital of the phosphinite P(OR) $_2$ is stabilized, making the phosphinite a better acceptor [53].

We have recently shown that chiral monodentate ferrocenyl-phosphinites ligands, which contain sterically and electronically different ligating fragments, are able to ensure high enantioselectivities in a variety of transition-metals [54]. Furthermore, considering the advantage of phosphinites, in recent years our research group has reported the synthesis [55–57], characterization and coordination properties of this kind of ligands [58–60]. With an aim to design the efficient catalysts for asymmetric transfer hydrogenation (ATH) of ketones, herein, we describe the synthesis and characterization of novel neutral iridium(III) ferrocenyl-phosphinite complexes. As far as we know, there are not so many reports on asymmetric transfer hydrogenation of ketones by using this kind of Iridium-complexes as catalyst. Thus, these iridium complexes have been employed successfully as catalysts in the asymmetric transfer hydrogenation of various ketones.

2. Results and discussion

2.1. Synthesis and characterization of the iridium(III) ferrocenyl-phosphinites complexes

We have had an ongoing interest in the synthesis and use of optically active ligands in asymmetric catalysis, especially ferrocenyl-phosphinites. The synthesis of D-, L-phenylglycinol, D-, L-phenylalaninol, D-, L-valinol, L-leucinol and L-isoleucinol were accomplished in one step from D-, L-phenylglycine, D-, L-phenylalanine, D-, L-valine, L-leucine or L-isoleucine, respectively, according to the procedures described in the literature [61,62]. The ferrocene based amino alcohols were synthesized by the condensation reaction between ferrocenecarboxaldehyde [63] and amino alcohols in the presence of the base catalyst [64]. The synthetic process for the preparation of the ferrocenyl-phosphinites [65,66] is shown in Scheme 1. Ferrocenyl-phosphinite ligands, **9–16** were prepared by a hydrogen abstraction from the described ferrocene based chiral amino alcohols **1–8**, by a base (Et_3N) and the subsequent reaction with one equivalents of Ph_2PCL , in anhydrous toluene under inert argon atmosphere (Scheme 1). The progress of this reaction was conveniently followed by $^{31}\text{P}\{-^1\text{H}\}$ NMR spectroscopy. The $^{31}\text{P}\{-^1\text{H}\}$ NMR spectra of compounds, **9–16** show single resonances due to phosphinite at approximately δ 115 ppm [67–71] in line with the

values previously observed for similar compounds [72–75]. The structures for these ferrocene based chiral amino alcohols are consistent with the data obtained from a combination of multinuclear NMR spectroscopy, IR spectroscopy and elemental analysis.

The whole reactions of $[\text{Ir}(\eta^5\text{-C}_5\text{Me}_5)(\mu\text{-Cl})\text{Cl}]_2$ with ferrocenyl-phosphinite ligands, **17–24** are shown in Scheme 1. Treatment of $[\text{Ir}(\eta^5\text{-C}_5\text{Me}_5)(\mu\text{-Cl})\text{Cl}]_2$ with ferrocenyl-phosphinites **9–16** in 1/2:1 molar ratio in CH_2Cl_2 resulted the formation of mononuclear complexes **17–24** as crystalline solids. All neutral iridium(III) complexes were readily synthesized in good yields, which are air stable and orange microcrystalline powders. The ferrocenyl-phosphinite ligands were expected to cleave the $[\text{Ir}(\eta^5\text{-C}_5\text{Me}_5)(\mu\text{-Cl})\text{Cl}]_2$ dimer to give the corresponding complexes, **17–24** via monohapto coordination of the phosphinite group. All complexes were isolated as indicated by singlets in the $^{31}\text{P}\{-^1\text{H}\}$ NMR spectra at approximately δ 74 ppm, with a coordination shift of approximately δ 50 ppm (see supporting information, SI) attributed to formation of the corresponding iridium(III) ferrocenyl-phosphinite complexes. The assignment of the ^1H chemical shifts was derived from 2D HH-COSY spectra and the appropriate assignment of the ^{13}C chemical shifts from DEPT and 2D HMQC spectra. Furthermore, elemental analyses of the complexes are also consistent with the suggested molecular formulas. The absorption bands corresponding to ferrocenyl-phosphinite ligands in Ir(II) complexes in the IR spectra of complexes do not exhibit significant differences with respect to those of free ligands (see Experimental section).

2.2. Asymmetric transfer hydrogenation of prochiral ketones with 2-propanol

The usage of π -arene metal complexes as catalysts for asymmetric transfer hydrogenation from an appropriate donor (usually 2-propanol or formic acid) has been a subject of ongoing research for some decades. It is well-known that hydrogen gas presents considerable safety hazards especially for large scale reactions [76,77]. The use of a solvent that can donate hydrogen overcomes these difficulties. 2-propanol is a popular reactive solvent for transfer hydrogenation reactions since it is easy to handle and relatively non-toxic, environmentally benign, and inexpensive. The volatile acetone by-product can also be easily removed to shift unfavourable equilibrium.

It was found that ferrocenyl-phosphinites demonstrate outstanding air stability and their design does not need any extreme conditions, and thus their preparation is rather easy [78]. Thus, this kind of ligands combines a number of characteristics making uniquely attractive for asymmetric catalysis [79–83]. Encouraged by our recent success in the development of new chiral and highly active catalysts [84,85, and references therein], we initiated a study of the synthesis of a series of iridium(III) ferrocenyl-phosphinite complexes in the asymmetric transfer hydrogenations.

Firstly, complexes **17–24** were evaluated as precursors for the catalytic asymmetric transfer hydrogenation of acetophenone by 2-propanol and the results were summarized in Table 1. Catalytic experiments were carried out under argon atmosphere using standard Schlenk-line techniques. To an 2-propanol solution of Ir(III) ferrocenyl-phosphinite complex, an appropriate amount of acetophenone and KOH/2-propanol solutions were added, at room temperature. The solution was stirred, and then examined with capillary GC analysis. At room temperature, transfer hydrogenation of acetophenone occurred very slowly [86], with low conversion (up to 20%, 24 h) and moderate to high enantioselectivity (up to 92% ee) (Table 1, entries 1–8). As a result of the reversibility at room temperature prolonging the reaction time (72 h) led to a decreasing of enantioselectivity, as indicated by the catalytic results collected

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