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New C_2-symmetric chiral phosphinite ligands based on amino alcohol scaffolds and their use in the ruthenium-catalysed asymmetric transfer hydrogenation of aromatic ketones

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ABSTRACT

Asymmetric transfer hydrogenation processes of ketones with chiral molecular catalysts are attracting increasing interest from synthetic chemists due to their operational simplicity. C_2-symmetric catalysts have also received much attention and been used in many reactions. A series of new chiral C_2-symmetric bis(phosphinite) ligands has been prepared from corresponding amino acid derivated amino alcohols or (*R*)-2-amino-1-butanol through a three- or four-step procedure. Their structures have been elucidated by a combination of multinuclear NMR spectroscopy, IR spectroscopy and elemental analysis. ^1H-^{31}P NMR, DEPT, ^1H-^{13}C HETCOR or ^1H-^1H COSY correlation experiments were used to confirm the spectral assignments. In situ prepared ruthenium catalytic systems were successfully applied to ruthenium-catalyzed asymmetric transfer hydrogenation of acetophenone derivatives by *iso*-PrOH. Under optimized conditions, these chiral ruthenium catalyst systems serve as catalyst precursors for the asymmetric transfer hydrogenation of acetophenone derivatives in *iso*-PrOH and act as good catalysts, giving the corresponding optical secondary alcohols in 99% yield and up to 79% ee.

1. Introduction

The asymmetric hydrogenation of prochiral ketones provides good opportunities for producing a range of chiral alcohols. Chiral alcohols are very important building blocks and synthetic intermediates in organic synthesis and in the pharmaceutical industry [1].

Extensive efforts have been devoted to their reduction into secondary alcohols especially via hydrogenation [2]. Noyori et al. provided an elegant solution for the asymmetric catalytic molecular hydrogenation of simple aryl ketones [3]. The use of hydrogen gas in the molecular hydrogenation processes presents considerable safety hazards and requires pressure vessels and other equipment especially for large-scale reactions [4]. However, use of a solvent that can donate hydrogen, such as *2*-propanol, overcomes these difficulties. The volatile acetone by-product can also be easily removed to shift unfavourable equilibria. The most commonly used catalysts for this reaction are ruthenium(II) complexes, but several rhodium and iridium derivatives have also been used. Ru catalysts have excellent performances [3a,5] and Ru enjoyed a cost advantage relative to other asymmetric hydrogenation metals such as Rh [6].

The use of organometallic complexes as catalysts for asymmetric transfer hydrogenation from a suitable donor (usually *2*-propanol or formic acid) has been the subject of ongoing researches for some decades. In particular, the metals coordinated by one or more chiral phosphorus ligands exhibit exciting enantioselectivity and reactivity [7]. Complexes of the type *trans*-$RuCl_2$(diamine)(diphosphine) with matching configurations of chiral diphosphine and

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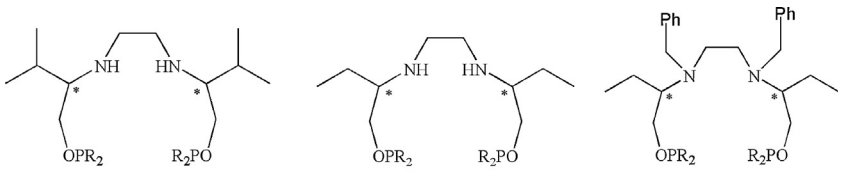


Scheme 1. D- or L-valinol and (*R*)-2-amino-1-butanol derivatives of C_2-symmetric chiral bis(phosphinite) ligands used in this study.

diamine, e.g. (*S*)-BINAP/(*S,S*)-DPEN, show high reactivity and enantioselectivity [8]. In general, the most successful chiral ligands used in the asymmetric hydrogenation reactions are rigid chelating diphosphines possessing a C_2-symmetry axis thus reducing the number of diastereomeric transition states [9]. Phosphines and phosphinites are among the most important phosphorus-based ligands with a wide range of steric and electronic properties. Phosphine ligands have found widespread applications in transition metal catalyzed asymmetric transformations [10], phoshinite-derived ligands have also attracted a considerable attention for catalytic hydrogenation [11–13]. The metal-phosphorus bond is often stronger for phosphinites compared to the related phosphine due to the presence of an electron-withdrawing P-OR group. This feature of the phosphinites provides different chemical, electronic and structural properties compared to phosphines. Additionally, the empty σ^*-orbital of the phosphinite $P(OR)R_2$ is stabilized, making the phosphinite a better acceptor [14]. So, phosphinites open many opportunities to design new improved ligands for asymmetric catalysis. The most important advantage of chiral phosphinite ligands over the corresponding phosphine ligands is the easiness of preparation [12c].

A ligand is more likely to induce high enantioselectivity if it has C_2-symmetry [1a,15] (first example: diop) or is very strongly unsymmetrical [16] (e.g. josiphos) in order to reduce the number of possible isomeric catalyst-substrate complexes [12c]. So, C_2-symmetric phosphinite derivated catalysts have received much attention and have been used in many asymmetric hydrogenation reactions and other metal-catalyzed processes [17] and it is expected that chiral amino alcohol based C_2-symmetric phosphinite ligands may result in unique properties for suitable catalytic reactions. As part of our research program on this subject, herein, we aim to synthesize new bis-phosphinites based on C_2-symmetric chiral amino alcohols (Scheme 1) and use them with Ru(II) precursor as a catalyst in the asymmetric transfer hydrogenation of acetophenone derivatives with *iso*-PrOH under varying conditions.

2. Results and discussion

2.1. Synthesis of chiral C_2-symmetric ligands and their corresponding Ru(II) complexes

C_2-symmetric catalysts have received much attention and have been used in many reactions [18,19]. We paid particular attention to C_2-symmetric phosphinite ligands, because a C_2-symmetric ligand with two equivalent phosphorus atoms can reduce the number of possible isomeric metal complexes, as well as the number of different substrate–catalyst arrangements and reaction pathways, when compared with a nonsymmetrical ligand. This consequence of C_2-symmetry can have a beneficial effect on enantioselectivity because the competing less-selective pathways are possibly eliminated [20].

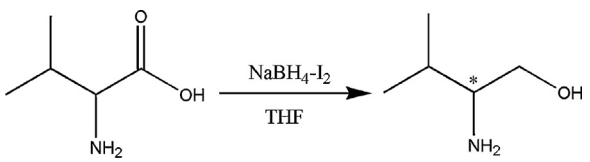
We began this study by preparing D- or L-valinol from the D- or L-valine which were reduced under standard conditions using $NaBH_4$-I_2 in dry THF according to the literature procedure [21] (Scheme 2).

We also prepared chiral C_2-symmetric amino alcohols from the D- or L-valinol, (*R*)-2-amino-1-butanol and (*R*)-N-benzyl-2-amino-1-butanol according the procedures described in the literature [22,23] as shown in Scheme 3. The structures for these chiral amino alcohols are consistent with the data obtained from ^{1}H NMR, ^{13}C NMR, IR spectra and elemental analyses (for details see experimental section).

Chiral C_2-symmetric bis(phosphinite) ligands were prepared from the corresponding C_2-symmetric amino alcohols and two equivalents of chlorodiphenylphosphine or chlorodiisopropylphosphine, in freshly distilled anhydrous toluene or CH_2Cl_2 respectively, under argon atmosphere in the presence of Et_3N as the base at room temperature in high yield as outlined in Scheme 4.

The progress of this reaction was conveniently followed by ^{31}P-{^{1}H} NMR spectroscopy. The signals of the starting materials Ph_2PCl at $\delta = 81.0$ ppm and $^iPr_2PCl$ at $\delta = 133.8$ ppm disappeared and new singlets appeared in downfield due to the phosphinite ligands. The ^{31}P-{^{1}H} NMR spectra of compounds **1**, **2**, **5**, **7** show a single resonance due to the diphenylphosphinite moiety at 114.78, 113.81, 113.84, 113.79 ppm (Fig. 1), respectively, and compounds **3**, **4**, **6**, **8** also exhibit a single resonance due to the diisopropylphosphinite moiety at 150.93, 151.93, 151.98, 153.84 ppm (Fig. 2), respectively. These spectra indicate that two phosphorus atoms in the each molecule are equivalent [24].

The ^{31}P-{H} NMR spectra also display formation of PPh_2PPh_2 and $P(O)Ph_2PPh_2$, as indicated by signals



Scheme 2. Synthesis of D- or L-valinol.