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Journal of Molecular Catalysis A: Chemical 273 (2007) 284–288
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
www.elsevier.com/locate/molcata

Synthesis of novel chiral macrocyclic ONNO-type ligands and use in asymmetric transfer hydrogenation

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Received 19 January 2007; received in revised form 6 April 2007; accepted 15 April 2007
Available online 19 April 2007

Abstract

The interaction of 1,3-bis(2-formylphenoxy)-2-propanol with chiral 1,2-diaminocyclohexane gave novel chiral macrocyclic ONNO-type ligands which were fully characterized by IR, NMR, MS and CD. The catalyst systems generated in situ from the chiral cyclic ONNO ligands and the iridium hydride complex $[IrHCl_2(COD)]_2$ have been used for the first time in the asymmetric transfer hydrogenation of aromatic ketones using 2-propanol as a source of hydrogen, giving the corresponding optically active alcohols with high chemical yields and good to excellent enantioselectivities (up to 92% ee). The reactions can be performed in air and the catalytic experiments are greatly simplified.

Keywords: Chiral macrocyclic ligands; Asymmetric transfer hydrogenation; Aromatic ketone; Chiral alcohols

1. Introduction

Macrocyclic ligands often contain multi-coordination donor atoms, such as O or N and mixed O, N or N, S atoms, and exhibit remarkable properties in coordination chemistry [1–3]. On the other hand, based on the size-fitting effects of cyclic ligands, macrocyclic ligands usually show special selectivity for reaction substrates during the catalytic reactions [4–7]. Macrocyclic ligands and their metal complexes are being widely used, serving as medicine, catalysts and biological model systems [8–14].

For the past years, chiral macrocyclic ligands have had a versatile utility in asymmetric synthesis [15–22]. Firstly, the high effectiveness of chiral macrocyclic compounds in enantiomeric separation has been demonstrated by chromatographic methods, and then chiral macrocyclic compounds as enantiomeric recognition agents have been extensively studied [4]. Recently, Meunier and co-workers reported that a series of chiral macrocyclic Mn(II) salen complexes were efficient catalysts for the asymmetric epoxidation and cyclopropanation of olefins with up to 96% ee [18,19]. A chiral macrocyclic ether as catalytic precursor for promoting the asymmetric aldol reaction with high diastero- and enantioselectivities was reported by Kobayashi et al. [20]. Woo and co-workers have published the synthesis of novel chiral tetraaza macrocyclic ligands and their ability to catalyze the cyclopropanation of styrene, producing two cyclopropylesters with high diastereoselectivities and good yields [21]. Recently, Gao et al. reported studies on asymmetric aldol reactions catalyzed by novel chiral macrocyclic trimetallic center complex catalysts, and an enantioselective synergism has been observed in the reaction [22]. Gao and his co-workers also synthesized novel tetra-schiff base chiral cyclic ligands and their Robson-type macrocyclic complexes, which catalyzed asymmetric cyclopropanation of styrene with up to 94% ee [23]. However, chiral macrocyclic ligands have seldom been used in the asymmetric hydrogenation to date [24].

For the past 10 years, asymmetric transfer hydrogenation of prochiral ketones has made great progress. Most research works in this area were carried out by using the chirally modified transition metals, such as Ru, Rh and Ir, as catalyst precursors [25–32]. Compared with Ru and Rh complexes, the iridium complexes have been scarcely employed in this area [33–42].

In this paper, we describe the synthesis of chiral cyclic tetradentate ONNO-type ligands and the use in asymmetric transfer hydrogenation of ketones, giving the corresponding optically active alcohols with high chemical yield and enantioselectivity of up to 92% ee.

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doi:10.1016/j.molcata.2007.04.017

2. Experimental

2.1. General methods

All experiments were carried out under ambient conditions. IR spectra were recorded on a Nicolet Avatar 360 FT-IR spectrophotometer. NMR spectra were recorded on a Bruker AV 400 instrument using TMS as an internal standard in $CDCl_3$. Mass spectra were recorded on a Finnigan LCQ mass spectrometer. All melting points were determined on a X-4 digital melting point apparatus and were uncorrected. CD spectra were measured with a JASCO J-810 spectrophotometer. The yields and ee values were determined by GC analysis with a chiral G-TA column. The solvents were dried and purified according to standard methods.

2.2. Synthesis and characterization of 1,3-bis(2-formylphenoxy)-2-propanol

This compound was synthesized according to literature procedures in Ref. [43] in 56% yield, as white needles. Mp: 109–110 °C (dec.) IR (KBr): 3463m, 2756w, 1678vs, 1599m, 1581vs, 1485m, 1249m, 1032m cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.32–4.52 (m, 5H, CH_2CHCH_2), 7.02–7.81 (m, 8H, ArH), 10.39 (s, 2H, CHO). EIMS (*m/z*): 301.2 $(M+1)^+$.

2.3. Synthesis and characterization of chiral cyclic tetradentate ONNO-type ligand [(R, R)-$C_6O_2N_2$]

The chiral cyclic tetradentate ONNO-type ligand (*R*, *R*)-$C_6O_2N_2$ **II** was synthesized by a modification of literature procedure that was used for the synthesis of nonchiral ONNO-ligands [43]. To a warm solution of 1,3-bis(2-formylphenoxy)-2-propanol (0.60 g, 2 mmol) in 150 ml of methanol, (*R*, *R*)-1,2-diaminocyclohexane (0.23 g, 2 mmol) in 20 ml of methanol was added dropwise. The reaction solution was refluxed for 10 h, and then sodium borohydride (0.10 g, 4 mmol) was added in portions. The solution was continued refluxing with stirring for another 10 h. The solution was cooled to room temperature and H_2O (10 ml) was added. A white precipitate was removed by filtration and the filtrate was concentrated. The residue was dissolved in H_2O and extracted with $CHCl_3$ (3 × 50 ml). The combined extracts were washed with H_2O and then was dried over anhydrous Na_2SO_4. The crude product was purified by successive chromatographic separations. The ligand **II** was obtained as a white solid (0.5 g, 65% yield). Mp: 72–73 °C (dec.), $[\alpha]_D^{20} = -80.17$ (c 1.00, MeOH); IR (KBr): 3415m, 1641m, 1601s, 1493s, 1241s, 1049m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.97 (m, 2H, -CH_2-), 1.20 (m, 2H, -CH_2-), 1.68 (m, 2H, -CH-), 2.00–2.14 (m, 4H, -CH_2-), 3.55–3.64 (m, 4H, ArCH_2-), 4.00–4.31 (m, 5H, CH_2CHCH_2), 6.88–7.20 (m, 8H, ArH). EIMS (*m/z*): 383.2 $(M+1)^+$.

2.4. Synthesis and characterization of chiral cyclic tetradentate ONNO-type ligand [(S, S)-$C_6O_2N_2$]

In a similar fashion as described for (*R*, *R*)-$C_6O_2N_2$, except (*S*, *S*)-1,2-diaminocyclohexane was used, the ligand (*S*, *S*)-$C_6O_2N_2$ **III** was obtained as a white solid (0.46 g, 60% yield). Mp: 72.5–73 °C (dec.), $[\alpha]_D^{20} = +80.20$ (c 1.00, MeOH); IR (KBr): 3416m, 1643m, 1602s, 1494s, 1242s, 1050m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.98 (m, 2H, -CH_2-), 1.21 (m, 2H, -CH_2-), 1.69 (m, 2H, -CH-), 2.02–2.15 (m, 4H, -CH_2-), 3.56–3.66 (m, 4H, ArCH_2-), 4.03–4.32 (m, 5H, CH_2CHCH_2), 6.89–7.22 (m, 8H, ArH). EIMS (*m/z*): 383.2 $(M+1)^+$.

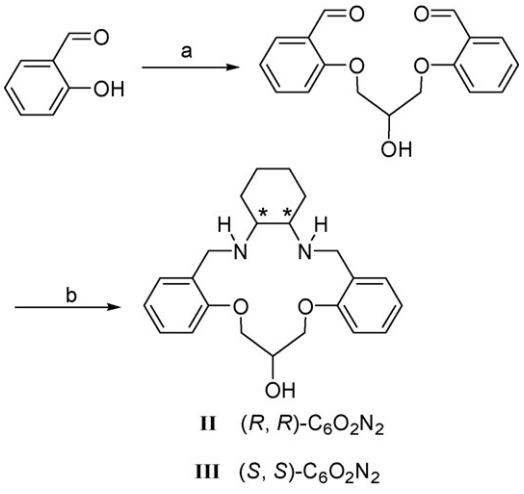
2.5. Typical experimental procedure for asymmetric transfer hydrogenation of ketones

Typical procedure for asymmetric transfer hydrogenation of ketones was as follows: $[IrHCl_2(COD)]_2$ (1.9 mg, 0.0025 mmol) and ligand **II** (3.6 mg, 0.005 mmol) were added to a Schlenk tube, then 2-propanol (10 ml) and KOH/*iso*-PrOH were introduced under air. After the mixture was stirred for 30 min, ketone was introduced and the solution was stirred at the desired temperature for the required reaction time. At the end of catalytic reaction, the product was determined by GC using a chiral G-TA column.

3. Results and discussion

3.1. Preparation and characterization of chiral cyclic tetradentate ONNO-type ligands

The interaction of salicyladehyde and epichlorohydrin gave 1,3-bis(2-formylphenoxy)-2-propanol with high yield, which further reacted with (*R*, *R*)-1,2-diaminocyclohexane in refluxing methanol and then reductant $NaBH_4$ was added. After performing reaction, the crude product was purified by successive chromatographic separations. (*R*, *R*)-$C_6O_2N_2$ (**II**) was obtained as white solid, which has been fully characterized by IR, NMR, MS and CD. In an analogous manner and using (*S*, *S*)-1,2-diaminocyclohexane instead of (*R*, *R*)-1,2-diaminocyclohexane, the ligand **III** was also prepared (Scheme 1). The CD spectra of chiral macrocyclic ligands **II** and **III** have been measured in



II (*R*, *R*)-$C_6O_2N_2$

III (*S*, *S*)-$C_6O_2N_2$

Scheme 1. Reagents and conditions: (a) epichlorohydrin, NaOH/H_2O, 60 °C, 3 h; (b) (*R*, *R*)- or (*S*, *S*)-1,2-diaminocyclohexane, MeOH, reflux, 10 h, then $NaBH_4$.