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

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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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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 $(M+1)^+$.

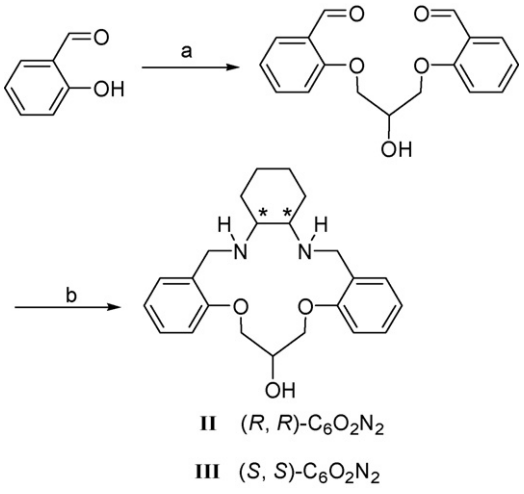
2.5. Typical experimental procedure for asymmetric transfer hydrogenation of ketones

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 $NaBH_4$.

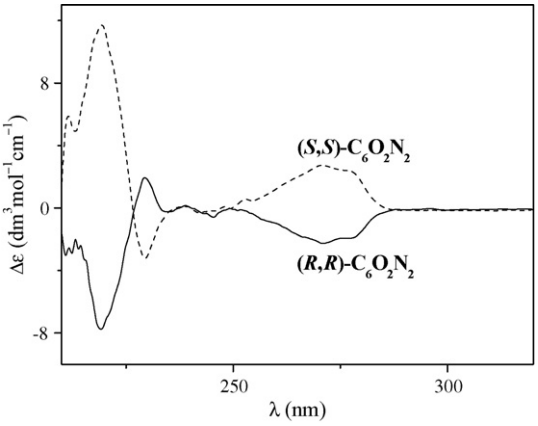


Fig. 1. The CD spectra of chiral cyclic ligand $C_6O_2N_2$.

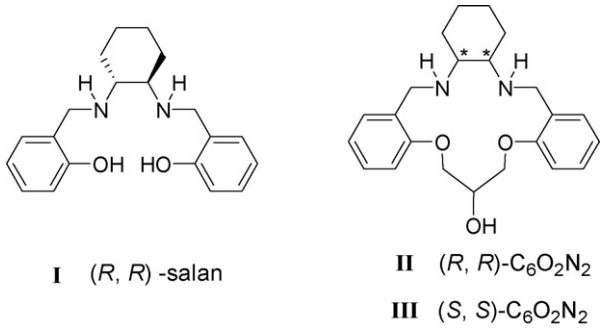


Fig. 2. Chiral tetradentate ONNO-type ligands.

methanol as solvent and exhibited the mirror-image relationship with $\Delta\varepsilon_{max}$ at 219 nm (Fig. 1).

3.2. Asymmetric transfer hydrogenation of ketones

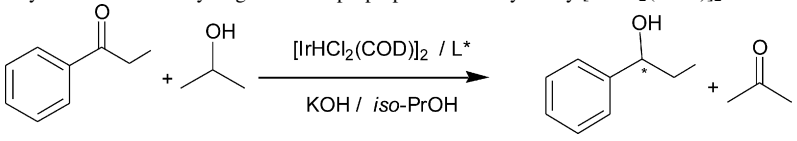
The effect of the macrocyclic ONNO ligands **II** and **III**, and their analogous open-chain salan ligand **I** [44] (Fig. 2), as catalytic precursors for asymmetric transfer hydrogenation of propiophenone, has been tested. The results are summarized in Table 1.

For the ligand **I**, the catalytic reactions proceeded very slowly with low enantioselectivity (Table 1, entries 1 and 2). When the catalytic system generated in situ from the cyclic ligand **II** and $[IrHCl_2(COD)]_2$ was employed as catalyst precursor, high yield (93–98%) was obtained. Interestingly, the increase in reactions temperature from 25 to 40 °C enhanced the enantioselectivity (Table 1, entries 3 and 4). The amount of added base did not delicately affect the yield and ee (Table 1, entries 4 and 7). Noticeably, these catalytic systems were very stable to air and water. The catalytic reactions were carried out even in air, 95% yield and 84% ee being achieved (Table 1, entry 8). The addition of water, did not affect the enantiomeric purity of the product but slowed the rate (Table 1, entry 9).

The catalytic system, consisting of $[IrHCl_2(COD)]_2$ and the macrocyclic ligand **II**, was further employed for the enantioselective reduction of a variety of aromatic ketones, as exemplified in Table 2. These catalytic experimentals were all operated in air and 2-propanol as solvent, which was used without further purification and removal of the water before use.

As shown in Table 2, a range of aromatic ketones can be reduced to the corresponding optically active alcohols with high chemical yields and moderate to good ee's. The reaction rate and enantioselectivity are delicately affected by the steric and electronic properties of the ketones. Favourably, the enantioselectivity gradually increased by increasing bulkiness of alkyl groups (methyl < propyl < butyl < isopropyl), while the high conversions were still maintained (91–96% yield, 78–92% ee, Table 2, entries 1–5). The position and electronic

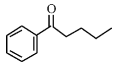
Table 1
Asymmetric transfer hydrogenation of propiophenone catalyzed by $[IrHCl_2(COD)]_2$ and the ONNO-type ligands[a]



Entry	Ligand	S/C/KOH	Temperature (°C)	Time (h)	Alcohol		
					Yield[b] (%)	Ee[b] (%)	Config.[c]
1	**I**	100:1:12	40	8	7	29	*S*
2	**I**	100:1:12	60	8	16	14	*S*
3	**II**	100:1:12	25	24	93	74	*S*
4	**II**	100:1:12	40	7	95	84	*S*
5	**III**	100:1:12	40	8	98	83	*R*
6	**II**	100:1:12	60	4	98	82	*S*
7	**II**	100:1:20	40	7	98	84	*S*
8[d]	**II**	100:1:12	40	7	95	84	*S*
9[e]	**II**	100:1:12	40	10	48	85	*S*

[a] The reactions were carried out in the presence of $[IrHCl_2(COD)]_2/L^*$ using a 0.1 M solution of ketones in *iso*-PrOH; the catalysts were generated in situ by stirring a solution of $[IrHCl_2(COD)]_2$ and chira ligand in *iso*-PrOH.
[b] Yields and enantiomeric excesses were determined by GC analysis using chiral G-TA column.
[c] The configurations were determined by comparison of the retention times of the enantioners on the GC traces with literature values.
[d] Carried out in air.
[e] Added 0.5 ml of H_2O into the reaction solution.

Table 2
Asymmetric transfer hydrogenation of various ketones catalyzed by $[IrHCl_2(COD)]_2$/ligand **II**[a]

Entry	Substrate	Time (h)	Alcohol Yield[b] (%)	Ee[b] (%)	Config.[c]
1		3	95	78	*S*
2		8	96	80	*S*
3		6	91	87	*S*
4		10	94	92	*S*
5[d]		10	94	91	*R*
6		6	99	88	*S*
7		17	85	56	*S*
8		18	41	52c	*S*
9		6	99	68	*S*
10		6	99	50	*S*

[a] The reactions were carried out in the presence of $[IrHCl_2(COD)]_2$/(*R*, *R*)-$C_6O_2N_2$ using a 0.1 M solution of ketones in *iso*-PrOH at 40 °C; the catalysts were generated in situ by stirring a solution of $[IrHCl_2(COD)]_2$ and chiral ligand in *iso*-PrOH; Sub:Cat.:KOH = 100:1:12.
[b] Yields and enantiomeric excesses were determined by GC analysis using G-TA column.
[c] Determined by HPLC using chiralcel OD column.
[d] The reactions were carried out in the presence of $[IrHCl_2(COD)]_2$/ligand **III**.

property of the ring substituents also influenced the hydrogenation results. The introduction of an electron-donating methyl group to the *ortho*-position gave higher reactivity and selectivity (99% yield, 88% ee, Table 2, entry 6), compared with the corresponding *meta*-substrate (Table 2, entry 7). However, the substrates with electron-withdrawing substituents, such as chloro, at the *ortho*-position of acetophenone, only gave lower reactivity and enantioselectivity (Table 2, entry 8). The *meta*- and *para*-substituented chloroacetophenone reacted very smoothly with moderate enantioselectivity (Table 2, entries 9 and 10).

The mechanism is not clear at the present stage. Among many possibilities, a metal hydride complex is considered to be the key active intermediate for transfer hydrogenation [33,39]. If this is the case, the open-chain chiral ONNO-type ligand **I** can theoretically form several isomers [45,46], which may lead to the lower enantioselectivity. The chiral cyclic ONNO-type ligands, more rigid ligands in which N and O atoms were fixed in a plane, resulting in only one isomer, gave higher enantioselectivity. Due to the weak O–Ir bond, attempts to isolate the iridium complexes of the chiral cyclic ONNO-type ligands have been unsuccessful. The detailed mechanistic study is now underway.

4. Conclusion

In summary, this work presented the synthesis of novel macrocyclic tetradentate ONNO ligands and their first use for asymmetric transfer hydrogenation of aromatic ketones with high reactivity and good ee's. The catalyst systems, coupled with $[IrHCl_2(COD)]_2$ and cyclic-ONNO ligands, are very stable to oxygen and moisture. Thus, catalytic reactions can be performed in air and the catalytic experiments are greatly simplified. Although the enantioselectivity remains to be further improved, the present work will provide a useful insight to catalytic asymmetric synthesis.

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