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Synthesis, Crystal Structure of Chiral Ferrocenyl Amino Alcohols, and Its Use for Asymmetric Transfer Hydrogenation[1]

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Abstract—Two chiral ferrocenyl amino alcohols (**IIIa** and **IIIb**) have been synthesized for the iridium catalyzed asymmetric transfer hydrogenation of aromatic ketones. The structures of two chiral ferrocenyl amino alcohols have been determined by single crystal X-ray diffraction (CIF files CCDC nos. 1056737 (**IIIa**) and 1056734 (**IIIb**)). The results show that the activity and enantioselectivity of the chiral iridium catalyst are very sensitive to the substrate structure. Ir(I)-catalyzed asymmetric transfer hydrogenation of acetophenone resulted in moderate to good yield and lower enantioselectivity; asymmetric transfer hydrogenation of propiophenone and 2-benzoylpyridine resulted in lower yield and lower enantioselectivity; as for 4-benzoylpyridine, good results have been achieved.

Keywords: synthesis, crystal structure, chiral ferrocenyl amino alcohol, asymmetric transfer hydrogenation, chiral iridium complex

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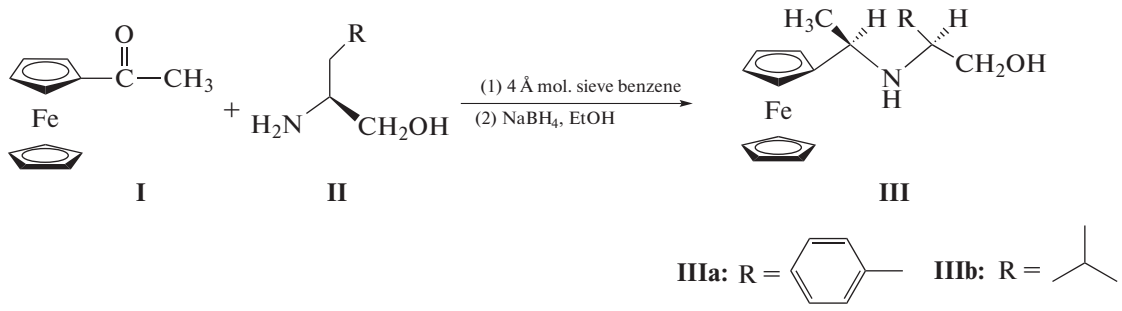
INTRODUCTION

Enantiomerically pure ferrocenyl amino alcohol compounds have been found for widespread use as chiral ligands in several reactions [1–4]. Considerable efforts have been focused on the design of ferrocenyl amino alcohols with potential applications in drug delivery and biomedical engineering. These compounds are very effective catalysts for a wide range of reactions because of the ligands of nitrogen atom and oxygen atom with many metals [5]. In addition, the steric effect of the specific microenvironment created by the ferrocene skeletone structure could modulate the catalytic behaviors of the chiral ferrocenyl amino alcohols. In particular, asymmetric transfer hydrogenation of prochiral ketones to optically active alcohols using chiral catalysts has become one of the most attractive research fields, because it has those advantages, such as high chemical yields, experimental simplicity, and no necessary requirment for the use of molecule hydrogen and high-pressure equipment [6]. We are interested in the preparation of this kind of optically active catalysts and in using them to achieve enantioselective reduction. In this paper, we are reporting the synthetic and structural investigation of two chiral ferrocenyl amino alcohol compounds (*S*,*R*)-**IIIa** and (*S*,*R*)-**IIIb** (Scheme 1), applied in the iridium catalyzed asymmetric transfer hydrogenation of acetophenone.



Scheme 1.

[1] The article is published in the original.

EXPERIMENTAL

Materials and methods. Reagents and solutions. Organic solvents were analytical pure grade and obtained from Sinopharm Chemical Reagent Co. Ltd. Benzene was dried by Na and distilled under vacuum. (*S*)-amino alcohols **IIa**, **IIb** were obtained from Daruichemistry company. Acetylferrene **I** was prepared by literature methods [7]. All reactions were carried out under argon and monitored by thin-layer chromatograph (TLC). Melting point (uncorrected) was measured with a XT4 melting point apparatus. ^{1}H NMR spectra were recorded on a Mercuryplus instrument at 500 Hz, using $CDCl_3$ as solvent and TMS as the internal standard. IR spectra were determined on a Nicolet 6700 spectrophotometer using KBr pellets. Optical rotations were measured on a WZZ-2s polarimeter.

Synthesis of compound IIIa. Acetylferrene (**I**) (1.18 g, 5.0 mmol) and L-phenylalaninol (**IIa**) (0.83 g, 5.5 mmol) were dissolved in 20 mL benzene and added drop wise glacial acetic acid (0.25 mL), and the mixture was heated under reflux. After the reaction was completed, the resulting solution was washed with saturated aqueous sodium chloride (2 × 10 mL), dried over anhydrous sodium sulfate. Then the solvent was removed under reduced pressure. The residue was resolved in ethanol (15 mL) and the mixture was cooled to 0°C. To the mixture was added $NaBH_4$ (0.19 g, 5.0 mmol) in portions, then stirred at room temperature until the reaction was over (checked by TLC). The reaction was quenched by addition of water, and the mixture was extracted with benzene. The combined extracts were dried over anhydrous sodium sulfate. After removal of the solvent by distillation, the residue was purified by column chromatography (silica gel, eluent: petroleum ether–AcOEt (v : v = 3 : 1) to give yellow crystals **IIIa**.

(*S,R*)-**IIIa**: 70.1%, m.p. = 100–102°C; $[\alpha]_D^{20}$ = –24.8 (*c* 0.83, EtOH); ^{1}H NMR ($CDCl_3$; δ, ppm): 1.25–1.27 (d., *J* = 6.8 Hz, 3H, CH_3), 1.57 (b., 1H, OH), 2.78–2.80 (d., *J* = 6.8 Hz, 2H $PhCH_2$), 3.09–3.12 (m., 1H, $CHCH_2OH$), 3.29–3.33 (m., 1H, C**H**HOH), 3.56–3.60 (m., 2H, CH**H**OH, FcCH), 4.03 (s., 5H, C_5H_5), 4.06–4.11 (m., 4H, C_5H_4), 4.20 (s, 1HNH), 7.21–7.34 (m., 5H, ArH); IR (KBr; ν, cm^{-1}): 3314, 3171 (OH, NH_2); 1100.9 and 997.6 (the unsubstituted cyclopentadienyl ring), 1022.0–1147.6 (single substituted cyclopentadienyl), 486.1, 509.9 ν(Fe–C); 748, 698 (single substituted phenyl).

For $C_{21}H_{25}NOFe$

Anal. calcd., %	C, 69.43	H, 6.94	N, 3.86
Found, %	C, 69.12	H, 6.99	N, 3.79

Compound **IIIb** was similarly prepared from L-leucinol (**IIb**).

(*S,R*)-**IIIb**: 65%, m.p. = 65–67°C; $[\alpha]_D^{20}$ = –23.6. (*c* 0.88, EtOH); ^{1}H NMR ($CDCl_3$; δ, ppm): 0.92–0.94 (d., *J* = 7.2 Hz, 3H, CH_3), 0.96–0.98 (d., *J* = 7.2 Hz, 3H, CH_3), 1.42–1.44 (d., *J* = 7.1 Hz, 3H, CH_3), 1.63 (b., 2H, NH, OH), 1.75–1.82 (m., 1H, $(CH_3)2CH$), 2.50–2.55 (m., 1H, $CHCH_2OH$), 3.35–3.63 (m., 2H, CH_2OH), 3.53–3.63 (q., *J* = 6.4 Hz, 1H, FcCH), 4.12–4.20 (m., 9H, C_5H_5, C_5H_4); IR (KBr; ν, cm^{-1}): 3372 (OH, NH_2); 1103.9 and 996.6 (the unsubstituted cyclopentadienyl ring), 1022.0–1147.6 (single substituted cyclopentadienyl), 486.1 and 509.9 (ν_{Fe-C}).

For $C_{17}H_{25}NOFe$

Anal. calcd., %	C, 64.77	H, 7.99	N, 4.44
Found, %	C, 64.70	H, 7.83	N, 4.28

Slow evaporation of the compounds **IIIa** and **IIIb** in petroleum ether and ethylacetate yielded single crystals suitable for X-ray analysis.

X-ray structure determination. Single-crystal X-ray diffraction data for **III** were collected on a Bruker Apex II CCD diffractometer with MoK_α radiation (λ = 0.71073 Å) by using ϕ/ω scan technique at 113(2) K (**IIIa**) and 298(2) K (**IIIb**). The structure was solved by direct methods with SHELXS-97 [8]. The hydrogen atoms were assigned with common isotropic displacement factors and included in the final refinement by use of geometrical restrains. A full-matrix least-squares refinement on F^2 was carried out using SHELXL-97 [9]. The empirical absorption corrections were applied by the SADABS program. The H-atoms of carbon were assigned with common isotropic displacement factors and included in the final refinement by the use of geometrical restraints. The crystallographic data for complex **III** are listed in Table 1. Hydrogen-bonding geometry are listed in Table 2. The molecular structure and packing arrangement in the unit cell of the title compounds are shown in Figs. 1 and 2, respectively.

The atomic coordinates and other parameters of the complexes have been deposited with the Cambridge Crystallographic Data Center (CCDC nos. 1056737 (**IIIa**) and 1056734 (**IIIb**); deposit@ccdc.cam.ac.uk).

The catalyst was generated in situ by refluxing ligands **IIIa** and **IIIb** (1.0 mmol %) with $[Ir(COD)Cl]_2$ (1.0 mmol %) in 2-propanol at 50°C under argon for 4 h. After being cooled down to room temperature, acetophenone (2.0 mmol) was added, followed by KOH (1.5 mg, 0.03 mmol) under argon. The transfer hydrogenation was conducted at desired temperature under argon for a given time. The resulting solution was purified by flash chromatography on a silica gel column eluted by petroleum ether/ethyl acetate (9/1) and the product was analyzed by HPLC.

Table 1. Crystallographic data and structure refinement summary of **IIIa** and **IIIb**

Parameter	Value	
	IIIa	**IIIb**
Formula weight	363.27	333.25
Temperature, K	113(2)	298(2)
Wavelength, MoK_α, Å	0.71073	0.71073
Crystal system	Orthorhombic	Monoclinic
Space group	$P2_12_12_1$	$P2_1$
a, Å	5.6467(11)	10.4849(9)
b, Å	10.323(2)	7.3600(5)
c, Å	29.563(6)	11.9561(11)
β, deg	90	111.735(2)
Volume, Å^3	1723.2(6)	857.04(12)
Z	4	2
Crystal size	0.20 × 0.18 × 0.12	0.40 × 0.15 × 0.13
ρ_{calcd}, mg/m^{-3}	1.400	1.291
Absorption coefficient, mm^{-1}	0.882	0.884
F(000)	768	356
Reflections collected/unique (R_{int})	14069/3953 (0.0338)	4279/2745 (0.0481)
Completeness to θ = 27.88° (25.01°), %	99.2	98.8
Data/restraints/parameters	3953/32/240	2745/1/194
Limiting indices	$-6 \le h \le 7$, $-12 \le k \le 13$, $-38 \le l \le 37$	$-7 \le h \le 12$, $-7 \le k \le 8$, $-14 \le l \le 12$
Goodness of fit on F^2	0.983	1.069
Final R indices ($I > 2\sigma(I)$)	$R_1 = 0.0271$, $wR_2 = 0.0570$	$R_1 = 0.0688$, $wR_2 = 0.1578$
R indices (all data)	$R_1 = 0.0332$, $wR_2 = 0.0595$	$R_1 = 0.0883$, $wR_2 = 0.1727$
Absolute structure parameter	−0.008(12)	−0.03(4)
Largest diff. peak and hole, e Å^{-3}	0.293 and −0.388	0.547 and −0.423

Table 2. Geometric parameters of hydrogen bond for **IIIa** and **IIIb** *

D–H···A	Distance, Å			Angle DHA, deg
	D–H	H···A	D···A	
		IIIa		
O(1)–H(1*A*)···N(1)	0.828(10)	2.082(10)	2.909(2)	179(2)
		IIIb		
O(1)–H(1)···O(2)	0.82(11)	1.85(11)	2.672(8)	176(10)
O(2)–H(2*C*)···O(1)$^{\#1}$	0.85(10)	1.92(10)	2.764(8)	173(9)
O(2)–H(2*D*)···N(1)$^{\#2}$	0.85(10)	2.10(10)	2.949(8)	174(9)

* Symmetry transformations used to generate equivalent atoms: $x - 1, y, z$ (**IIIa**); $^{\#1}$ $-x, y + 1/2, -z + 1$; $^{\#2}$ $x, y + 1, z$ (**IIIb**).

RESULTS AND DISCUSSION

The title compounds, chiral ferrocenyl amino alcohols **IIIa** and **IIIb** were prepared from acetylferrene **I** and (*S*)-amino alcohols **IIa** and **IIb**. Compounds **IIIa** and **IIIb** were characterized by X-ray diffraction, their molecular structure is shown in Fig. 1. Single crystal X-ray diffraction analysis reveals that the configuration of chiral center formed in the reductive amination of acetylferrene

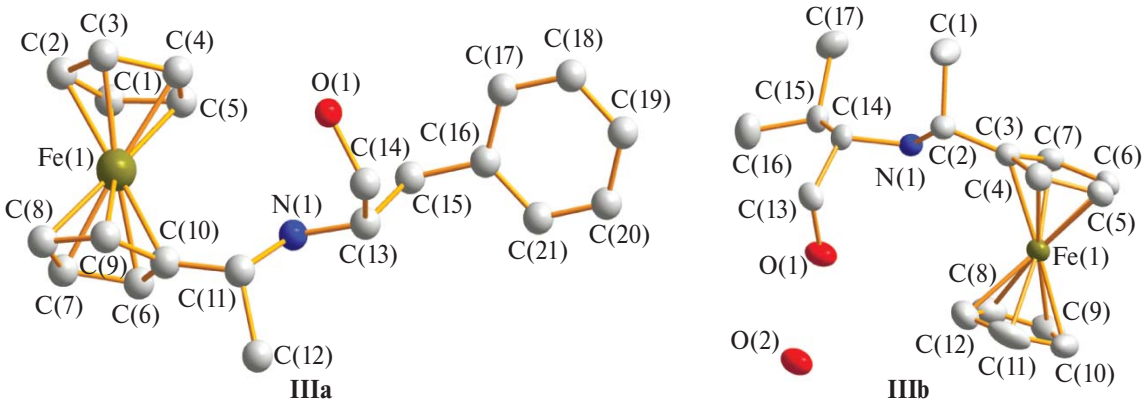
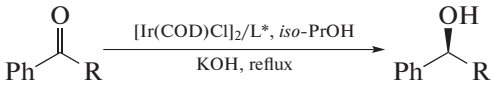
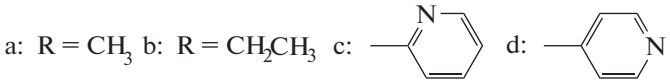


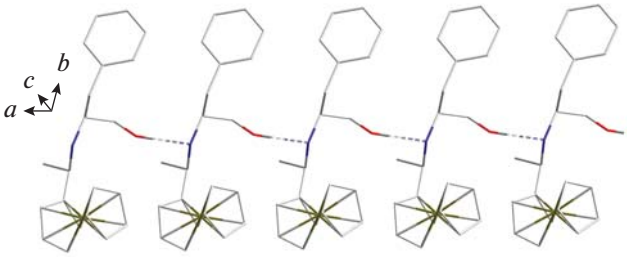
Fig. 1. Molecule **IIIa** and **IIIb** with an atom numbering.

was assigned to be (*R*) (Fig. 1). The crystal structure of **IIIa** is associated by strong intermolecular hydrogen bonds O(1)–H(1*A*)···N(1). In the crystal packing the molecules of **IIIb** are connected into a chain by three pairs of the O(2)–H(2*D*)···N(1), O(2)–H(2C)···O(1), O(1)–H(1)···O(2) hydrogen bonds which involve axially coordinated water molecule (Table 2).

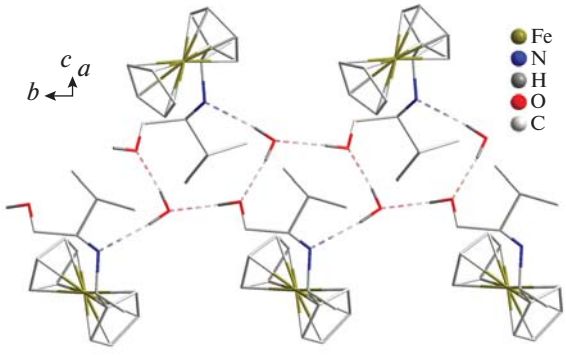




Scheme 2.



IIIa



IIIb

Fig. 2. Three-dimensional molecular-packing diagram of compounds **IIIa** and **IIIb**.

The chiral ferrocenyl amino alcohols **III** were applied to Ir-catalyzed asymmetric transfer hydrogenation of acetophenone using 2-propanol as a source of hydrogen. The results of asymmetric transfer hydrogenation of acetophenone by Ir(I)/**IIIa** and Ir(I)/**IIIb** are listed in Table 3. The results show that Ir(I)-catalyzed asymmetric transfer hydrogenation of acetophenone resulted in moderate yield and enantioselectivity (Table 3), preferring the *S* enantiomer. The absolute configuration was assigned by comparing the literature [10]. The catalytic activity of complex **IIIa** is better than complex **IIIb**. We speculated that the difference of the product's enantiomer may be related to the steric effect created by the substituent rigid benzene ring of the ferrocenyl amino alcohols ligands.

Asymmetric transfer hydrogenation of prochiral ketones to provide chiral alcohols has received a great deal of attention in the last decade or so. The chiral ferrocenyl amino alcohols (**IIIa** and **IIIb**) were applied to Ir-catalyzed asymmetric transfer hydrogenation of various aromatic ketones (acetophenone, proopiophenone, 2-benzoylpridine, 4-benzoylpridine) using 2-propanol as a source of hydrogen.

The results of asymmetric transfer hydrogenation of ketones by Ir(I)/**IIIa** and Ir(I)/**IIIb** are listed in Table 3. It can be seen from Table 1 that the results

Table 3. Asymmetric transfer hydrogenation of ketones in isopropanol catalyzed by chiral Ir(I) complexes

Entry[a]	Ligand	Ketones[b]	Time, h	Temperature, °C	Yield, %[c]	ee, %[d]
1	**IIIa**	a	4	50	75.0	51.5
2		b	4	50	50.0	31.7
3		c	6	50	40.0	10.1
4		d	4	25	89.0	62.0
5	**IIIb**	a	6	50	63.0	54.0
6		b	6	50	54.0	30.8
7		c	6	50	35.0	4.0
8		d	4	25	80.0	81.9

[a] L : M : KOH = 1 : 1 : 2 (L = ligand, M = metal) [$Ir(COD)Cl_2$].
[b] See the Scheme 2.
[c] Yield was calculated as alcohol after chromatography.
[d] ee values were determined by HPLC analysis of the isolated alcohol with Chiralcel OD columns.

obtained clearly demonstrate that the title compounds have moderate catalytic activity and enantioselectivity Ir(I) towards catalytic transfer hydrogenation. The results show that the activity and enantioselectivity of the chiral iridium catalyst are very sensitive to the substrate structure. Ir(I)-catalyzed asymmetric transfer hydrogenation of acetophenone resulted in moderate yield and moderate enantioselectivity(entry 1 and 5, Table 1, 63–75% yield, 51.4–54.0% ee); asymmetric transfer hydrogenation of proopiophenone (entry 2 and 6, Table 3, 50.0–54.0% yield, 30.8–31.7% ee) and 2-benzoylpridine resulted in lower yield and lower enantioselectivity (entry 3 and 7, Table 3, 35–40% yield, 4.0–10.1% ee); as for 4-benzoylpridine, good results have been achieved (entry 4 and 8, Table 3, 80–89% yield, 62.0–81.9% ee).

Thus, two chiral ferrocenyl amino alcohols have been synthesized and the structures of the chiral ferrocenyl amino alcohols have been determined by single crystal X-ray diffraction. Furthermore, they were applied to Ir-catalyzed asymmetric transfer hydrogenation of acetophenone using 2-propanol as a source of hydrogen. The results showed that two chiral ferrocenyl amino alcohols are efficient ligand in asymmetric transfer hydrogenation reaction. It catalyzed asymmetric transfer hydrogenation of 4-benzoylpridine with mediates c good enantioselectivity (62.0–81.9% ee).

ACKNOWLEDGMENTS

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