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The synthesis of novel chiral *N*,*O*-ferrocenyl ligands and their application in the addition of diethylzinc to aldehydes

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Abstract

Novel chiral *N*,*O*-ferrocenyl ligands, in which *N* and *O* groups were attached to two different Cp rings of ferrocene, were synthesized from easily available ferrocene, and applied to the asymmetric diethylzinc addition to aldehydes. High chemical yields and good enantioselectivities (up to 90.9% ee) were obtained by using ferrocene ligand **6**. © 2000 Published by Elsevier Science Ltd. All rights reserved.

1. Introduction

The ferrocene-based chiral ligand has became a noteworthy class of ligand in asymmetric catalysis and at least two of them have been used in industrial processes.¹ In recent years, much effort has been made to study chiral 1,2-disubstituted bidentate ferrocene ligands because of the inherent nature of their planar chirality, for example compounds $1,^2 2^3$ and 3^4 (Scheme 1). However, the study of 1,1'-disubstituted bidentate ferrocene ligands 4-7, and their application in the ligand-accelerated addition of diethylzinc to aldehydes.⁴



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2. Results and discussion

Quite recently, Ahn and Bryce^{5b,6} synthesized ferrocene derivative **8a** with a versatile functional group (bromine) on the second Cp ring of the ferrocene. It seems that the bromo–lithium exchange followed by trapping with various electrophiles such as PhSSPh, Ph₂PCl, Ph₂CO, etc., should give a series of 1,1'-disubstituted ferrocenyloxazolines which could be used as chiral ligands in asymmetric catalysis. In fact, compound **8a** is equal to a key intermediate to afford all kinds of ligands. In order to realize this new idea, firstly, compound **8a** was synthesized with high yield according to Bryce's method,⁶ then this method was successfully extended to the synthesis of a series of 1'-bromo-ferrocenyloxazolines **8c**-d, with different substituents on the oxazoline ring, in high chemical yields. Ferrocene derivatives **8a**-d were then treated with *n*-BuLi in THF at -78° C for 30 min followed by trapping with benzophenone, as we expected, to afford the target products **4**-**7** in reasonable yields (Scheme 2).



In order to examine the effectiveness of these ligands, the addition of diethylzinc to aldehyde as a model reaction was tested. Table 1 shows that this kind of ligand showed good catalytic activities and enantioselectivities.

In pursuit of a good enantioselective and high-yielding catalytic system, we examined the effects of a variety of reaction conditions including solvent, temperature, ligand and the amount of ligand (entries 1–7). After much experimentation, it was found that the use of 5 mol% ferrocene **6** as the ligand in toluene at 0°C gave the best result (98% yield, 88.6% ee, entry 6).

Next, the standard set of reaction conditions was applied to the addition of diethylzinc to various aldehydes. In all cases, the ligand **6** proved to be effective to induce formation of the secondary alcohols of (R)-configuration with high chemical yields and moderate to good enantioselectivity (up to 90.9% ee). Moreover, for aromatic aldehydes, an electron-donating group on the benzene ring turned out to slightly reduce the level of asymmetric induction (entries 9, 11 and 15). For aliphatic aldehydes, moderate enantioselectivity was obtained (71.7% ee, 64.2% ee).

In summary, novel *N*,*O*-ferrocenyl ligands **4–7** in which the *N*- and the *O*-groups were attached to the two different Cp rings of ferrocene were synthesized. With this novel kind of ligand, the addition of diethylzinc to aldehyde was carried out in high chemical yield and with good ee values. Further studies on the preparation of these kinds of novel *N*,*O*-ferrocenyl ligands and their applications in asymmetric synthesis are in progress.

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		L* (5mol%) 0 °C Et₂Zn, Toluene		ОН	
	RCHO			\sim	
	9	10			
Entry	R	Ligands	Yield (%) ^b	e.e. (%) ^c	Config. ^d
1	Ph (9a)	4	98	80.9	R
2^{e}	Ph (9a)	4	91	81.9	R
3 ^f	Ph (9a)	4	98	79.4	R
4 ^g	Ph (9a)	4	99	81.2	R
5	Ph (9a)	5	98	71.6	R
6	Ph (9a)	6	98	88.6	R
7	Ph (9a)	7	92	81.5	S
8	p-ClC ₆ H ₄ (9b)	6	95	89.3	R
9	p-MeOC ₆ H ₄ (9 c)	6	89	86.6	R
10	p-BrC ₆ H ₄ (9d)	6	97	90.9	R
11	$p-\text{Me}_2\text{NC}_6\text{H}_4$ (9e)	6	87	84.5	R
12	Biphenyl (9f)	6	98	88.4	R
13	1-Naphthyl (9g)	6	96	89.9	R
14	<i>o</i> -MeOC ₆ H ₄ (9h)	6	94	85.9	R
15	PhCH=CH (9i)	6	97	64.2	R
16	Cyclohexyl (9i)	6	88	71.1	R

 Table 1

 Enantioselective addition of diethylzinc to aldehydes using 4–7 as ligand^a

^{*a.*} The reaction was carried out in hexane-toluene (1:1) with 5mol% of ligand (**4-7**) and 2.0 equiv of diethylzinc to aldehydes. ^{*b.*} Isolated yield based on aldehyde. ^{*c.*} Determined by HPLC analysis using Chiralcel OD column. ^{*d.*} Configurations were assigned by comparison with the sign of optical rotation of known compound and known elution order from a Chiralcel OD column. ^{*e.*} The reaction was carried out at -20 °C. ^{*f.*} Hexane as reaction solvent. ^{*g.*} 10mol% of ligand was used.

3. Experimental

3.1. General

All of the reactions were performed under a dry argon atmosphere. Toluene, hexane and THF were freshly distilled from sodium. The commercially available reagents were used as received without further purification. Melting points are uncorrected. ¹H NMR spectra were recorded on a Bruker AMX-300 (300 MHz) spectrometer in CDCl₃ at room temperature. Chemical shifts are given in parts per million downfield from tetramethylsilane. Optical rotations were measured on a Perkin–Elmer 241 MC polarimeter with a thermally jacketed 10 cm cell at 25°C (concentration c given as g/100 mL). IR spectra were recorded in KBr and measured in cm⁻¹, using a Shimadzu IR-440 infrared spectrophotometer. Mass spectra and high-resolution mass spectra were taken using HP 5989A and Finnigan MAT mass

spectrometers, respectively. Elemental analyses were performed on a Foss-Heraeus Vario EL instrument. Enantiomeric excesses were determined by chiral HPLC on a Chiralcel OD column.

3.2. $1-[(S)-4-Isopropyl-2,5-oxazolinyl]-1'-(\alpha-diphenylhydroxymethyl)$ ferrocene 4

To a solution of **8a** (113 mg, 0.3 mmol) in THF (4 mL) was added *n*-butyllithium (1.6 M in hexane, 0.2 mL, 0.32 mmol) at -78° C. The reaction mixture was stirred for an additional 30 min and then trapped with benzophenone (109 mg, 0.6 mmol) at this temperature. After stirring at 0°C for 20 min, the reaction mixture was washed with water and then with brine and dried over Na₂SO₄. After the solvent was removed under reduced pressure, the residue was purified by column chromatography with ethyl acetate:petroleum (60–90°C, 1:3) as an eluent to afford **4** (133 mg, 93%) as an orange solid. M.p. 97–98°C. [α]_D²⁵=-86.0 (c 0.2, EtOH). ¹H NMR δ 0.92 (d, *J*=6.74 Hz, 3H), 1.06 (d, *J*=6.74 Hz, 3H), 1.84 (m, 1H), 3.95–4.20 (m, 6H), 4.30–4.46 (m, 3H), 4.76 (s, 3H), 7.17–7.38 (m, 10H). MS *m/z* 479 (M⁺, 100.0), 249 (83.8), 163 (67.8), 229 (65.3), 230 (43.3), 228 (41.9). IR (KBr) 3441, 2955, 1643, 1485, 1117, 753, 768, 485. Anal. calcd for C₂₉H₂₉NO₂Fe: C, 72.66; H, 6.10; N, 2.92. Found: C, 72.72; H, 6.14; N, 3.17.

3.3. $1-[(S)-4-Benzyl-2,5-oxazolinyl]-1'-(\alpha-diphenylhydroxymethyl)$ ferrocene 5

Compound **8b** (212 mg, 0.5 mmol) was allowed to react according to the procedure for **4** to afford **5** (216 mg, 82%) as an orange solid. M.p. 64–65°C. $[\alpha]_D^{25}=-51.0$ (c 0.22, EtOH). ¹H NMR δ 2.69 (dd, J=8.94, 13.69 Hz, 1H), 3.25 (dd, J=4.98, 13.7 Hz, 1H), 4.03–4.13 (m, 3H), 4.13–4.21 (m, 2H), 4.25–4.39 (m, 3H), 4.42–4.56 (m, 1H), 4.62 (br, 1H), 4.77 (s, 2H), 7.19–7.36 (m, 15H). MS m/z 527 (M⁺, 91.4), 297 (100.0), 279 (51.2), 229 (81.1), 188 (64.5), 91 (67.8). IR (KBr) 2924, 1645, 1489, 1445, 1122, 751, 700, 496. Anal. calcd for C₂₉H₂₉NO₂Fe: C, 75.15; H, 5.54; N, 2.66. Found: C, 75.15; H, 5.55; N, 2.56.

3.4. $1-[(S)-4-tert-Butyl-2,5-oxazolinyl]-1'-(\alpha-diphenylhydroxymethyl) ferrocene 6$

Compound **8c** (195 mg, 0.5 mmol) was allowed to react according to the procedure for **4** to afford **6** (220 mg, 90%) as an orange solid. M.p. 137–138°C. $[\alpha]_D^{25}=-125.0$ (c 0.2, EtOH). ¹H NMR δ 0.96 (s, 9H), 3.97 (dd, J=8.04, 9.71 Hz, 1H), 4.05–4.23 (m, 5H), 4.25–4.35 (m, 2H), 4.38 (s, 1H), 4.75 (d, J=9.25 Hz, 2H), 4.91 (br, 1H), 7.15–7.46 (m, 10H). MS m/z 493 (M⁺, 24.4), 311 (26.4), 310 (95.2), 254 (100.0), 226 (42.4), 211 (53.26). IR (KBr) 3283, 2965, 1648, 1486, 1123, 957, 754, 703, 499 cm⁻¹. Anal. calcd for C₂₉H₂₉NO₂Fe: C, 73.03; H, 6.33; N, 2.84. Found: C, 73.00; H, 6.32; N, 3.12.

3.5. $1-[(R)-4-Phenyl-2,5-oxazolinyl]-1'-(\alpha-diphenylhydroxymethyl) ferrocene 7$

Compound **8d** (205 mg, 0.5 mmol) was allowed to react according to the procedure for **4** to afford **7** (186 mg, 73%) as an orange solid. M.p. 139–140°C. $[\alpha]_D^{25}$ =+98.6 (c 0.21, EtOH). ¹H NMR δ 4.08–4.27 (m, 5H), 4.37 (dd, *J*=1.2, 23.1 Hz, 3H), 4.73 (t, *J*=9.02 Hz, 1H), 4.87 (d, *J*=11.2 Hz, 2H), 5.27 (t, *J*=8.26 Hz, 1H), 7.18–7.47 (m, 15H). MS *m*/*z* 513 (M⁺, 99.2), 283 (39.9), 229 (57.9), 193 (100.0), 163 (36.6). IR (KBr) 3260, 1637, 1446, 1121, 1023, 749, 709, 491 cm⁻¹. Anal. calcd for C₂₉H₂₉NO₂Fe: C, 74.86; H, 5.30; N, 2.73. Found: C, 74.90; H, 5.29; N, 2.76.

3.6. General procedure for catalytic asymmetric addition of diethylzinc to various aldehydes

To a solution of ferrocene ligand **6** (0.05 mmol) in toluene (2.5 mL) was added Et_2Zn (2.0 mL, 2.0 mmol, 1 M in hexane) at room temperature. After 30 min, the reaction system was cooled to 0°C, and the aldehyde (1.0 mmol) was added under an argon atmosphere. After being stirred for the appropriate time, the reaction was quenched with 3N HCl. The mixture was extracted with ether. The organic layer was washed with brine, dried and evaporated under reduced pressure to give an oily residue. Purification of the residue by preparative TLC gave the optically active alcohol. The enantiomeric excess was determined by HPLC analysis using a Chiralcel OD column. Configurations were assigned by comparison with the sign of specific rotation of known compounds.

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