

Chiral Ferrocenyl Amino Alcohols: Preparation and Application as Catalysts in the Enantioselective Reduction of Ketones Using NaBH_4/I_2

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Five novel chiral ferrocenyl amino alcohols were prepared from natural amino acids and used as catalysts in the asymmetric reduction of prochiral ketones with NaBH_4/I_2 combination. The incorporation of the ferrocenyl moiety into the molecule of the chiral amino alcohols greatly improved their enantioselectivity in the catalysis. The optically active secondary alcohols were obtained in moderate to good enantiomeric excesses and high chemical yields.

Keywords asymmetric reduction, prochiral ketone, NaBH_4/I_2 combination, ferrocene

Introduction

In recent years, considerable attention has been devoted to the preparation of optically active compounds, especially chiral secondary alcohols, which are important starting materials for many biologically active compounds.¹ Since Corey and co-workers found the chiral oxazaborolidine catalyzed reduction (CBS reduction) of prochiral ketones, this method for the generation of chiral secondary alcohols has become one of the most attractive research fields.^{2,3} This kind of catalyst provides excellent enantioselectivity for the asymmetric reduction of most prochiral ketones. Meanwhile, the method has other advantages, such as mild reaction conditions, short reaction time, easy recoverability of the catalyst precursor and high chemical yield. Therefore, in organic synthesis, many important transformations of prochiral substrates into chiral compounds can be achieved in very high enantiomeric purity by utilizing a catalytic amount of an enantiomeric pure amino alcohol as chiral auxiliary. We are interested in the preparation of this kind of optically active catalysts.

In this paper, we report the syntheses of five new chiral ferrocenyl amino alcohols **4a–4e**, and their application in the catalytic asymmetric reduction of ketones with the combined reagent of NaBH_4/I_2 .

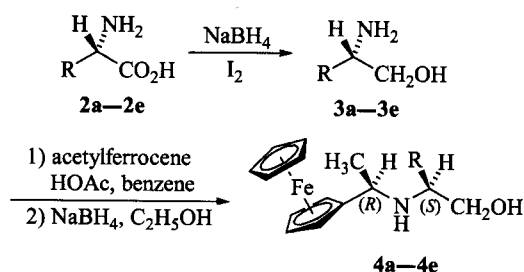
Results and discussion

To develop new effective catalysts for the CBS reduction, we examined the effects of incorporation of a ferrocenyl

group into the catalyst molecule on the selectivity of the catalysis. For this purpose, five ferrocenyl-bearing chiral amino alcohols were prepared by the reductive amination of acetylferrocene with aminoalcohols which were obtained by the reduction of the corresponding natural amino acids directly. The CBS reduction always requires borane-dimethyl sulfide complex, borane-tetrahydrofuran, borane-1,4-thioxane or catecholborane, which are toxic and rather expensive. The expanding utility of the CBS reduction in organic synthesis or pharmaceutical industries has created a need for development of more convenient processes for reduction of prochiral ketones to chiral secondary alcohols. $\text{NaBH}_4/\text{Me}_2\text{SiCl}$ or NaBH_4/I_2 combination can afford borane *in situ* in THF and can be directly used as a reducing agent.⁴ Sodium borohydride has become one of the most widely used reagents for both laboratory and industrial scale application in chemistry.^{5,6} In this research work, we employed the combined reagent of NaBH_4/I_2 instead of borane. This *in situ* procedure provided an effective and simple method for enantioselective reduction of prochiral ketones.

As shown in Scheme 1, chiral ferrocenyl amino alcohols **4a–4e** were prepared from acetylferrocene and (*S*)-amino alcohols **3a–3e** as a single diastereomer (checked by HPLC). The configuration of chiral center formed in the reductive amination of acetylferrocene, was assigned to be (*R*) by X-ray single crystal analysis. Fig. 1 shows the X-ray structure of **4c** as an example.

Scheme 1 Synthesis of chiral ferrocenyl amino alcohols **4a–4e**



a: R = benzyl; **b:** R = isopropyl;
c: R = isobutyl; **d:** R = *sec*-butyl; **e:** R = methyl

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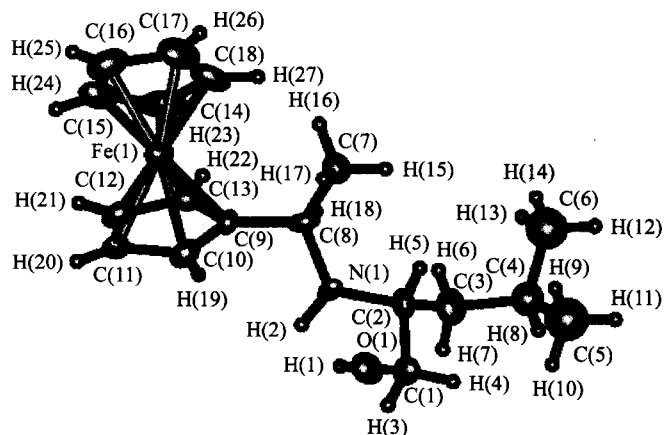
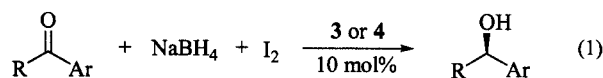


Fig. 1 X-Ray structure of 4c.

In the presence of 10 mol% of chiral amino alcohol, aryl alkyl ketones can be reduced by NaBH_4/I_2 to optically

active secondary alcohols (Eq. 1). For comparison, both 3a–3e and 4a–4e were tested. The results are summarized in Table 1.



It can be seen from the data shown in Table 1 that (1) incorporation of the ferrocenyl group into amino alcohols 3a–3e dramatically increased the enantioselectivity of the catalysts (Entries 1 ~ 10); (2) changing R in the series 3 and 4 has similar effects on the selectivity with the order of benzyl > isopropyl > isobutyl ~ *sec*-butyl > methyl; (3) for the various ketones, the order of enantioselectivity was observed as butyrophenone > propiophenone > acetophenone > *p*-methoxyacetophenone; (4) in all cases, (*R*)-form of secondary alcohols was obtained as the major enantiomer and the chemical yields are good.

Table 1 Enantioselective reduction of prochiral ketones in the presence of 10 mol% of 3a–3e/4a–4e

Entry	Ketone	Cat.	$[\alpha]_D$	<i>ee</i> (%) ^a	Config. ^b	Yield (%) ^c
1	$\text{C}_6\text{H}_5\text{COMe}$	3a	+ 9.1	21	<i>R</i>	83
2	$\text{C}_6\text{H}_5\text{COMe}$	4a	+ 32.1	76	<i>R</i>	81
3	$\text{C}_6\text{H}_5\text{COMe}$	3b	+ 6.9	16	<i>R</i>	80
4	$\text{C}_6\text{H}_5\text{COMe}$	4b	+ 30.2	71	<i>R</i>	89
5	$\text{C}_6\text{H}_5\text{COMe}$	3c	+ 6.2	15	<i>R</i>	82
6	$\text{C}_6\text{H}_5\text{COMe}$	4c	+ 30.8	73	<i>R</i>	82
7	$\text{C}_6\text{H}_5\text{COMe}$	3d	+ 5.9	14	<i>R</i>	83
8	$\text{C}_6\text{H}_5\text{COMe}$	4d	+ 29.7	70	<i>R</i>	86
9	$\text{C}_6\text{H}_5\text{COMe}$	3e	+ 4.2	10	<i>R</i>	85
10	$\text{C}_6\text{H}_5\text{COMe}$	4e	+ 25.4	60	<i>R</i>	89
11	$\text{C}_6\text{H}_5\text{COEt}$	4a	+ 38.4	82	<i>R</i>	85
12	$\text{C}_6\text{H}_5\text{COEt}$	4b	+ 32.7	70	<i>R</i>	90
13	$\text{C}_6\text{H}_5\text{COEt}$	4c	+ 34.6	74	<i>R</i>	88
14	$\text{C}_6\text{H}_5\text{COEt}$	4d	+ 32.9	70	<i>R</i>	86
15	$\text{C}_6\text{H}_5\text{COEt}$	4e	+ 24.6	52	<i>R</i>	87
16	$\text{C}_6\text{H}_5\text{COPr-}n$	4a	+ 40.5	86	<i>R</i>	88
17	$\text{C}_6\text{H}_5\text{COPr-}n$	4b	+ 32.8	73	<i>R</i>	90
18	$\text{C}_6\text{H}_5\text{COPr-}n$	4c	+ 32.5	72	<i>R</i>	94
19	$\text{C}_6\text{H}_5\text{COPr-}n$	4d	+ 32.8	73	<i>R</i>	88
20	$\text{C}_6\text{H}_5\text{COPr-}n$	4e	+ 18.8	42	<i>R</i>	91
21	<i>p</i> -MeOC ₆ H ₄ COMe	4a	+ 37.1	71	<i>R</i>	88
22	<i>p</i> -MeOC ₆ H ₄ COMe	4b	+ 34.0	65	<i>R</i>	87
23	<i>p</i> -MeOC ₆ H ₄ COMe	4c	+ 33.7	65	<i>R</i>	91
24	<i>p</i> -MeOC ₆ H ₄ COMe	4d	+ 33.2	64	<i>R</i>	89
25	<i>p</i> -MeOC ₆ H ₄ COMe	4e	+ 20.7	40	<i>R</i>	82

^a Enantiomeric excess values were determined by optical rotations. ^b Absolute configurations were assigned by the comparison of the sign of the specific rotation with those reported in literature: $[\alpha]_D^{25} + 42.5$ (*c* 5, ethanol) for (*R*)-1-phenyl-1-ethanol,⁷ $[\alpha]_D^{25} + 47$ (*c* 6.9, acetone) for (*R*)-1-phenyl-1-propanol,⁸ $[\alpha]_D^{25} - 45.2$ (*c* 4.81, benzene) for (*S*)-1-phenyl-1-butanol,⁹ $[\alpha]_D^{25} + 44.2$ (*c* 1, CHCl_3 , 94% opt. pure) for (*R*)-1-(4-methoxyphenyl)-1-ethanol.¹⁰ ^c Isolated yield.

Experimental

Apparatus and reagents

Melting points were measured in capillaries and uncorrected. Elemental analyses were performed with a Carlo-Erba-1110 analyzer. ^1H NMR spectra were recorded on a Varian-I-nova-400 instrument. Specific rotations were measured on a WZZ-11S automatic polarimeter. The X-ray diffraction was performed on a Rigaku Mercury CCD X-ray diffractometer. HPLC analyses were performed with a Waters 515 equipment on a C_{18} reversed-phase column (250 mm \times 4.6 mm I.D.). Organic solvents were dried and distilled prior to use.

Preparation of acetylferrocene 1

1 was prepared from ferrocene following the description in literature.¹¹

Preparation of (*S*)-amino alcohols 3a–3e

3a–3e were prepared from (*S*)-amino acids 2a–2e following the description in literature.⁶

Preparation of 4a

To a solution of acetylferrocene (2.28 g, 10 mmol) and 3a (1.66 g, 11 mmol) in 30 mL of benzene was added dropwise glacial acetic acid (0.25 mL, 4.5 mmol), and the mixture was heated under reflux using a Soxhlet apparatus containing 4A molecular sieves. After the reaction was completed (checked by TLC), the resulting solution was washed with saturated aqueous sodium chloride (2 \times 10 mL), dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was resolved in ethanol (15 mL) and the mixture was cooled to 0 $^{\circ}\text{C}$. To the mixture was added NaBH_4 (0.76 g, 20 mmol) in portions, then stirred at room temperature until the reaction was over (checked by TLC). The reaction was quenched by addition of water (50 mL), and the mixture was extracted with benzene (3 \times 15 mL). The combined extracts were dried over anhydrous sodium sulfate. After removal of the solvent by distillation, the residue was subjected to chromatography (petroleum/ether = 1:2) to afford 4a (2.58 g) in 71.1% yield, m. p. 101–102 $^{\circ}\text{C}$, $[\alpha]_{\text{D}}^{20}$ – 25.3 (*c* 0.83, EtOH); ^1H NMR (CDCl_3) δ : 1.26 (d, J = 6.8 Hz, 3H, CH_3), 1.57 (brs, 2H, NH, OH), 2.79 (d, J = 6.8 Hz, 2H, PhCH_2), 3.09–3.16 (m, 1H, CHCH_2OH), 3.29–3.33 (m, 1H, CHHOH), 3.56–3.60 (m, 2H, CHHOH , FcCH), 4.03 (s, 5H, Fc), 4.06–4.11 (m, 4H, Fc), 7.21–7.34 (m, 5H, Ph). Anal. calcd for $\text{C}_{21}\text{H}_{25}\text{FeNO}$: C 69.43, H 6.94, N 3.86; found C 68.98, H 6.98, N 3.58.

4b–4e were similarly prepared from 3b–3e:

4b 68.8%, m. p. 65–66 $^{\circ}\text{C}$, $[\alpha]_{\text{D}}^{30}$ – 25.3 (*c* 0.89, EtOH); ^1H NMR (CDCl_3) δ : 0.93 (d, J = 7.2 Hz, 3H, CH_3), 0.97 (d, J = 7.2 Hz, 3H, CH_3), 1.43 (d,

J = 7.1 Hz, 3H, FcCHCH_3), 1.64 (brs, 2H, NH, OH), 1.74–1.82 (m, 1H, Me_2CH), 2.50–2.55 (m, 1H, CHCH_2OH), 3.33 (dd, J = 10.8, 5.6 Hz, 1H, CHHOH), 3.52 (dd, J = 10.8, 5.2 Hz, 1H, CHHOH), 3.62 (q, J = 6.4 Hz, 1H, FcCH), 4.12–4.20 (m, 9H, Fc). Anal. calcd for $\text{C}_{17}\text{H}_{25}\text{FeNO}$: C 64.77, H 7.99, N 4.44; found C 64.69, H 7.84, N 4.27.

4c 65.6%, m. p. 54–55 $^{\circ}\text{C}$, $[\alpha]_{\text{D}}^{30}$ – 6.26 (*c* 1.30, EtOH); ^1H NMR (CDCl_3) δ : 0.92 (d, J = 6.8 Hz, 6H, $\text{CH}_3 \times 2$), 1.18–1.28 (m, 1H, Me_2CH), 1.31–1.38 (m, 2H, Me_2CHCH_2), 1.44 (d, J = 6.8 Hz, 3H, CH_3), 1.63 (brs, 2H, NH, OH), 2.77–2.83 (m, 1H, CHCH_2OH), 3.12–3.20 (m, 1H, FcCH), 3.56–3.66 (m, 2H, CH_2OH), 4.13–4.15 (m, 9H, Fc). Anal. calcd for $\text{C}_{18}\text{H}_{27}\text{FeNO}$: C 65.66, H 8.27, N 4.25; found C 65.71, H 8.32, N 4.20.

4d 66.7%, m. p. 35–36 $^{\circ}\text{C}$, $[\alpha]_{\text{D}}^{20}$ – 16.8 (*c* 0.88, EtOH); ^1H NMR (CDCl_3) δ : 0.88 (d, J = 6.4 Hz, 3H, CHCH_3), 0.93 (t, 3H, J = 8.0 Hz, CH_3CH_2), 1.16–1.26 (m, 2H, CH_3CH_2), 1.45 (d, J = 6.4 Hz, 3H, FcCHCH_3), 1.55–1.61 (m, 1H, *sec*-BuCH), 1.74 (brs, 2H, NH, OH), 2.63–2.67 (m, 1H, CHCH_2OH), 3.29 (q, J = 6.4 Hz, 1H, FcCH), 3.48–3.64 (m, 2H, CH_2OH), 4.13 (s, 5H, Fc), 4.15–4.19 (m, 4H, Fc). Anal. calcd for $\text{C}_{18}\text{H}_{27}\text{FeNO}$: C 65.66, H 8.27, N 4.25; found C 65.51, H 8.15, N 4.21.

4e 69.5%, oil, $[\alpha]_{\text{D}}^{20}$ – 26.8 (*c* 1.10, EtOH); ^1H NMR (CDCl_3) δ : 1.33 (d, J = 6.0 Hz, 3H, $\text{CH}_3\text{CHCH}_2\text{OH}$), 1.45 (d, J = 5.8 Hz, 3H, FcCHCH_3), 1.63 (brs, 2H, NH, OH), 3.17 (q, J = 5.8 Hz, 1H, FcCH), 3.42–3.51 (m, 1H, CHCH_2OH), 3.63–3.68 (m, 2H, CH_2OH), 4.14–4.18 (m, 9H, Fc). Anal. calcd for $\text{C}_{15}\text{H}_{21}\text{FeNO}$: C 62.73, H 7.37, N 4.88; found C 62.45, H 7.46, N 4.58.

Table 2 Crystallographic data of 4c

Empirical formula	$\text{C}_{18}\text{H}_{27}\text{FeNO}$
Formula weight	329.26
Crystal color, habit	Yellow, platelet
Crystal dimensions	0.20 \times 0.20 \times 0.20 mm
Crystal system	Orthorhombic
Lattice type	Primitive
Lattice parameters	a = 0.8317(5) nm b = 0.8330(5) nm c = 2.487(2) nm V = 1.7228(17) nm ³
Space group	$P2_12_12_1$
Z value	4
Density (calculated)	1.269 g/cm ³
$F(000)$	704.00
μ (Mo $K\alpha$)	8.74 cm ⁻¹

X-Ray structure determination of 4c

A yellow platelet crystal of $C_{18}H_{27}FeNO$ having approximate dimensions of 0.30 mm \times 0.30 mm \times 0.10 mm was mounted on a glass fiber. All measurements were made on a Rigaku with graphite monochromated Mo $K\alpha$ radiation.

Of the 19124 reflections collected, 2268 were unique ($R_{int} = 0.177$), and equivalent reflections were merged. Data were collected and processed using CrystalClear (Rigaku). The structure was solved by direct method using the SIR92. The crystallographic data are given in Table 2. Selected bond lengths and angles are listed in Table 3.

General procedure for the catalytic enantioselective reduction of prochiral ketones, using acetophenone as an example

The reaction was carried out in flame-dried glassware, under nitrogen atmosphere. The solution of I_2 (1.53 g, 6

mmol) in dry THF (5 mL) was dropped to a stirred suspension of $NaBH_4$ (0.46 g, 12 mmol) in dry THF (10 mL) while cooling with an ice bath. After stirring for 30 min, the temperature was allowed to raise to 25 °C. To the mixture was added amino alcohols **4a** (363 mg, 1 mmol), stirred for 15 min. A solution of acetophenone (1.20 g, 10 mmol) in THF (15 mL) was dropped slowly to the reductive system during 45 min. After the reduction completed (checked by TLC), the reaction was quenched by addition of methanol (2 mL) with ice-bath cooling, and stirred for 30 min. The mixture was washed with saturated aqueous sodium chloride (2×10 mL), dried with anhydrous sodium sulfate. The solvent was removed and the residue was subjected to chromatography (petroleum/ethyl acetate = 10:1) to afford a solution of product. After removal of the solvent, the residue was distilled under reduced pressure to give the optically active secondary alcohol 0.99 g (81%), $[\alpha]_D^{30} + 32.1$ (c 5, ethanol).

Table 3 Selected bond lengths (nm) and angles (°)

Fe(1)—C(9)	0.2035(6)	Fe(1)—C(18)	0.2048(9)
O(1)—C(1)	0.1396(8)	N(1)—C(2)	0.1496(8)
N(1)—C(8)	0.1456(8)	C(1)—C(2)	0.1509(9)
C(2)—C(3)	0.1547(9)	C(3)—C(4)	0.1545(10)
C(4)—C(5)	0.1498(13)	C(4)—C(6)	0.1487(12)
C(7)—C(8)	0.1512(9)	C(8)—C(9)	0.1486(9)
C(9)-Fe(1)-C(10)	41.2(3)	C(10)-Fe(1)-C(14)	110.0(3)
O(1)-C(1)-C(2)	112.2(5)	C(2)-N(1)-C(8)	116.7(5)
N(1)-C(2)-C(3)	111.9(6)	N(1)-C(2)-C(1)	109.0(5)
C(2)-C(3)-C(4)	115.4(6)	C(1)-C(2)-C(3)	110.5(6)
C(3)-C(4)-C(6)	112.6(7)	C(3)-C(4)-C(5)	110.2(7)
N(1)-C(8)-C(7)	111.1(6)	C(5)-C(4)-C(6)	110.8(7)
C(7)-C(8)-C(9)	114.3(5)	N(1)-C(8)-C(9)	109.0(5)
Fe(1)-C(9)-C(10)	69.8(3)	Fe(1)-C(9)-C(8)	130.6(4)
C(8)-C(9)-C(10)	125.8(5)	C(8)-C(9)-C(13)	127.5(6)
C(9)-C(10)-C(11)	107.7(6)	C(10)-C(11)-C(12)	109.4(6)

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