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Article

Catalytic Enantioselective Reduction of Prochiral Ketones with Chiral Ferrocenyl Amino Alcohols

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The asymmetric reduction of prochiral ketones was catalyzed by a class of recoverable and highly stable chiral ferrocenyl amino alcohols derived from natural amino acids to yield optically active secondary alcohols in high chemical yields and moderate to good enantiomeric excesses.

Keywords enantioselective reduction, prochiral ketone, $NaBH_4/I_2$ combination, ferrocenyl amino alcohol

Introduction

The enantioselective reduction of prochiral ketones is a pivotal reaction for the preparation of chiral alcohols[1] that form an extremely important class of intermediates for fine chemicals and pharmaceuticals. Since Itsuno *et al*.[2] found that chiral alkoxy-amino-borane complexes reduced aromatic ketones enantioselectively, the asymmetric reduction of prochiral ketones to optically active alcohols using chiral catalysts has become one of the most attractive research fields, because it has the advantages of high chemical yields, mild reaction conditions, short reaction time, easy recoverability of the catalyst precursor and experimental simplicity.

In recent years, enantiopure ferrocenyl derivatives have been reported as active catalysts in several reactions[3] and are very attractive compounds for the design of new ligand-metal complexes owing to their different chirality features according to the substitution pattern on the ferrocene backbone. We are interested in the preparation of this kind of optically active catalysts and in using them into enantioselective reduction. We have finished some research work in the field of enantioselective reduction of ketones and acquired interesting results. In this paper, we would like to report the synthesis of another five new chiral ferrocenyl amino alcohols **3a**—**3e**, and their application in the catalytic asymmetric reduction of ketones with the combined reagent of $NaBH_4/I_2$ in high chemical yields and moderate to good enantioselectivities.

Results and discussion

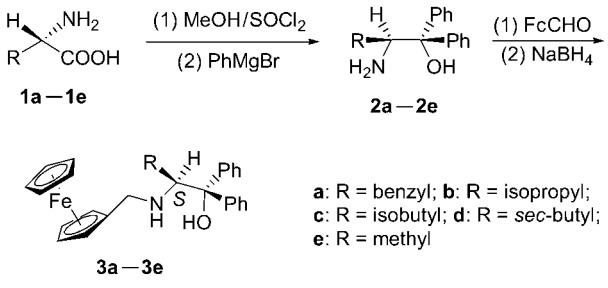
The chiral oxazaborolidine-catalyzed reduction (CBS reduction) of prochiral ketones has been believed as a useful tool for synthetic chemists. A large number of chiral β-aminoalcohols have been synthesized and utilized in the preparation of the corresponding oxazborolidine catalysts. For all that, to design and develop new efficient catalysts is still a challenging task for organic chemists.

We have reported the preparation of several ferroceneyl-bearing amino alcohols and their application as catalysts in the enantioselective reduction of ketones using $NaBH_4/I_2$.[4] The incorporation of the ferrocenyl group into amino alcohols can increase the enantioselectivity of the catalysts. So we designed and synthesized another five new chiral ferrocenyl amino alcohols as the catalysts for the CBS reduction. These new chiral ferrocenyl amino alcohols were prepared by reaction of ferrocenecarboxaldehyde with (*S*)-1,1-diphenyl-2-amino alcohols which were obtained by treatment of the corresponding natural amino acids with methanol/thionyl chloride, then stirred with phenyl magnesium bromide in THF.

In this paper, we still employed the combined reagent of $NaBH_4/I_2$ instead of borane which is very toxic and unstable. This *in situ* procedure provides an effective and simple method for enantioselective reduction of prochiral ketones.

As shown in Scheme 1, chiral ferrocenyl amino alcohols **3a**—**3e** were prepared from ferrocenecarboxal-

Scheme 1 Synthesis of chiral ferrocenyl amino alcohols **3a**—**3e**



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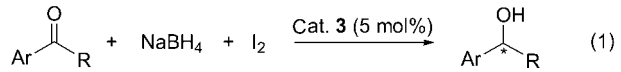
dehyde and (*S*)-amino acids **1a—1e**. The X-ray structure of **3a** is shown in Figure 1.

In the presence of 5 mol% chiral amino alcohols **3a—3e**, aryl alkyl ketones were reduced by $NaBH_4/I_2$ to optically active secondary alcohols [Eq. (1)]. The results are given in Table 1.



It can be seen from the data shown in Table 1 that: (1) in all cases (*R*)-form of secondary alcohol was obtained as the major enantiomer; (2) for the various ketones, the order of enantioselectivity was observed as butyrophenone > propiophenone > acetophenone; (3) ferrocenyl amino alcohols **3a—3e** have moderate to good enantioselectivities in the catalytic asymmetric reduction of ketones; (4) chemical yields are good.

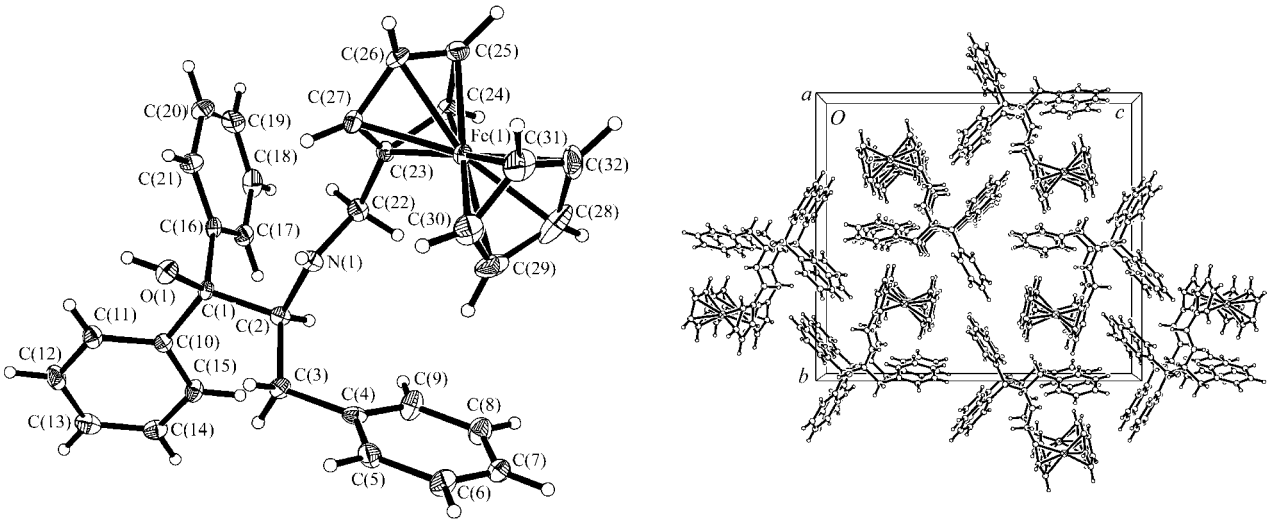


Figure 1 Molecular structure and packing diagram of **3a**.

Table 1 Enantioselective reductions of ketones in the presence of 5 mol% **3a—3e**

Entry	Ketone	Cat.	$[\alpha]_D$	*ee*[a]/%	Config.[b]	Yield[c]/%
1	C_6H_5COMe	**3a**	+25.5	60	R	92
2	C_6H_5COMe	**3b**	+17.9	42	*R*	82
3	C_6H_5COMe	**3c**	+23.4	55	*R*	80
4	C_6H_5COMe	**3d**	+22.1	52	*R*	89
5	C_6H_5COMe	**3e**	+17.0	40	*R*	90
6	C_6H_5COEt	**3a**	+35.3	75	*R*	94
7	C_6H_5COEt	**3b**	+32.9	70	*R*	90
8	C_6H_5COEt	**3c**	+32.9	70	*R*	92
9	C_6H_5COEt	**3d**	+29.1	62	*R*	85
10	C_6H_5COEt	**3e**	+25.9	55	*R*	86
11	C_6H_5COPr-*n*	**3a**	+37.1	82	*R*	90
12	C_6H_5COPr-*n*	**3b**	+30.7	68	*R*	81
13	C_6H_5COPr-*n*	**3c**	+29.8	66	*R*	89
14	C_6H_5COPr-*n*	**3d**	+33.9	75	*R*	92
15	C_6H_5COPr-*n*	**3e**	+24.9	55	*R*	88
16	C_6H_5COBu-*n*	**3a**	+28.1	90	*R*	84
17	C_6H_5COBu-*n*	**3b**	+22.5	72	*R*	87
18	C_6H_5COBu-*n*	**3c**	+25.0	80	*R*	83
19	C_6H_5COBu-*n*	**3d**	+25.6	82	*R*	84
20	C_6H_5COBu-*n*	**3e**	+22.8	73	*R*	90

[a] Enantiomeric excess values were determined by optical rotations. [b] Absolute configurations were assigned by the comparison of the specific rotation with those reported in literature: $[\alpha]_D^{25}$+42.5 (*c* 5, ethanol) for (*R*)-1-phenyl-1-ethanol,[5] $[\alpha]_D^{25}$+47 (*c* 6.9, acetone) for (*R*)-1-phenyl-1-propanol,[6] $[\alpha]_D^{25}$−45.2 (*c* 4.81, benzene) for (*S*)-1-phenyl-1-butanol,[7] $[\alpha]_D$+27.5 (*c* 2.98, benzene, 88% opt. pure) for (*R*)-1-phenyl-1-pentanol.[8] [c] Isolated yield.

In conclusion, the ferrocenyl aminoalcohols **3a—3e,** readily prepared from the ferrocenyl carboxaldehyde and the corresponding chiral amino alcohols, are effective catalysts for the enantioselective borane reduction of prochiral ketones producing optically active secondary alcohols in high yield with high enantiomeric excesses.

Experimental

Apparatus and reagents

Melting points were measured in capillaries and uncorrected. Elemental analyses were performed with a Carlo-Erba-1110 analyzer. ^{1}H NMR spectra were recorded on a Varian-Inova-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. Organic solvents were dried and distilled prior to use.

Ferrocenecarboxaldehyde was prepared from ferrocene following the method reported in literature.[9] **2a—2e** were prepared from (*S*)-amino acids **1a—1e** following the method reported in literature.[10]

Preparation of 3

To a solution of ferrocenecarboxaldehyde (1.07 g, 5.0 mmol) and **2a** (1.52 g, 5.0 mmol) in 10 mL of CH_2Cl_2 was added anhydrous sodium sulfate (2 g), and the mixture was stirred at room temperature until the reaction was over (checked by TLC). After the solid material was removed by filtration and the solvent was distilled under reduced pressure, the residue was dissolved in ethanol (10 mL) and THF (10 mL). The mixture was cooled to 0 ℃, to which was added $NaBH_4$ (0.38 g, 10.0 mmol) in portions, then stirred at room temperature until the reaction was over (checked by TLC). After the reaction was quenched by addition of water (50 mL), the stirring was continued for 30 min. A yellow solid was obtained by filtration. Recrystallization of the solid material from ethanol gave 1.83 g of **3a** (73.2%). m.p. 148—149 ℃, $[\alpha]_D^{25}+13.3$ (*c* 1.35, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ: 2.38 (dd, J=14.8, 10.6 Hz, 1H, PhCH**H**), 2.73 (d, J=12.6 Hz, 1H, FcCH**H**), 2.83 (d, J=12.6 Hz, 1H, FcCH**H**), 2.94 (d, J=14.8 Hz, 1H, PhCH**H**), 3.58 (bs, 1H, CH), 3.64—4.04 (m, 9H, Fc), 5.01 (bs, 1H, NH), 7.17—7.77 (m, 15H, PhH); IR (KBr) ν: 3318 cm^{-1}; MS *m/z* (%): 501 (M$^+$, 5.73), 317 (30.87), 284 (20.32), 199 (100), 120 (42.86), 105 (44.33), 91 (14.03), 77 (25.83). Anal. calcd for $C_{32}H_{31}FeNO$: C 76.65, H 6.23, N 2.79; found C 76.78, H 6.32, N 2.74.

3b—3e were similarly prepared from **2b—2e.**

3b 75.2%, m.p. 154—155 ℃, $[\alpha]_D^{25}-38.6$ (*c* 1.35, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ: 0.70 (d, J=7.2 Hz, 3H, CH_3), 0.98 (d, J=7.6 Hz, 3H, CH_3), 2.01—2.05 (m, 1H, CH), 3.00 (d, J=12.0 Hz, 1H, FcCH**H**), 3.16 (d, J=12.0 Hz, 1H, FcCH**H**), 3.59 (s, 1H NCH), 4.00—4.08 (m, 9H, Fc), 5.20 (s, 1H NH), 7.10—7.73 (m, 10H, PhH); IR (KBr) ν: 3349 cm^{-1}; MS *m/z* (%): 453 (M$^+$, 7.48), 270 (20.85), 236 (48.50), 199 (100), 120 (66.50), 105 (54.85), 91 (7.86), 77 (34.57). Anal. calcd for $C_{28}H_{31}FeNO$: C 74.17, H 6.89, N 3.09; found C 74.16, H 6.92, N 3.03.

3c 68.8%, m.p. 142—144 ℃, $[\alpha]_D^{25}-46.9$ (*c* 1.21, benzene); ^{1}H NMR ($CDCl_3$) δ: 0.83 (d, J=7.2 Hz, 3H, CH_3), 0.85 (d, J=6.0 Hz, 3H, CH_3), 1.10—1.16 (m, 1H, CH**H**), 1.30—1.40 (m, 1H, CH**H**), 1.41—1.57 (m, 1H, $(CH_3)_2$C**H**), 2.92 (d, J=12.8 Hz, 1H, FcCH**H**), 3.12 (d, J=12.8 Hz, 1H, FcCH**H**), 3.68 (d, J=8.4 Hz, 1H NCH), 3.94—4.05 (m, 9H, Fc), 4.80 (brs, 1H, NH), 7.15—7.70 (m, 10H, PhH); IR (KBr) ν: 3372 cm^{-1}; MS *m/z* (%): 467 (M$^+$, 2.04), 284 (9.23), 199 (100), 105 (32.43), 91 (4.01), 77 (14.65). Anal. calcd for $C_{29}H_{33}FeNO$: C 74.52, H 7.12, N 3.00; found C 74.68, H 7.04, N 2.85.

3d 74.6%, m.p. 160—162 ℃, $[\alpha]_D^{25}-50.8$ (*c* 1.42, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ: 0.57 (t, J=7.2 Hz, 3H, CH_2CH_3), 0.70—0.81 (m, 1H, CH_3CH**H**), 1.00 (d, J=6.0 Hz, 3H, CHC**H**$_3$), 1.45—1.67 (m, 2H, CH_2), 3.07 (d, J=12.8 Hz, 1H, FcCH**H**), 3.25 (d, J=12.8 Hz, 1H, FcCH**H**), 3.60 (s, 1H, NCH), 4.00—4.25 (m, 9H, Fc), 5.57 (bs, 1H, NH), 7.16—7.70 (m, 10H, PhH); IR (KBr) ν: 3353 cm^{-1}; MS *m/z* (%): 467 (M$^+$, 3.05), 283 (13.61), 199 (100), 120 (24.67), 105 (23.1), 91 (2.39), 77 (10.36). Anal. calcd for $C_{29}H_{33}FeNO$: C 74.52, H 7.12, N 3.00; found C 74.79, H 7.26, N 2.95

3e 71.8%, m.p. 108—109 ℃, $[\alpha]_D^{25}-48.2$ (*c* 1.35, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ: 1.01 (d, J=6.0 Hz, 3H, CH_3), 3.29 (d, J=12.8 Hz, 1H, FcCH**H**), 352 (d, J=12.8 Hz, 1H, FcCH**H**), 3.83—3.90 (m, 1H, CH), 3.91—4.09 (m, 9H, Fc), 4.46 (bs, 1H, NH), 7.17—7.63 (m, 10H, PhH); IR (KBr) ν: 3360 cm^{-1}; MS *m/z* (%): 425 (M$^+$, 2.68), 241 (13.47), 199 (100), 120 (22.74), 105 (26.8), 77 (10.28). Anal. calcd for $C_{26}H_{27}FeNO$: C 73.42, H 6.40, N 3.29; found C 73.38, H 6.54, N 2.99.

X-ray structure determination of 3a

A yellow platelet crystal of $C_{32}H_{31}FeNO$ having approximate dimensions of 0.22 mm×0.10 mm×0.07 mm was mounted on a glass fiber. All measurements were made on a Rigaku with graphite monochromated Mo Kα radiation (λ=0.071073 nm).

Of the 23485 reflections collected, 5381 were unique (R_{int}=0.0961), and equivalent reflections were merged. Data were collected and processed using CrystalClear (Rigaku). The structure was solved by direct method using the SHELXS-97. The crystallographic data are given in Table 2. Selected bond lengths and angles are listed in Table 3.

Catalytic enantioselective reduction of prochiral ketones

The reaction was carried out in flame-dried glassware under nitrogen atmosphere. A solution of I_2 (1.53 g, 6.0 mmol) in dry THF (5 mL) was dropped to a stirred suspension of $NaBH_4$ (0.46 g, 12.0 mmol) in dry THF (10 mL) while cooling with an ice bath. After stir ring for 30 min, the temperature was allowed to rise to

Table 2 Crystallographic data of **3a**

Empirical formula	$C_{32}H_{31}FeNO$
Formula weight	501.43
Crystal color, habit	Yellow, platelet
Crystal dimensions/mm^3	0.22×0.10×0.07
Crystal system	Orthorhombic
Lattice type	Primitive
Lattice parameters	a=0.60550(12) nm b=1.9196(4) nm c=2.1623(4) nm V=2.5133(9) nm^3
Space group	$P2_12_12_1$
Z value	4
Density (calculated)/(g • cm^{-3})	1.325
Absorption coefficient/nm^{-1}	0.652
F(000)	1056
μ(Mo Kα)/cm^{-1}	6.25
Final R indices [$I>2\sigma(I)$]	R_1=0.0661, wR_2=0.1493
R indices (all data)	R_1=0.0773, wR_2=0.1554
Absolute structure parameter	0.04(2)
Largest diff. peak and hole/(e • nm^{-3})	322 and 376

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

Fe (1)—C (23)	0.2064(4)
Fe(1)—C(30)	0.2067(5)
O(1)—C(1)	0.1443(4)
N(1)—C(2)	0.1471(5)
N(1)—C(22)	0.1471(5)
C(1)—C(16)	0.1540(5)
C(1)—C(10)	0.1538(5)
C(2)—C(3)	0.1545(6)
C(3)—C(4)	0.1514(6)
C(22)—C(23)	0.1499(6)
C(2)-N(1)-C(22)	117.3(3)
N(1)-C(2)-C(3)	108.5(3)
N(1)-C(2)-C(1)	107.0(3)
O(1)-C(1)-C(16)	109.9(3)
O(1)-C(1)-C(10)	107.2(3)
O(1)-C(1)-C(2)	105.5(3)
C(3)-C(2)-C(1)	114.2(3)
C(4)-C(3)-C(2)	114.5(3)
C(16)-C(1)-C(10)	108.0(3)
C(11)-C(10)-C(1)	119.2(4)
C(15)-C(10)-C(1)	121.7(3)
C(17)-C(16)-C(1)	120.0(3)
C(9)-C(4)-C(3)	121.5(4)
C(5)-C(4)-C(3)	122.2(4)
N(1)-C(22)-C(23)	112.0(3)
C(24)-C(23)-C(22)	124.7(4)
C(27)-C(23)-C(22)	128.0(4)
C(22)-C(23)-Fe(1)	129.8(3)

25 ℃. To the mixture was added amino alcohols **3a** (0.25 g, 0.5 mmol), stirred for 15 min. A solution of acetophenone (1.2 g, 10.0 mmol) in THF (15 mL) was dropped slowly to the reductive system during 45 min. After the accomplishment of the reduction (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, $V∶V$) to afford a solution of product. After removal of the solvent, the residue was distilled under reduced pressure to give the optically active phenyl ethyl alcohol 1.12 g (92%), $[\alpha]_D^{25}$+25.5 (c 5, ethanol).

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