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Achiral and planar chiral ferrocene diols: preparation and complexation with titanium(IV)☆

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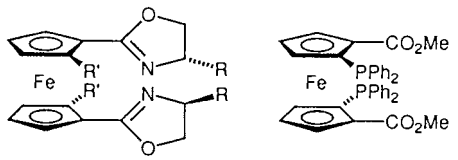
Abstract

Achiral ferrocene diol, 1,1′-bis(diphenylhydroxymethyl)ferrocene **5**, was prepared by the direct dilithiation of ferrocene with *n*-butyllithium in the presence of TMEDA followed by treatment with benzophenone, while the first chiral C_2-symmetric ferrocene diol possessing only the planar chirality, (+)-(*R*,*R*)-1,1′-bis(diphenylhydroxymethyl)-2,2′-dimethylferrocene **6**, was prepared from (+)-(*R*,*R*)-1,1′-bis(oxazolinyl)-2,2′-dimethylferrocene **1b** by the transformation of the oxazoline moieties. It was shown that diols **5** and **6** can form 1:1 complexes with tetraisopropyl titanate with ease. The X-ray crystal structure analysis of **5** with an intramolecular hydrogen-bonding showed that the phenyl groups in the molecule occupy *quasi*-axial and *quasi*-equatorial positions and these structures can be taken as the models of the titanium complexes of ferrocene diols. As a preliminary experiment, the titanium-catalyzed hydrosilylation of a ketone with **6** has also been carried out.

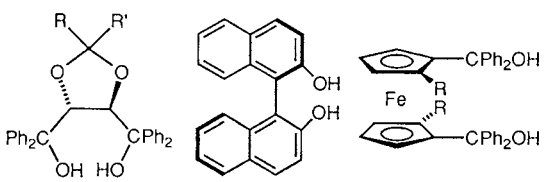
Keywords: Ferrocene; Diol; Titanium; Oxazoline; Planar chirality; Crystal structure

1. Introduction

The authors' recent attention has been focused on the development of C_2-symmetric ligands possessing the planar chirality of ferrocene for asymmetric catalytic reactions [1]. In the preceding papers, they described the preparation of C_2-symmetric 1,1′,2,2′-tetrasubstituted ferrocene compounds **1** via the highly diastereoselective dilithiation of 1,1′-bis(oxazolinyl)ferrocene [1a].



1 (**a**, R' = PPh_2; **b**, R = *i*-Pr, R' = Me) **2**



3 **4** **5** (R = H); **6** (R = Me)

Compound **1a** can be directly used as a *P*,*N*-chelating chiral ligand [1b]; furthermore, it can also be transformed to novel C_2-symmetric *P*,*P*-chelating ligand **2** [1c], which is the first C_2-symmetric ligand with only the planar chirality of ferrocene. With these novel C_2-symmetric ligands **1a** and **2**, excellent enantiomeric excesses have been attained for the palladium-catalyzed asymmetric allylic alkylation [1b,c]. Meanwhile, in recent years, chiral titanium reagents derived from C_1- and C_2-symmetric chiral α,α,α′,α′-tetraphenyl diol, such as TADDOLs **3** and chiral binaphthol **4**, have received

☆ Dedicated to the memory of the late Professor Rokuro Okawara.

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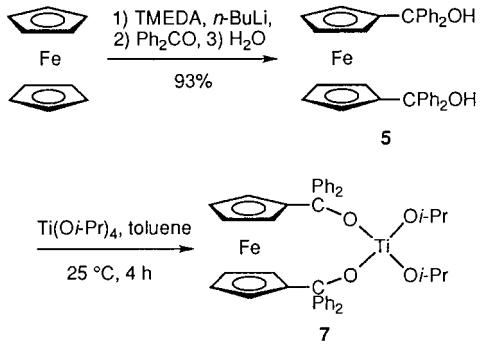


Scheme 1.

much attention as chiral Lewis acid catalysts in asymmetric synthesis [2,3]. However, the chiral titanium reagents derived from other types of diols are rarely reported [4]. Based on a preceding study, therefore, the authors prepared achiral and planar chiral C_2-symmetric $\alpha,\alpha,\alpha',\alpha'$-tetraphenyl diol **5** and **6**, respectively, with a ferrocene backbone and examined their complexation behavior with titanium(IV) and their probability as Lewis acid catalysts [5].

2. Results and discussion

Before the preparation of the chiral diol **6**, the achiral ferrocene diol **5** was first prepared and its complexation property with titanium(IV) and its crystal structure were examined.

Diol **5** can be prepared from ferrocene with ease in high yield in a one-pot synthesis (Scheme 1). Thus, ferrocene was first dilithiated with 2.6 equivalents of *n*-butyllithium in the presence of 2.6 equivalents of tetramethylethylenediamine (TMEDA) at r.t. for 1 day, and then the dilithiated species was treated with 2.7 equivalents of benzophenone. After the reaction mixture was stirred at r.t. overnight, **5** was isolated in 93% yield with silica gel column chromatography.

Then the complexation of **5** with titanium(IV) was examined. Compound **5** was reacted with one equivalent of tetraisopropyl titanate in toluene under argon at r.t. for 4 h. After the solvent and the liberated isopropanol were evaporated in vacuo, a 1:1 titanium complex **7** was formed as expected. The structure of **7** was determined by ^{1}H-NMR and fast atom bombardment mass spectroscopy (FAB MS) analysis (Scheme 1). Attempts to determine the X-ray crystal structure of this complex failed, because it is very sensitive to moisture in air.

However, a stable crystal of diol **5** was obtained from its ethyl acetate solution in the presence of a trace amount of piperidine. From the X-ray crystal analysis, it was found that two kinds of structures (A and B) existed in one crystal, and in both the two OH groups formed an intramolecular hydrogen bond (Fig. 1). The O–O distances in these diol structures (2.84 Å in A and 2.68 Å in B) are similar to those of diol **3** (ca. 2.6 Å) and its corresponding Ti complex (ca. 2.8 Å) [3g]. Similar to diol **3** and its corresponding Ti complex, the phenyl groups in both A and B also occupy *quasi*-axial and *quasi*-equatorial positions. Therefore, these structures of diol **5** can be taken as the models of its titanium complex [3g].

Then, the C_2-symmetric chiral diol **6** was prepared with only the planar chirality of ferrocene and its complexation property with tetraisopropyl titanate was examined. Diol **6** can be prepared with ease from **1b**

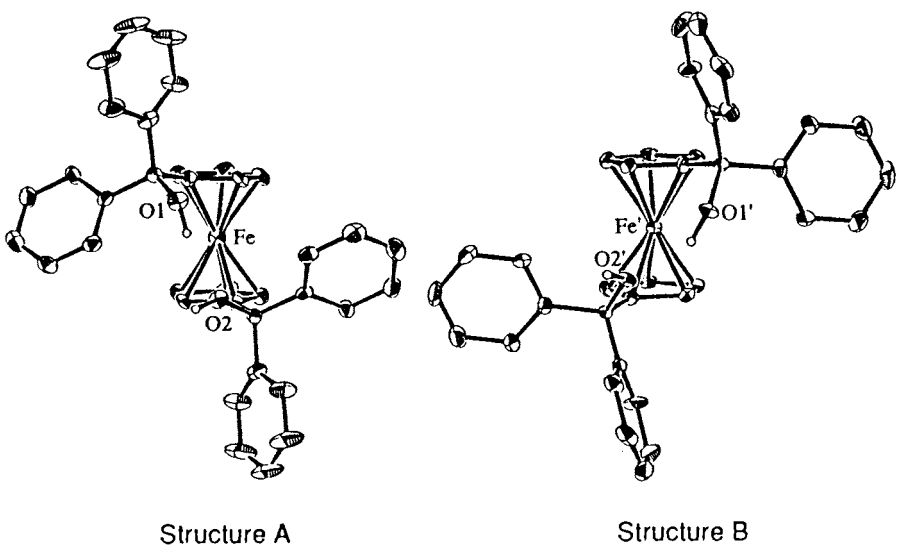
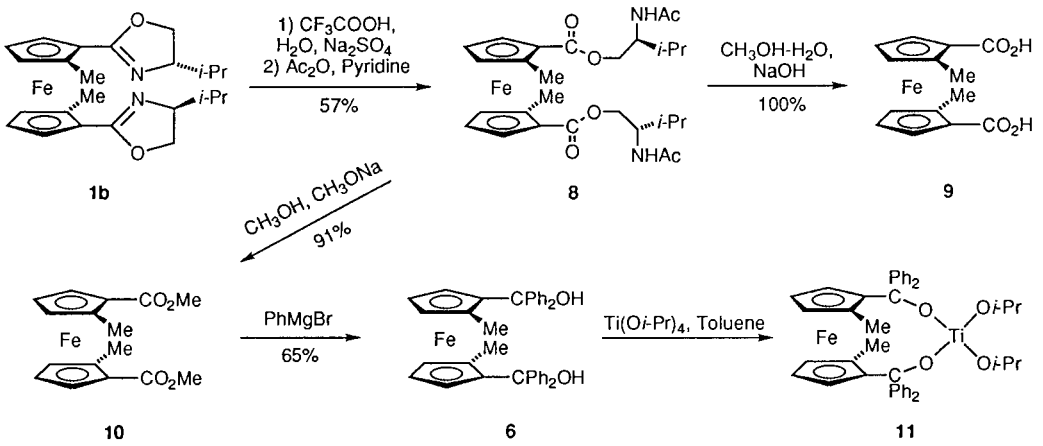


Fig. 1. Two crystal structures (A and B) of 5 (ORTEP, ellipsoids at the 20% probability level, $R = 0.073$, $R_w = 0.046$).



Scheme 2.

[1a] by the transformation of the oxazoline moieties (Scheme 2). Thus, treatment of **1b** with trifluoroacetic acid in aqueous THF caused ring opening of the oxazoline moiety, to give an unstable ammonium salt. The salt was successively acetylated, without isolation, with acetic anhydride in the presence of pyridine to provide the ester amide **8** in 57% yield. The hydrolysis of **8** in a methanol–water solution in the presence of sodium hydroxide gave quantitatively 2,2′-dimethyl-1,1′-ferrocenedicarboxylic acid **9**, which is a novel C_2-symmetric chiral dicarboxylic acid, with only the planar chirality of ferrocene, and may have great potential in molecular recognition and asymmetric synthesis. Transesterification of **8** using methanolic sodium methoxide at r.t. for 1 day gave the corresponding dimethyl ester **10** in 91% yield. Compound **10** was then treated with 7.5 equivalents of PhMgBr in THF at r.t. for 3 h to give **6** in 65% yield.

Compound **6** was then treated with 1.1 equivalents of tetraisopropyl titanate in dry toluene at r.t. under argon for 6 h. The isopropanol liberated by ligand exchange was removed thoroughly, along with the solvent, under high vacuum to give titanate **11**, the structure of which was determined by ^{1}H-NMR and FAB MS analysis (Scheme 2).

Recently, Nakai et al. reported a successful titanium-catalyzed asymmetric hydrosilylation of prochiral ketone with inexpensive triethoxysilane [6]. With the present new kind of diol **6** as a ligand, the current authors also carried out this reaction as a preliminary experiment. They found that the catalytic hydrosilylation of acetophenone with triethoxysilane proceeded cleanly at 50°C for 6 h to give 1-phenylethanol in 94% yield. No significant level of enantioselectivity has been observed for this reaction so far, and work on further modification of the ligand and the examination on other titanium-catalyzed asymmetric reactions is in progress.

3. Experimental

Melting points were measured on a Yanagimoto micromelting point apparatus and have not been corrected. Optical rotations were measured on a JASCO DIP-181 digital polarimeter. ^{1}H-NMR spectra were recorded on a JEOL GSX-400 spectrometer, and the chemical shifts were referenced to $CHCl_3$ (δ 7.27 in $CDCl_3$). IR spectra were obtained on a HORIBA FT-710 IR spectrophotometer. The FAB MS spectra were obtained on a JEOL JMS-DX303HF spectrometer. Elemental analyses were performed on a Yanagimoto CHN-Corder. The X-ray crystallography was performed on a Rigaku AFC5R diffractometer. Ether was freshly distilled from sodium, and toluene and TMEDA from CaH_2 before use. Merck 70–230 mesh silica gel was used for column chromatography. All other chemicals used in the synthetic procedures were of reagent grade.

3.1. 1,1′-Bis(diphenylhydroxymethyl)ferrocene, 5

To a mixture of TMEDA (11.1 ml, 73.7 mmol) and 1.6 M *n*-butyllithium (46.1 ml, 73.7 mmol) a solution of ferrocene (5.00 g, 26.9 mmol) was added dropwise in dry ether (60 ml) at 0°C and the reaction mixture was stirred at r.t. for 24 h. A solution of benzophenone (13.50 g, 74.0 mmol) in dry ether (60 ml) was added to the above reaction mixture at −10°C and the reaction mixture was stirred at r.t. overnight. HCl (1 N, 100 ml) was added to the reaction mixture. After separation, the organic layer was washed with water (100 ml), brine (100 ml) and dried over $MgSO_4$. After the solvent was evaporated, the residue was purified by silica gel column chromatography, eluted with a mixture of benzene and ethyl acetate (1:1, v/v) to give **5** (14.1 g, 93% yield).

A yellow solid, m.p. 166–168°C. $R_f = 0.14$ (benzene). ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 3.97$ (t, 4H, $J = 1.8$

Hz, FcH), 4.03 (s, 2H, OH), 4.18 (t, 4H, $J = 1.8$ Hz, FcH), 7.21–7.31 (m, 20H, ArH). IR (KBr): $\nu = 3340$, 3060, 1490, 1444, 1014, 752, 700 cm^{-1}; FAB MS: m/z: 550 (M^+). Anal. calc. for $C_{36}H_{30}O_2Fe$: C, 78.55; H, 5.49. Found: C, 78.28, H, 5.49.

3.2. Preparation of titanium complex 7

To a solution of **5** (0.50 g, 0.91 mmol) in dry toluene (12 ml) under argon, tetraisopropyl titanate (0.26 g, 0.91 mmol) was added. The resulting yellow solution was stirred for 3 h at r.t. The isopropanol liberated by ligand exchange was removed thoroughly, along with the solvent, under high vacuum at 40°C. The residue thus obtained was dried under these conditions for 2 h to give the titanium complex **7**.

^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 1.14$ (d, 12H, $J =$ 6.1 Hz, CH_3), 3.92 (brs, 4H, FcH), 4.26 (brs, 4H, FcH), 4.45 (m, 2H, $CHMe_2$), 7.19–7.41 (m, 20H, ArH). FAB MS: m/z: 715 ($M + H^+$).

3.3. Preparation of ester amide 8 (Scheme 2)

To a solution of **1b** (2.32 g, 5.31 mmol) in THF (130 ml), water (7.2 ml), trifluoroacetic acid (12.3 ml, 160 mmol) and Na_2SO_4 (60.0 g) were added, and the resulting suspension was stirred overnight at r.t. After removal of solid material by filtration and the solvent in vacuo below r.t., an unstable ester ammonium salt was obtained as a brown solid, which was used in the next step without purification. To a solution of this ester ammonium salt in dichloromethane (120 ml), pyridine (20 ml, 241 mmol) and acetic anhydride (33 ml, 340 mmol) were added, and the mixture was stirred at r.t. overnight. The mixture was washed with HCl (1N, 50 ml) three times, water (50 ml), and brine (50 ml) and dried over Na_2SO_4. After the removal of solid material by filtration and of the solvent in vacuo, a red residue was obtained. The residue was purified by silica gel chromatography, with ethyl acetate to afford pure ester amide **8** (1.69 g, 57% overall yield from compound **1b**).

A yellow solid, m.p. 102–104°C. $R_f = 0.11$ (ethyl acetate). ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 1.02$ (t, 12H, $J = 6.5$ Hz, CH_3), 1.95 (m, 2H, Me_2CH), 2.07 (s, 6H, $FcCH_3$), 2.19 (s, 6H, $COCH_3$), 4.20 (m, 4H, NCH and FcH), 4.28 (m, 4H, OCH_2), 4.32 (t, 2H, $J = 1.7$ Hz, FcH), 4.57 (t, 2H, $J = 1.7$ Hz, FcH), 6.36 (d, 2H, $J = 8.1$ Hz, NH). FAB MS: m/z: 556 (M^+).

3.4. (+)-(R,R)-2,2′-Dimethyl-1,1′ferrocenedicarboxylic acid, 9

To a solution of **8** (0.14 g, 0.25 mmol) in methanol:water (1:1, 12 ml) sodium hydroxide (0.40 g, 10 mmol) was added and the solution was stirred overnight. HCl (1 N) was added to this solution until pH 2 and then the resulting solid was filtered and purified by silica gel column chromatography with ethyl acetate to give **9** (0.075 g, 100%).

An orange solid, m.p. 219–221°C (decomp.). $R_f =$ 0.24 (ethyl acetate). $[\alpha]_D^{27} = +290$ (c 0.5, $CHCl_3$). ^{1}H-NMR (400 MHz, CD_3OD): $\delta = 2.13$ (s, 6H, CH_3), 4.27 (m, 4H, FcH), 4.67 (t, 2H, $_J = 1.3$ Hz, FcH). IR (KBr): $\nu = 3415$, 2960, 1709, 1261, 1030, 800 cm^{-1}.

3.5. (+)-(R,R)-2,2′-Dimethyl-1,1′-ferrocenedicarboxylic acid dimethyl ester, 10

To a solution of **8** (1.44 g, 2.59 mmol) in THF (10 ml), a sodium methoxide solution prepared by the dissolution of sodium (2.55 g, 111 mmol) in methanol (140 ml) was added. After stirring at r.t. for 24 h, the mixture was neutralized with methanolic acetic acid and the solvent was removed by rotary evaporation. The residue was dissolved in dichloromethane (100 ml) and the solution was washed with water (50 ml) and brine (50 ml) successively, and then dried over $MgSO_4$. After removal of the solvent, the residue was purified by silica gel chromatography with ethyl acetate to afford **10** (0.78 g, 91% yield).

A yellow solid, m.p. 198°C (decomp.). $R_f = 0.61$ (ethyl acetate). $[\alpha]_D^{24} = +120.3$ (c 0.61, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 2.25$ (s, 6H, $FcCH_3$), 3.95 (s, 6H, OCH_3), 4.22 (t, 2H, $J = 2.6$ Hz, FcH), 4.25 (t, 2H, $J = 1.7$ Hz, FcH), 4.68 (t, 2H, $J = 1.7$, 2.6 Hz, FcH). IR (KBr): $\nu = 2952$, 1712, 1440, 1278, 1214, 1093 cm^{-1}. FAB MS: m/z: 330 (M^+).

3.6. (+)-(R,R)-1,1′-Bis(diphenylhydroxymethyl)-2,2′-dimethylferrocene, 6

To a solution of PhMgBr in ether (3.0 ml) prepared from Mg (0.16 g, 6.50 mmol) and bromobenzene (1.02 g, 6.50 mmol), a solution of **10** (0.30 g, 0.92 mmol) in ether (4.0 ml) was added at 0°C, and then the reaction solution was stirred at r.t. overnight. The resulting dark oil was dissolved in benzene (50 ml) and washed with saturated NH_4Cl aqueous solution. The organic layer was dried over $MgSO_4$. After removal of the solvent, the residue was purified by silica gel chromatography with benzene to afford **6** (0.34 g, 65% yield).

A yellow solid, m.p. 47–49°C. $R_f = 0.39$ (benzene). $[\alpha]_D^{23} = +337.0$ (c 5.14, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 1.74$ (s, 6H, CH_3), 3.44 (s, 2H, OH), 3.55 (brs, 2H, FcH), 4.03 (brs, 2H, FcH), 4.35 (brs, 2H, FcH), 7.16–7.39 (m, 20H, ArH). IR (KBr): $\nu = 3535$, 3057, 2916, 1446, 1018, 750 cm^{-1}. FAB MS: m/z: 578 (M^+). Anal. calc. for $C_{38}H_{34}O_2Fe$: C, 78.90; H, 5.92. Found: C, 78.53, H, 6.05.

3.7. Preparation of chiral titanium complex **11**

To a solution of **6** (0.178 g, 0.308 mmol) in dry toluene (3 ml) under argon, tetraisopropyl titanate (0.096 g, 0.338 mmol) was added. The reaction mixture was stirred at r.t. for 6 h. The isopropanol liberated by ligand exchange was removed thoroughly, along with the solvent, under high vacuum at 40°C. The residue thus obtained was dried under these conditions for 2 h to give titanium complex **11**.

^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 1.15$ (d, 6H, $J =$ 6.2 Hz, $OCCH_3$), 1.27 (m, 12H, $OCCH_3$ and $FcCH_3$), 3.64 (dd, 2H, $J = 1.8$, 2.2 Hz, FcH), 4.07 (dd, 2H, $J = 1.8$, 2.2 Hz, FcH), 4.51 (m, 2H, $CHMe_2$), 4.68 (dd, 2H, $J = 1.8$, 2.2 Hz, FcH), 7.15–7.40 (m, 20H, ArH). FAB MS: m/z: 743 ($M + H^+$).

3.8. Procedure for the titanium-catalyzed asymmetric hydrosilylation of acetophenone

To a solution of titanium complex **11** prepared from **6** (0.190 g, 0.33 mmol) and (i-PrO)$_4$Ti (0.085 g, 0.30 mmol) in toluene (5 ml), acetophenone (0.360 g, 3.0 mmol) and $HSi(OEt)_3$ (2.96 g, 18.0 mmol) were added. The reaction solution was stirred at 50°C until the acetophenone disappeared by TLC analysis (5 h), then it was quenched by adding slowly methanol (5 ml), water (5 ml) and then NaOH (1N, 50 ml). The resulting mixture was stirred at r.t. for 2.5 h, then neutralized by 4 N HCl. After removal of insoluble material and the solvent by filtration and evaporation respectively, the residue was purified by silica gel column chromatography to give 1-phenylethanol (0.344 g, 94%).

3.9. X-ray crystal structure determination of **5**

An orange crystal of **5** ($C_{36}H_{30}O_2Fe$) with approximate dimensions of $0.20 \times 0.20 \times 0.20$ mm^3 was mounted on a glass fiber. The measurement was made on a Rigaku AFC5R diffractometer with graphite monochromated Mo–K_α radiation and a 12 kW rotating anode generator. Cell constants and an orientation matrix for data collection were obtained from least-squares refinement using the setting angles of 23 carefully centered reflections in the range $26.97° < 2\theta < 27.49°$ corresponding to a monoclinic cell with dimensions: $a = 13.267(5)$, $b = 23.229(8)$, $c = 18.760(3)$ Å; $V = 5571(2)$ Å^3. The data were collected at 23 ± 1°C using the ω–2θ scan technique to a maximum 2θ value of 55.1°. A total of 6888 reflections was collected. The structure was solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. The final cycle of full-matrix least-squares refinement was based on 2653 observed reflections ($I > 3.00\sigma(I)$) and 361 variable parameters. $R = 0.073$, $R_w = 0.046$. Tables of atomic co-ordinates, bond lengths, angles and thermal parameters are available from the authors.

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