Supporting Information for

Chirality Organization of Ferrocenes Bearing Dipeptide Chains of Heterochiral Sequence

Toshiyuki Moriuchi, Takayoshi Nagai, and Toshikazu Hirao*

Department of Applied Chemistry, Graduate School of Engineering,

Osaka University,

Yamada-oka, Suita, Osaka 565-0871, Japan

hirao@chem.eng.osaka-u.ac.jp

General Methods.

All reagents and solvents were purchased from commercial sources and were further purified by the standard methods, if necessary. Melting points were determined on a Yanagimoto Micromelting Point Apparatus and were uncorrected. Infrared spectra were obtained with a JASCO FT/IR-480 Plus spectrometer. ^{1}H NMR spectra were recorded on a JEOL JNM-ECP 400 (400 MHz) spectrometer with tetramethylsilane as an internal standard. Mass spectra were run on a JEOL JMS-700 mass spectrometer.

Dipeptide derivatives were prepared according to the method reported in a previous paper by coupling of Boc-Ala-Pro-OH with 2-aminopyridine using EDCI,

followed by removal of the *t*-butyloxycarbonyl protective group (Moriuchi, T.; Yoshida, K.; Hirao, T. *Organometallics* **2001**, *20*, 3101-3105). 1,1'-Bis(chlorocarbonyl)ferrocene was prepared according to the literature method (Knobloch, F. W.; Rauscher, W. H. *J. Polymer Sci.* **1961**, *54*, 651-656).

General Procedure for the Synthesis of Ferrocenes 1 and 2 Bearing Two Heterochiral Dipeptide Chains.

To a stirred mixture of H-Ala-Pro-NHPy (315 mg, 1.20 mmol), 4-dimethylaminopyridine (6.0 mg, 0.05 mmol), and triethylamine (836 μL, 6.0 mmol) in dichloromethane (20 mL) was dropwise added 1,1'-bis(chlorocarbonyl)ferrocene (187 mg, 0.60 mmol) in dichloromethane (25 mL) at 0 °C under argon. The mixture was stirred at 0 °C for 1 h and then at room temperature for 20 h. The resulting mixture was diluted with dichloromethane, washed with saturated $NaHCO_3$ aqueous solution and brine, and then dried over Na_2SO_4. The solvent was evaporated in vacuo and the residue was chromatographed on alumina column eluting with ethyl acetate. The ferrocene **1** or **2** was isolated by recrystallization from dichloromethane-hexane.

1: yield 70%; mp 191-194 °C (dec); IR (CH_2Cl_2, 1.0 x 10^{-2} M) 3309, 1712, 1632 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 1.0 x 10^{-2} M) δ 9.49 (s, 2H), 8.61 (d, 2H, J = 6.3 Hz), 8.42 (ddd, 2H, J = 4.9, 1.9, 0.9 Hz), 8.21 (ddd, 2H, J = 8.5, 1.1, 0.9 Hz), 7.67 (ddd, 2H, J = 8.5, 7.3, 1.9 Hz), 7.06 (ddd, 2H, J = 7.3, 4.9, 1.1 Hz), 4.83-4.75 (m, 4H), 4.72-4.70 (m, 2H), 4.54-4.53 (m, 2H), 4.34-4.29 (m, 2H), 3.98-3.96 (m, 2H), 3.66-3.60 (m, 2H), 3.10-3.09 (m, 2H), 2.44-2.36 (m, 2H), 2.28-2.16 (m, 4H), 2.15-2.07 (m, 2H), 1.48 (d, 6H, J = 7.2 Hz); FAB-MS *m/z* 762 (M^+); Anal. Calcd. for $C_{38}H_{42}N_8O_6Fe \cdot 0.5H_2O$: C, 59.15; H, 5.62; N, 14.52. Found: C, 59.03; H, 5.48; N, 14.41.

2: yield 64%; mp 191-194 °C (dec); IR (CH_2Cl_2, 1.0 x 10^{-2} M) 3309, 1712, 1632 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 1.0 x 10^{-2} M) δ 9.49 (s, 2H), 8.61 (d, 2H, *J* = 6.3 Hz), 8.42 (ddd, 2H, *J* = 4.9, 1.9, 0.9 Hz), 8.21 (ddd, 2H, *J* = 8.5, 1.1, 0.9 Hz), 7.67 (ddd, 2H, *J* = 8.5, 7.3, 1.9 Hz), 7.06 (ddd, 2H, *J* = 7.3, 4.9, 1.1 Hz), 4.83-4.75 (m, 4H), 4.72-4.70 (m, 2H), 4.54-4.53 (m, 2H), 4.34-4.29 (m, 2H), 3.98-3.96 (m, 2H), 3.66-3.60 (m, 2H), 3.10-3.09 (m, 2H), 2.44-2.36 (m, 2H), 2.28-2.16 (m, 4H), 2.15-2.07 (m, 2H), 1.48 (d, 6H, *J* = 7.2 Hz); FAB-MS *m/z* 762 (M^+); Anal. Calcd. for $C_{38}H_{42}N_8O_6Fe•0.5H_2O$: C, 59.15; H, 5.62; N, 14.52. Found: C, 58.91; H, 5.55; N, 14.18.

General Procedure for the Synthesis of Ferrocenes 3 and 4 Bearing One Heterochoral Dipeptide Chain.

To a stirred mixture of H-Ala-Pro-NHPy (315 mg, 1.20 mmol), 4-dimethylaminopyridine (6.0 mg, 0.05 mmol), and triethylamine (836 μL, 6.0 mmol) in dichloromethane (20 mL) was dropwise added (chlorocarbonyl)ferrocene (298 mg, 1.20 mmol) in dichloromethane (25 mL) 0 °C under argon at. The mixture was stirred at 0 °C for 1 h and then at room temperature for 20 h. The resulting mixture was diluted with dichloromethane, washed with saturated $NaHCO_3$ aqueous solution and brine, and then dried over Na_2SO_4. The solvent was evaporated in vacuo and the residue was chromatographed on alumina column eluting with ethyl acetate. The ferrocene **3** or **4** was isolated by recrystallization from dichloromethane-hexane.

3: yield 80%; mp 92-94 °C (uncorrected); IR (CH_2Cl_2, 2.0 x 10^{-2} M) 3421, 1712, 1646 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 2.0 x 10^{-2} M) δ 9.34 (s, 1H), 8.28 (ddd, 1H, *J* = 4.9, 2.0, 1.1 Hz), 8.14 (dt, 1H, *J* = 8.3, 1.1 Hz), 7.64 (ddd, 1H, *J* = 8.3, 7.2, 2.0 Hz), 6.99 (ddd, 1H, *J* = 7.2, 4.9, 1.1 Hz), 6.54 (d, 1H, *J* = 7.6 Hz), 4.97-4.89 (m, 1H), 4.76-

4.73 (m, 2H), 4.67-4.66 (m, 1H), 4.33-4.31 (m, 2H), 4.13 (s, 5H), 4.04-3.99 (m, 1H), 3.64-3.57 (m, 1H), 2.49-2.43 (m, 1H), 2.23-2.15 (m, 1H), 2.13-2.04 (m, 2H), 1.45 (d, 3H, J = 6.9 Hz); FAB-MS *m/z* 474 (M^+); Anal. Calcd. for $C_{24}H_{26}N_4O_3Fe \bullet 0.5H_2O$: C, 59.64; H, 5.63; N, 11.59. Found: C, 59.44; H, 5.50; N, 11.47.

4: yield 76%; mp 92-94 °C (uncorrected); IR (CH_2Cl_2, 2.0 x 10^{-2} M) 3421, 1712, 1646 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 2.0 x 10^{-2} M) δ 9.34 (s, 1H), 8.28 (ddd, 1H, J = 4.9, 2.0, 1.1 Hz), 8.14 (dt, 1H, J = 8.3, 1.1 Hz), 7.64 (ddd, 1H, J = 8.3, 7.2, 2.0 Hz), 6.99 (ddd, 1H, J = 7.2, 4.9, 1.1 Hz), 6.54 (d, 1H, J = 7.6 Hz), 4.97-4.89 (m, 1H), 4.76-4.73 (m, 2H), 4.67-4.66 (m, 1H), 4.33-4.31 (m, 2H), 4.13 (s, 5H), 4.04-3.99 (m, 1H), 3.64-3.57 (m, 1H), 2.49-2.43 (m, 1H), 2.23-2.15 (m, 1H), 2.13-2.04 (m, 2H), 1.45 (d, 3H, J = 6.9 Hz); FAB-MS *m/z* 474 (M^+); Anal. Calcd. for $C_{24}H_{26}N_4O_3Fe \bullet 0.5H_2O$: C, 59.64; H, 5.63; N, 11.59. Found: C, 59.65; H, 5.59; N, 11.27.

CD Measurements.

CD spectra were recorded using a JASCO J-720 spectropolarimeter in an deaerated dichloromethane solution with the concentration 1.0 x 10^{-4} M for **1** and **2**, and 2.0 x 10^{-4} M for **3** and **4** at 25 °C under argon.

Proton Magnetic Resonance Nuclear Overhauser Effect Measurements.

A sample was prepared under argon. Nuclear Overhauser effect experiments were performed with 2 second irradiation of a freeze-pump-thaw degassed 1.0 x 10^{-2} M solution in $CDCl_3$. The 400 MHz ^1H NMR spectra were recorded at 25 °C. Nuclear Overhauser enhancements were obtained by saturation of the desired resonance. Irradiation of the Cp proton at the β position enhanced the pyridyl protons (Figure S1)

and irradiation of the Cp proton at the α position enhanced the Ala NH, NH adjacent to the pyridyl moiety, and the pyridyl proton at the 3-position (Figure S2).

X-ray Structure Analysis.

All measurements for **1-4** were made on a Rigaku RAXIS-RAPID Imaging Plate diffractometer with graphite monochromated Mo Kα radiation. The structures of **1-4** were solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. The H atoms involved in hydrogen bonding were located in electron density maps. The remainder of the H atoms were placed in idealized positions and allowed to ride with the C atoms to which each was bonded. Crystallographic details are given in Table S1. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-271990 for **1**, CCDC-271991 for **2**, CCDC-271992 for **3**, and CCDC-271993 for **4**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

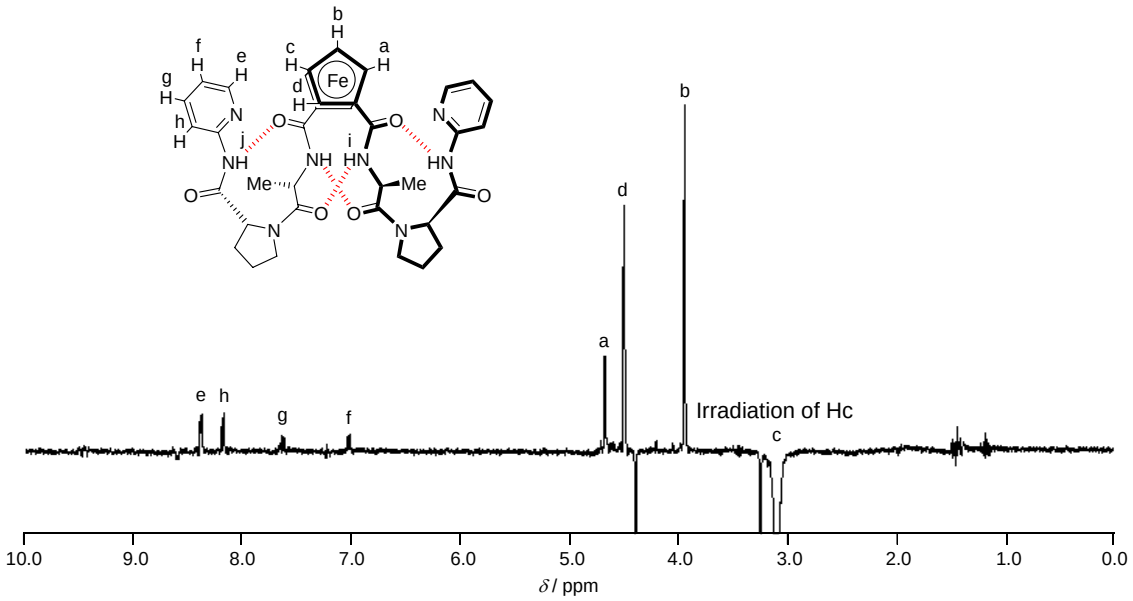

Figure S1. 400 MHz ^{1}H NMR difference NOE experiment performed at 25 °C with 2 second irradiation of a freeze-pump-thaw degassed 1.0 x 10^{-2} M solution of **1** in $CDCl_3$.

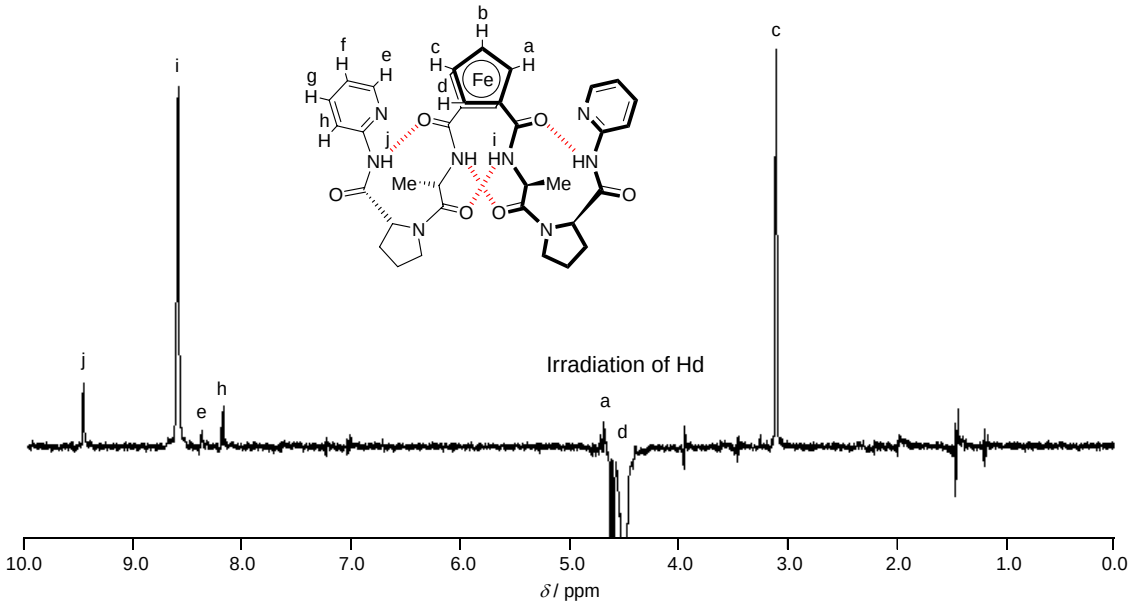

Figure S2. 400 MHz ^{1}H NMR difference NOE experiment performed at 25 °C with 2 second irradiation of a freeze-pump-thaw degassed 1.0 x 10^{-2} M solution of **1** in $CDCl_3$.

Table S1. Crystallographic Data for **1-4**

	1	**2**	**3**	**4**
formula	$C_{38}H_{42}N_8O_6Fe \cdot 5CH_2Cl_2$	$C_{38}H_{42}N_8O_6Fe \cdot 5CH_2Cl_2$	$C_{24}H_{26}N_4O_3Fe \cdot 0.5H_2O$	$C_{24}H_{26}N_4O_3Fe \cdot 0.5H_2O$
formula weight	1187.31	1187.31	483.35	483.35
crystal system	orthorhombic	orthorhombic	monoclinic	monoclinic
space group	$P2_12_12_1$ (No. 19)	$P2_12_12_1$ (No. 19)	$P2_1$ (No. 4)	$P2_1$ (No. 4)
a, Å	10.4525(2)	21.0852(5)	10.9029(2)	10.9323(2)
b, Å	21.2119(4)	24.6133(7)	19.5118(3)	19.5778(4)
c, Å	24.7104(4)	10.4010(2)	12.2690(1)	12.2868(3)
β, deg			94.684(1)	94.683(2)
V, Å^3	5478.7(2)	5397.9(5)	2601.33(6)	2620.97(9)
Z	4	4	4	4
D_{calcd}, g cm^{-3}	1.439	1.461	1.234	1.225
μ(Mo Kα), cm^{-1}	8.13	8.25	6.11	6.06
T, °C	23	4	4	4
λ(Mo Kα), Å	0.71069	0.71069	0.71069	0.71069
*R*1 [a]	0.098	0.096	0.087	0.082
*wR*2 [b]	0.268	0.264	0.228	0.220

[a] $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. [b] $wR2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$.

Table S2. Hydrogen Bonds for **1-4**

crystal	type [a]	donor	acceptor	D • • • A (Å)	D–H • • • A (°)
1	intra	N(1)	O(2*)	3.069(7)	161(6)
	intra	N(1*)	O(2)	2.973(7)	166(5)
	intra	N(3)	O(1)	3.223(7)	143(5)
	intra	N(3*)	O(1*)	3.153(7)	148(6)
2	intra	N(1)	O(2*)	3.059(6)	155(5)
	intra	N(1*)	O(2)	2.969(6)	163(4)
	intra	N(3)	O(1)	3.204(7)	146(5)
	intra	N(3*)	O(1*)	3.131(7)	150(6)
3 [b]	inter	N(1)	O(4)	2.828(9)	160(8)
	inter	N(3)	O(5a)	2.84(1)	167(6)
	inter	N(5)	O(1b)	2.880(9)	163(7)
	inter	N(7)	O(2)	2.79(1)	150(8)
	inter	N(3b)	O(5)	2.84(1)	167(6)
	inter	N(5a)	O(1)	2.880(9)	163(7)
4 [b]	inter	N(1)	O(4)	2.854(6)	164.0(6)
	inter	N(3)	O(5a)	2.854(7)	163.9(9)
	inter	N(5)	O(1b)	2.871(6)	154.7(7)
	inter	N(7)	O(2)	2.791(8)	159.0(9)
	inter	N(3b)	O(5)	2.854(7)	163.9(9)
	inter	N(5a)	O(1)	2.871(6)	154.7(7)

[a] inter: intermolecular, intra: intramolecular. [b] Two independent molecules exist in the asymmetric unit.

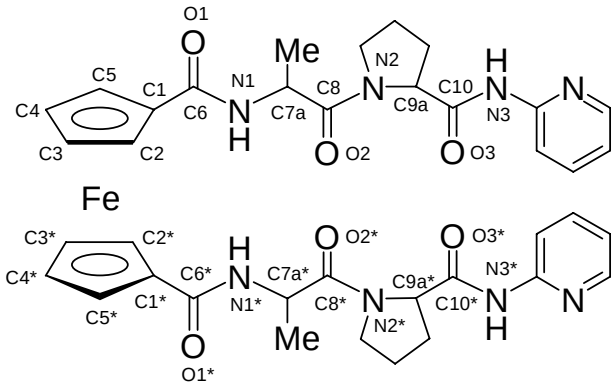

Table S3. Torsion Angles (deg) for **1-4**

	angle [a]	**1**	**2**	**3** [b]		**4** [b]	
ϕ_2	C(6)-N(1)-C(7a)-C(8)	-64.5(8)	65.0(7)	-68(1)	-78(1)	67.0(8)	80.4(8)
ψ_2	N(1)-C(7a)-C(8)-N(2)	134.0(6)	-134.7(6)	134.4(9)	127.5(8)	-134.5(7)	-127.0(6)
ω_2	C(7a)-C(8)-N(2)-C(9a)	178.7(6)	179.9(5)	-16(1)	-3(1)	17(1)	1.8(9)
ϕ_3	C(8)-N(2)-C(9a)-C(10)	68.7(8)	-67.5(8)	84(1)	74(1)	-85.3(8)	-72.5(8)
ψ_3	N(2)-C(9a)-C(10)-N(3)	19.2(10)	-18.7(9)	-160.5(7)	-163.7(7)	160.9(5)	163.6(6)
ϕ_2*	C(6*)-N(1*)-C(7a*)-C(8*)	-63.8(7)	64.0(7)				
ψ_2*	N(1*)-C(7a*)-C(8*)-N(2*)	136.0(6)	-136.3(6)				
ω_2*	C(7a*)-C(8*)-N(2*)-C(9a*)	175.4(6)	-176.2(6)				
ϕ_3*	C(8*)-N(2*)-C(9a*)-C(10*)	75.1(9)	-74.7(8)				
ψ_3*	N(2*)-C(9a*)-C(10*)-N(3*)	9(1)	-10.5(9)				

[a] Symbol used for torsion angles in peptides (IUPAC–IUB Commission on Biochemical Nomenclature).
[b] Two independent molecules exist in the asymmetric unit.

Table S4. Selected Spectroscopic Data for **1-4**

	^{1}H NMR N-H (ppm) [a]		FT-IR $\nu_{N\text{-}H}$ (cm^{-1}) [a]	$E_{1/2}$ (V) [b] Fc/Fc^+
	$CDCl_3$	$CDCl_3$/DMSO-d_6 (9:1)	CH_2Cl_2	CH_2Cl_2
1	9.49	9.53	3309	0.29
	8.61	8.64		
2	9.49	9.53	3309	0.29
	8.61	8.64		
3	9.34 [c]	9.75 [c]	3421 [c]	0.09
	6.54 [c]	7.03 [c]		
4	9.34 [c]	9.75 [c]	3421 [c]	0.09
	6.54 [c]	7.03 [c]		

[a] 1.0 x 10^{-2} M. [b] Volts vs Fc/Fc^+ as an internal standard.
0.5 x 10^{-3} M. [c] 2.0 x 10^{-2} M.