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Regioselective Aminolysis and Hydrolysis of Chiral 1,4-Ferrocenyl Diacetate

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The treatment of (1*R*,4*R*)-1,2-bis(phenylmethyl)ferrocenyl diacetate **2a** with aqueous ammonium in THF/MeOH at room temperature for 18 h gave the single diastereomer of the (1*R*,4*R*,*Sp*)-1,2-acetoamido alcohol **4a** with retention of the configuration. This result showed that the aminolysis occurred regioselectively at one side of the two acetates. Similarly, hydrolysis of the diacetate **2a** at room temperature for 18 h occurred regio- and stereoselectively to give the optically active half-ester **10** in a good yield. The ease of the substitution may depend on the geometry of the two stereogenic centers. Only one of the acetoxy groups is suitably aligned for ionization (*exo* to the ferrocenyl group) to proceed efficiently; the aminolysis takes place smoothly by iron-assisted ionization, i.e., neighboring group participation. The leaving group on the second acetoxy group is not suitably aligned (*endo* to the ferrocenyl group) and also cannot undergo a conformational change for it to adopt the appropriate orientation for ionization to occur. This reaction is the first case of substitution in a chiral molecule in which a conformational difference between two leaving groups happened to affect the rate of aminolysis and hydrolysis at two stereogenic centers.

Introduction

Chiral ferrocenes have been of interest especially in asymmetric catalysis as chiral ligands. Well-designed chiral ferrocenes may produce high stereoselectivities in asymmetric organic reactions. New preparative methods for a variety of chiral ferrocenes without optical resolution have attracted considerable attention.[1] We have already reported that the diastereoselective addition of organometallic reagents to the planar chiral *o*-dimethylaminobenzyl-substituted formyl ferrocene to give the (1-dimethylamino)phenylmethyl ferrocenyl alcohol **1**, which was converted into the corresponding optically active (1*R*,4*R*)-bis(phenylmethyl)ferrocenyl diacetate **2a** upon treatment with acetic anhydride with retention of the configuration.[2] A new 1,4-ferrocenyl diol ligand, (1*R*,4*R*)-1,2-bis(1-hydroxyphenylmethyl)ferrocene (**3**), was obtained by reduction of **2a** with lithium aluminum hydride.[3] Ferrocene **3** has been shown to be an effective ligand for the scandium complex that catalyzes the asymmetric Diels−Alder reaction of cyclopentadiene with 3-acyloxazolidin-2-one in high enantioselectivity.[4] The success of **3** as a chiral ligand in asymmetric synthesis prompted us to prepare the corresponding 1,4-ferrocenyl diamine ligand. During the study of the transformation of **2a** to its diamine derivative, we encountered the regioselective and stereospecific displacement of acetoxy groups in **2a**.

Results and Discussion

It was reported that optically active ferrocenyl acetate could be converted into the primary ferrocenylamine upon treatment with aqueous ammonia with retention of the configuration in a good yield.[5] We applied this method to the preparation of the diamine **6** from (1*R*,4*R*)-ferocenyldiacetate **2a**. However, the expected diamine was not obtained, and the formation of the ferrocenyl acetamide alcohol, **4a** or **5**, was observed instead as the sole diastereomer by ^{1}H and ^{13}C NMR measurements (Scheme 1). X-ray diffraction analysis revealed that the structure of the acetamide alcohol was (1*R*,4*R*,*Sp*)-**4a** (Figure 1), the acetamide group being attached at the C(6) carbon. The stereochemistry of both benzylic carbons was *R*, and the substitution by ammonia took place at only the C(6) carbon with retention of the configuration. The ease of the substitution depends on the geometry of the two stereogenic centers of the carbons. There is a

(1) For reviews, see: (a) Hayashi T. Asymmetric Catalysis with Chiral Ferrocenylphosphine Ligands. In *Ferrocenes*; Togni A., Hayashi, T., Eds.; VCH: Weinheim, 1995; pp 105−142. (b) Togni, A. New Chiral Ferrocenyl Ligands for Asymmetric Catalysis. In *Metallocenes*; Togni, A., Halterman, R. L., Eds.; VCH, Weinheim, 1998; Vol. 2, pp 689−721. (c) Richards C. J.; Locke, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2377. (d) Dai, L.-X.; Tu, T.; You, S.-L.; Deng, W.-P.; Hou, X.-L. *Acc. Chem. Res.* **2003**, *36*, 659.

(2) (a) Fukuzawa, S.; Tsuchiya, D.; Sasamoto, K.: Hirano, H.; Ohtaguchi, M. *Eur. J. Org. Chem.* **2000**, 2877. (b) Fukuzawa, S.; Fujimoto, K. *Synlett* **2001**, 1275.

(3) We have succeeded in the X-ray crystallographic analysis of **3** and found that the single-crystal lattice contained two ferrocene trimers which are connected with hydrogen bonds. The two-ferrocene trimers sandwich the benzene of the recrystallization solvent. See Supporting Information.

(4) Fukuzawa, S.; Fujimoto, K.; Komuro, Y.; Matuzawa, H. *Org. Lett.* **2002**, *4*, 707.

(5) Fukuda, T.; Takehara, A.; Haniu, N.; Iwao, M. *Tetrahedron: Asymmetry* **2000**, *11*, 4083.

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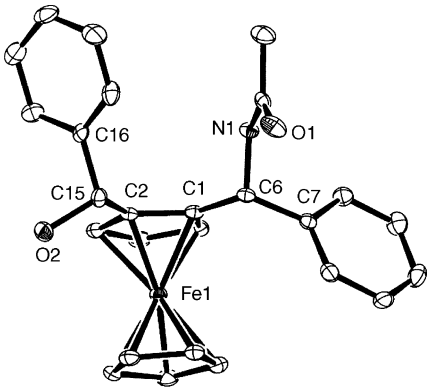
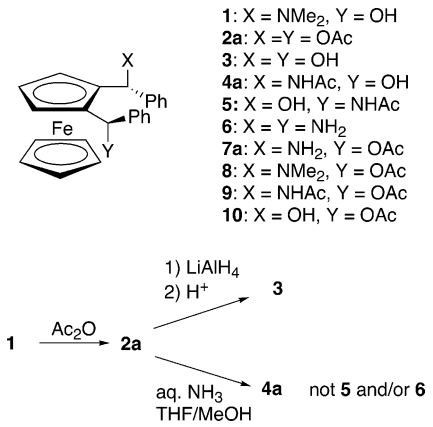


FIGURE 1. Molecular structure of **4a** (ORTEP plot). Selected bond lengths (Å): C(1)−C(6) = 1.51, N(1)−C(6) = 1.48, C(6)−C(7) = 1.53, C(2)−C(15) = 1.51, O(2)−C(15) = 1.44, C(15)−C(16) = 1.53. Selected torsion angle (deg): C(2)−C(1) C(6)−N(1) = −79.7, C(2)−C(1) C(6)−C(7) = 156.2, C(1)−C(2) C(15)−O(2) = −150.1, C(1)−C(2) C(15)−C(16) = 91.1.

SCHEME 1



relatively restricted bond rotation in the two acetoxy groups in the symmetrical 1,2-disubstituted ferrocene pattern.[6] Only one of the acetoxy groups at C(6) is suitably aligned for ionization to proceed efficiently; the aminolysis took place smoothly as a result of the iron-assisted ionization, i.e., neighboring group participation (NGP).[7] The leaving group on the second acetoxy group at C(15) is not suitably aligned and also cannot undergo a conformational change for it to adopt the appropriate orientation for ionization to occur.[8] Because it has been reported that the *exo* acetate of α-hydroxytetramethyleneferrocene **11** (leaving group is *anti* to the iron) undergoes solvolysis 2500 times faster that the *endo* isomer **12** (leaving group is *syn* to the iron) (Scheme 2),[9] it is reasonable to assume that the acetoxy groups at C(6) and C(15) were aligned *exo* and *endo*, respectively.[10] Indeed, the actual X-ray crystal structure of diacetate **2a** was consistent with this assumption (Figure 2). The elimination of the *exo* acetoxy group of C(6) was accelerated by the iron NGP to give the carbocation intermediate **15**, which was then attacked by ammonia retention of configuration. On the other hand, there is no NGP effect at the *endo* acetoxy group of C(15), which is sterically hindered by the bottom Cp group, and then the substitution is inhibited by this steric hindrance.[8]

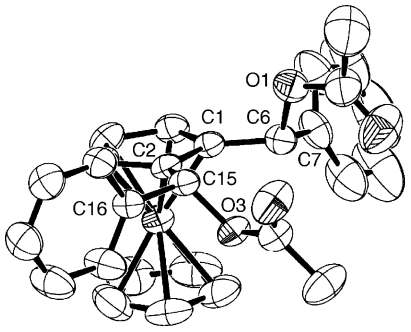
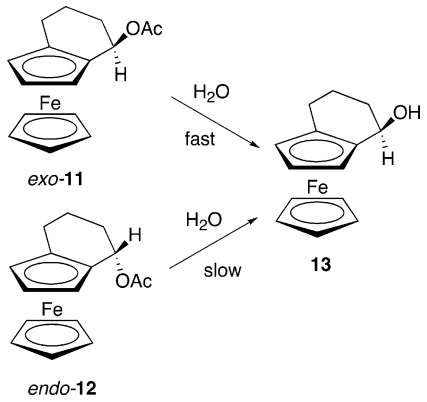


FIGURE 2. Molecular structure of **2a** (ORTEP plot). Selected bond length (Å): C(1)−C(6) = 1.51, O(1)−C(6) = 1.47, C(6)−C(7) = 1.51, C(2)−C(15) = 1.51, O(3)−C(15) = 1.47, C(15)−C(16) = 1.51. Selected torsion angle (deg): C(2)−C(1) C(6)−O(1) = −57.7, C(2)−C(1) C(6)−C(7) = 179.8, C(1)- C(2) C(15)−O(3) = −72.5. C(1)−C(2) C(15)−C(16) = 166.6.

SCHEME 2



The plausible reaction mechanism is illustrated in Scheme 3. First the acetoxy group of C(6) is displaced by ammonia to give the 1,4-ferrocenyl amino acetate **7a** with retention of the configuration by an S_N1 mechanism. The amino group of C(6) intramoleculary attacks the acetoxy carbonyl carbon of C(15) to give the intermediate **16**, and then the acetyl group transfers to the amino group to give the 1,4-ferrocenyl acetamide alcohol **4a**. The hydroxy group of C(15) no longer undergoes substitution. The aminolysis was usually carried out at room temperature for 18 h, but when the reaction was quenched in a shorter time (less than 10 min), the amino acetate **7a** was certainly obtained as the intermediate in 31% yield.

(6) A 1,2-disubstituted ferrocene such as **2a** and **3** does not have a planar chirality because they have the same substituent.

(7) Marquarding, D.; Klussacek, H.; Gokel, G.; Hoffmann, P.; Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 5389.

(8) The stereochemistry at a benzylic carbon of an arene chromium complex affects the reactivity of the S_N1 reaction at this carbon. Kündig, E. P.; Ratni, H.; Crousse, B.; Bernardinelli, G. *J. Org. Chem.* **2001**, *66*, 1852.

(9) Pearson, A. J. *Metallo-organic Chemistry*; Wiley: Chichester, 1985; pp 320−321. *Iron Compounds in Organic Synthesis*; Academic Press: London, 1994; pp 149−150.

(10) The reaction rate of an *exo* ferrocenyl alcohol with dimethylamine is faster that that of an *endo* one. Dixneuf, P. *Tetrahedron Lett.* **1971**, *12*, 1561.

SCHEME 3

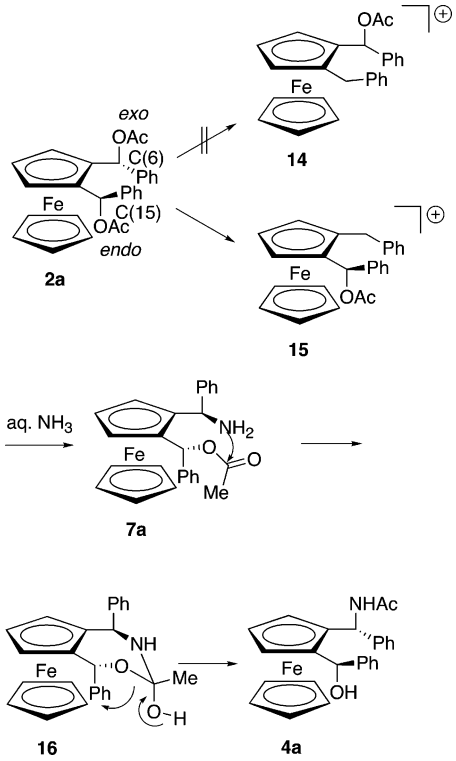


TABLE 1. Aminolysis of 1,4-Ferrocenyl Diester 2 with Aqueous Ammonia

entry	diester	conditions	product yield (%)
1	**2a**: R = Me	aq NH_3/THF/MeOH, rt, 18 h	**4a**, 89
2	**2a**: R = Me	NH_3/MeOH, −78 °C to rt, 18 h	**4a**, 22
3	**2a**: R = Me	aq NH_3/THF/MeOH, rt, 0.1 h	**7a**, 31
4	**2b**: R = *i*-Pr	aq NH_3/THF/MeOH, rt, 18 h	**4b**, 47
5	**2c**: R = *t*-Bu	aq NH_3/THF/MeOH, rt, 5 d	**7c**, 33

To avoid the intramolecular acyl transfer, the aminolysis was examined using the more sterically hindered 1,4-bis(phenylmethyl)-ferrocenyl diester **2b,c** (Scheme 4,

SCHEME 4

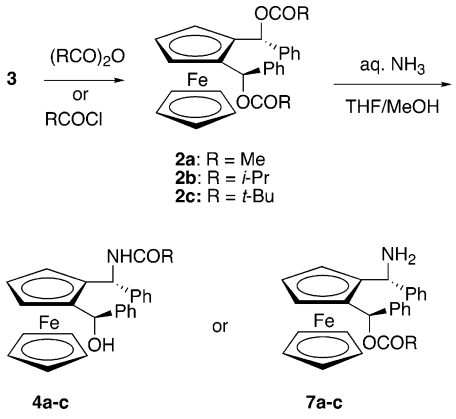
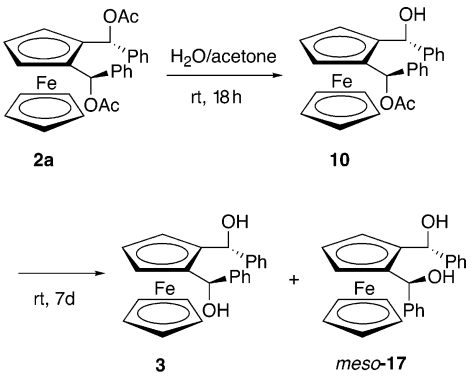


Table 1). These compounds were prepared by acylation of **3** with isobutyric anhydride and pivalic chloride, respectively. The treatment of **2b** (R = *i*-Pr) with aqueous ammonia in THF/MeOH at room temperature for 18 h gave the amide alcohol **4b** in 47% yield similar to the diacetate **2a** (entry 4). The reaction with **2c** (R = *t*-Bu) at room temperature for 5 days gave the (1*R*,4*R*)-ferrocenyl amino ester **7c** in 33% yield (entry 5), suggesting that there was no intramolecular amino acylation with **2c**.

The reaction of **2a** with dimethylamine gave the (1*R*,4*R*,*Sp*)-dimethylaminobenzyl ferrocenyl acetate **8** (X = NMe_2, Y = OAc) exclusively in 70% yield with retention of the configuration, demonstrating that the substitution by an amine took place at only the *exo* acetate, C(6). The acetylation of **4a** gave the corresponding acetamide acetate **9** (X = NHAc, Y = OAc) of which the acetoxy group could no longer be replaced by ammonia.

The hydrolysis of **2a** in H_2O/acetone at room temperature for 18 h gave the half-ester **10** as a single diastereomer (75%) mainly together with the (1*R*,4*R*)-diol **3** (25%).[11] In this reaction, retentive hydrolysis preferentially occurred at the *exo* acetate similarly to the aminolysis (Scheme 5). The formation of **3** can be explained

SCHEME 5



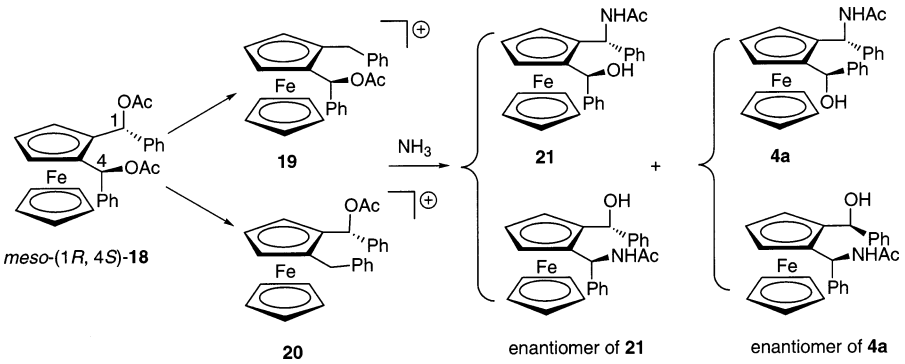
by a retentive S_N1 reaction at the *exo* acetate together with acyl hydrolysis at the *endo* acetate. When the reaction was carried out for 7 days, **10** was no longer observed, and a mixture of **3** and *meso*-(1*R*,4*S*)-diol **17** was observed as a major (83%) and minor (17%) product, respectively, by ^{1}H NMR measurement. The formation of the *meso*-diol suggests that S_N2 inversion at the *endo* acetate should be involved in the hydrolysis as well as the retentive acyl cleavage.

We finally examined the aminolysis of *meso*-(1*R*, 4*S*)-ferrocenyl diacetate (**18**) (C(6);*R*,C(15);*S*) under the same conditions as the aminolysis with **2a**. Because both acetoxy groups of this ferrocene could be directed toward *exo* and they should be equally undergoing aminolysis via carbocation intermediates **19** and **20**,[12] we expected that the aminolysis would give the *meso*-diamine or the single diastereomer of acetamide alcohol as a racemic mixture of (1*R*,4*S*,*Sp*)-**21** and its enantiomer

(11) The structure of **10** was determined by ^{13}C NMR spectrum by comparing other 1,2-disubstituted ferrocene derivatives. As the *endo* alcoholic carbon appears at 70.5 ppm in compounds **1** and **4a**, it is reasonable to assign 70.0 and 72.0 ppm signals as the *endo* and the *exo* alcoholic carbon of **3**, respectively. The *endo* acetate carbon appears at 72.5−73.2 in compounds **8** and **9**. We assigned signals at 72.2 and 72.5 in **10** as the *exo* alcoholic carbon and the *endo* acetate carbon, respectively.

(12) The X-ray crystallographic result of *meso*-**18** shows that both acetoxy groups are directed toward *exo*. See Supporting Information.

SCHEME 6



(Scheme 6).[13] However, the actual reaction was very complicated, the ^{1}H NMR analysis of the crude product showing the presence of two diastereomers. Chiral HPLC analysis revealed that one of the diastereomers was a pair of racemates of **4a** using the authentic samples, which were prepared by aminolysis with **2a** and its enantiomer. The identification of the diastereomer was also reasonable by ^{1}H and ^{13}C NMR spectra that were consistent with the authentic samples. We tentatively assigned the other diastereomer to be a pair of racemates of **21** from the assumed mechanism, although we do not have any evidence other than NMR spectra. We could not give a reasonable explanation of how the racemate of **4a** was produced from the *meso*-ferrocenyl diacetate **18**, but an S_N2 inversion process could be involved in the reaction in addition to an S_N1 retention process.

In conclusion, this reaction is the first case of substitution in a chiral molecule in which a conformational difference between two leaving groups happened to affect the rate of aminolysis and hydrolysis at two stereogenic centers.

Experimental Section

Preparation of (1*R*,4*R*,*Sp*)-1-[(1-Dimethylamino)phenylmethyl]-2-[(1-hydroxy)phenylmethyl]ferrocene, 1.[2] A 50-mL Schlenk tube containing a magnetic stirring bar was charged with (*R*,*Sp*)-1-[(1-dimethylamino)phenylmethyl]-2-formylferrocene (1.74 g, 5.0 mmol) and dry THF (5 mL) under a slight pressure of nitrogen. Phenylmagnesium bromide (1.2 equiv) was then added by means of a syringe through the septum under magnetic stirring at −78 °C. The resulting mixture was stirred at the same temperature for 15 min and then allowed to warm to room temperature over a period of 2 h. The reaction was subsequently quenched with water, and the resulting solution was extracted with ethyl acetate (3 × 20 mL). The combined extracts were washed (brine) and dried (K_2CO_3), and the solvent was removed by a rotary evaporator to leave a brown solid. Recrystallization of the solid gave pure **1** as a single diastereomer. Yield 1.74 g (4.1 mmol, 82%). Yellow solid mp = 123−125 °C. $[\alpha]^{25}_D$ = −26.8 (*c* = 1.00, $CHCl_3$). IR (KBr) 3081, 3031 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.06 (s, 6H), 3.84 (s, 5H), 3.90 (br s, 1H), 4.02 (br s, 1H), 4.03 (br s, 1H), 4.21 (br s, 1H), 4.59 (s, 1H), 5.56 (s, 1H), 7.3−7.6 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 42.2, 66.2, 68.3, 68.6, 69.2, 70.5, 72.1, 87.5, 95.0, and phenyl signals (120−140). Anal. Calcd for $C_{26}H_{27}FeNO$: C, 73.42; H, 6.40; N 3.29. Found: C, 73.59; H, 6.03; N 3.33. The crystals suitable for X-ray analysis were obtained by recrystallization from $CHCl_3$−hexane. CCDC 232221.

(13) Distinguished ^{1}H NMR signals for **21**: δ 1.81 (s, CH_3CO), 3.90 (s, Cp), 5.77 (s, CHO), 6.11 (d, *J* = 7.5 Hz, CHN), 6.84 (d, *J* = 7.5 Hz, NHCO).

Preparation of (1*R*,4 *R*)-1,2-Bis[(1-acetoxy)phenylmethyl]ferrocene, 2a. A mixture of **1** (1.70 g, 4.0 mmol) and acetic anhydride (20 mL) was stirred at room temperature for 2 days. The solvent was then removed under reduced pressure, and almost pure (1*R*,4*R*)-1,2-bis[(1-acetoxy)phenylmethyl]ferrocene was left as a yellow solid. Yield 1.80 g (3.7 mmol, 93%); mp = 142−143 °C. $[\alpha]^{25}_D$ = −59.3 (*c* = 0.842, $CHCl_3$). IR (KBr) 1737 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.61 (s, 3H), 2.20 (s, 3H), 3.94 (s, 1H), 4.07 (s, 5H), 4.20 (s, 1H), 4.38 (s, 1H), 6.79 (s, 1H), 6.94 (s, 1H), 7.20−7.51 (m, 10H); ^{13}C NMR δ 20.6, 21.3, 67.3, 68.4, 69.1, 69.6, 72.2, 73.6, 84.5, 87.3, 127.3, 127.9, 128.0, 128.3, 139.2, 140.0, 169.6, 169.8. Anal. Calcd for $C_{28}H_{26}FeO_4$: C, 69.72; H, 5.43. Found: C, 70.14; H, 5.07. The crystals suitable for X-ray analysis were obtained by recrystallization from $CHCl_3$−hexane. CCDC 228158.

Preparation of (1*R*,4*R*)-1, 2-Bis[(1-hydroxy)phenylmethyl]ferrocene, 3. A 100-mL Schlenk tube containing a magnetic stirring bar was charged with $LiAlH_4$ and dry THF-(10 mL) under a slight pressure of nitrogen. A mixture of **2a** (1.10 g, 2.3 mmol) and dry THF (5 mL) was added by means of a syringe through the septum under magnetic stirring at room temperature, and the resulting mixture was stirred for 3 h. The reaction was then quenched with water, and the aqueous solution was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed (brine), dried ($MgSO_4$), and filtered, and the solvent was removed by a rotary evaporator to leave a yellow residue. The crude product was purified by column chromatography on silica gel (hexane−ethyl acetate = 10/1) to give pure **3**. Yield 0.75 g (1.89 mmol, 82%). Yellow solid mp = 52−53 °C. $[\alpha]^{25}_D$ = −206.9 (*c* = 0.175, $CHCl_3$). IR (KBr) 3166 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.35 (br s, 2H), 3.85 (s, 1H), 4.17 (s, 1H), 4.27 (s, 1H), 4.40 (s, 5H), 5.41 (s, 1H), 5.62 (s, 1H), 7.24−7.39 (m, 10H); ^{13}C NMR δ 66.1, 69.1, 69.3, 69.6, 69.9, 71.9, 89.9, 91.9, 126.1, 126.6, 127.2, 127.6, 128.1, 142.5, 142.9. Anal. Calcd for $C_{24}H_{22}FeO_2$: C, 72.38; H, 5.57. Found: C, 72.41; H, 5.55. The crystals suitable for X-ray analysis were obtained by recrystallization from $CHCl_3$−hexane. CCDC 228159.

Preparation of (1*R*,4*R*)-1, 2-Bis[(1-isobutyryloxy)phenylmethyl]ferrocene, 2b. A mixture of **3** (100 mg, 0.25 mmol), iosbutyric anhydride (120 μL), 4-*N*,*N*-(dimethylamino)-pyridine (DMAP) (7 mg), and pyridine (1.0 mL) in CH_2Cl_2 (5.0 mL) was stirred at room temperature for 18 h. Evaporation of the solvent left a crude **2b** as a brown oil. Yield 120 mg (0.22 mmol, 88%). The product was purified by column chromatography on silica gel (hexane−ethyl acetate = 4/1 as eluent). Brown oil $[\alpha]^{25}_D$ = −41.0 (*c* =0.210, $CHCl_3$). IR (neat) 1734 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.97 (d, 3H, *J* = 7.2 Hz), 0.99 (d, 3H, *J* = 6.9 Hz), 1.24 (d, 3H, *J* = 7.2 Hz), 1.27 (d, 3H, *J* = 6.9 Hz), 2.12 (sept, 1H, *J* = 6.9 Hz), 2.68 (sept, 1H, *J* = 7.2 Hz), 4.06−4.34 (m, 3H), 4.07 (s, 5H), 6.78 (s, 1H), 7.03 (s, 1H), 7.2 (s, 10H); ^{13}C NMR δ 18.3, 19.0, 33.5, 34.3, 67.2, 68.3, 69.3, 69.7, 72.3, 73.6, 84.5, 87.3, 127.0−128.2 (several phenyl signals), 139.7, 140.5, 175.6. Anal. Calcd for $C_{32}H_{34}FeO_4$: 71.38; H, 6.36. Found: C, 71.41; H, 6.55

Preparation of (1*R*,4*R*)-1,2-Bis[(1-pivalyloxy)phenylmethyl]ferrocene, 2c. A mixture of **3** (300 mg, 0.76 mmol), pivaloyl chloride (0.46 mL, 3.8 mmol), and pyridine (6.0 mL) was stirred at room temperature for 2 days. The solution was poured into water, and the aqueous solution was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed (brine), dried ($MgSO_4$), and filtered. The solvent was then removed under reduced pressure and almost pure **2c** was left as a brown oil. Yield 362 mg (0.64 mmol, 84%). $[\alpha]^{25}_D = -41.6$ ($c = 0.828$, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.98 (s, 9H), 1.21 (s, 9H), 3.97−4.16 (m, 3H), 4.02 (s, 5H), 6.69 (s, 1H), 6.90 (s, 1H), 7.13 (s, 10H); ^{13}C NMR δ 26.9, 27.1, 38.5, 38.9, 66.9, 68.6, 69.3, 69.6, 71.9, 73.6, 84.3, 87.0, 126.5−128.4 (several phenyl signals), 139.8, 140.2, 176.9. Anal. Calcd for $C_{34}H_{38}FeO_4$: C, 72.08; H, 6.76. Found: C, 72.22; H, 6.73.

Preparation of *meso*-(1*R*,4*S*)-1,2-Bis[(1-acetoxy)phenylmethyl]ferrocene, 18. A 50-mL Schlenk tube containing a magnetic stirring bar was charged with (*R*,*Sp*)-1-[(1-dimethylamino)phenylmethyl]-2-formylferrocene (1.0 g, 2.90 mmol) and dry diethyl ether (20 mL) under a slight pressure of nitrogen.[14] Phenylmagnesium bromide (1.2 equiv) was then added by means of a syringe through the septum under magnetic stirring at −78 °C. The resulting mixture was stirred at the same temperature for 15 min and then allowed to warm to room temperature over a period of 2 h. The reaction was subsequently quenched with water, and the resulting solution was extracted with ethyl acetate (3 × 20 mL). The combined extracts were washed (brine) and dried (K_2CO_3), and the solvent was removed by a rotary evaporator to leave a yellow solid. The crude product was revealed to be a mixture of **18** as a major product with **1** as a minor product by ^{1}H NMR measurement (71% de). The crude product was subjected to column chromatography on basic alumina (hexane−ethyl acetate = 10:1 as eluent) to give pure (1*R*,4*S*,*Sp*)-ferrocenyl amino alcohol. Yield 0.65 g (1.53 mmol, 53%); mp = 63−65 °C. $[\alpha]^{25}_D = -60.4$ ($c = 0.225$, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.06 (s, 6H), 3.57 (s, 1H), 3.84 (s, 5H), 3.96 (s, 1H), 4.21 (s, 1H), 5.12 (s, 1H), 6.05 (s, 1H), 7.2−7.6 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 40.0, 66.1, 68.8, 69.4, 69.5, 69.8, 72.3, 86.0, 93.2, and several phenyl peaks (120−140). Anal. Calcd for $C_{26}H_{27}FeNO$: C, 73.42; H, 6.40; N 3.29. Found: C, 73.28; H, 6.13; N 3.44.

A mixture of the (1*R*,4*S*,*Sp*)-ferrocenyl amino alcohol (650 mg, 1.53 mmol) and acetic anhydride (10 mL) was stirred at room temperature for 2 days. The solvent was then removed under reduced pressure, and almost pure *meso*-ferrocenyl diacetate **18** was left as a yellow solid. Yield 600 mg (1.24 mmol, 81%); mp = 168−170 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.94 (s, 6H), 3.91 (s, 5H), 4.1−4.20 (m, 3H), 6.94 (s, 2H), 7.20−7.51 (m, 10H); ^{13}C NMR δ 21.2, 68.0, 69.9, 70.4, 73.9, 85.4, 127.4, 128.2, 128.5, 140.3, 169.9. Anal. Calcd for $C_{28}H_{26}FeO_4$: C, 69.72; H, 5.43, found C, 69.54; H, 5.47. The crystals suitable for X-ray analysis were obtained by recrystallization from $CHCl_3$−hexane. CCDC 232220.

Reaction of 2a with Aqueous Ammonia. Compound **2a** (100 mg, 0.21 mmol) was placed in a 50-mL two-neck round-bottom flask and dissolved in THF−MeOH (5.0 mL/5.0 mL) with magnetic stirring. An aqueous solution of ammonia (28%, 5.0 mL) was then added to the solution at room temperature, and the mixture was stirred at the same temperature for 18 h. After removal of most of the THF and MeOH by a rotary evaporator, the aqueous solution was extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed (brine), dried ($MgSO_4$), and filtered, and the solvent was removed by a rotary evaporator to leave a yellow solid. The crude product was subjected to column chromatography on silica gel (hexane−ethyl acetate = 4/1) to give pure (1*R*,4*R*,*Sp*)-[1-(1-acetylamino)phenylmethyl]-2-[(1-hydroxy)phenylmethyl]-ferrocene **4a**. Yield 82 mg (0.19 mmol, 89%). Yellow solid mp = 63−65 °C. $[\alpha]^{25}_D = -49.0$ ($c = 0.510$, $CHCl_3$). IR (KBr) 3253, 1742 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.66 (s, 3H), 2.76 (br s, 1H), 4.03−4.08 (m, 3H), 4.19 (s, 5H), 5.45 (s, 1H), 5.97 (d, 1H, $J = 8.1$ Hz), 6.62 (d, 1H, $J = 8.1$ Hz), 7.32 (s, 10H); ^{13}C NMR δ 22.9, 51.8, 66.3, 68.8, 69.4, 70.1, 70.4, 88.0, 91.2, 126.9−128.4 (several phenyl signals), 141.3, 142.7, 168.3 (C=O). Anal. Calcd for $C_{26}H_{25}NO_2Fe$: C, 71.08; H, 5.74; N, 3.19. Found: C, 70.98; H, 5.73; N, 3.22. The crystals suitable for X-ray analysis were obtained by recrystallization from $CHCl_3$−hexane. CCDC 228157.

(1*R*,4*R*,*Sp*)-1-[(1-Isobutyrylamino)phenylmethyl]-2-[(1-hydroxy)phenylmethyl]-ferrocene, 4b. The title compound was obtained by aminolysis of **2b** (134 mg, 0.25 mmol) in THF−MeOH (5.0 mL/5.0 mL) at room temperature of 18 h. Yield 60 mg (0.12 mmol, 47%). Yellow solid mp = 181−183 °C. $[\alpha]^{25}_D = -149.8$ ($c = 0.207$, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.01 (d, 3H, $J = 7.2$ Hz), 1.06 (d, 3H, $J = 7.2$ Hz), 2.12 (sept, 1H, $J = 7.2$ Hz), 2.80 (br s, 1H), 3.93−4.24 (m, 3H), 4.19 (s, 5H), 5.34 (s, 1H), 5.97 (d, 1H, $J = 7.8$ Hz), 6.88 (d, 1H, $J = 7.8$ Hz), 7. 30 (s, 10H); ^{13}C NMR δ 19.2, 20.0, 35.5, 51.7, 66.2, 69.5, 69.7, 70.3, 70.6, 88.2, 91.3, 126.9−128.4 (several phenyl signals), 142.0, 142.9, 175.3 (C=O). Anal. Calcd for $C_{28}H_{29}FeNO_2$: C, 71.95; H, 6.25; N, 3.00. Found: C, 72.21; H, 6.58; N, 2.84.

(1*R*,4*R*,*Sp*)-1-[(1-Acetoxy)phenylmethyl]-2-[(1-amino)-phenylmethyl]ferrocene, 7a. The title compound was obtained by aminolysis of **2a** (100 mg, 0.21 mmol) in THF−MeOH at room temperature for 5 min. Yield 29 mg (0.065 mmol, 31%). Brown oil $[\alpha]^{25}_D = -5.76$ ($c = 0.278$, $CHCl_3$). IR (neat) 3379, 1729 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.20 (s, 3H), 3.96 (s, 5H), 3.64−4.39 (m, 3H), 4.94 (s, 1H), 7.20 (s, 1H), 7. 23−7.38 (m, 10H); ^{13}C NMR δ 21.3, 54.5, 66.6, 66.9, 67.7, 69.3, 72.5, 86.2, 91.7, 126.9−128.6 (several phenyl signals), 140.7, 144.2, 169.8 (C=O). Anal. Calcd for $C_{26}H_{25}FeNO_2$: C, 71.08; H, 5.74; N, 3.19. Found: C, 71.15; H, 5.61; N, 3.01.

(1*R*,4*R*,*Sp*)-1-[(1-Amino)phenylmethyl]-2-[(1-pivalyloxy)phenylmethyl]ferrocene, 7c. The title compound was obtained by aminolysis of **2c** (85 mg, 0.15 mmol) in THF−MeOH at room temperature for 3 days. Yield 24 mg (0.05 mmol, 33%). Brown oil $[\alpha]^{25}_D = -19.6$ ($c = 0.225$, $CHCl_3$). IR (neat) 3256, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20 (s, 9H), 3.87 (s, 5H), 3.91−4.34 (m, 3H), 4.85 (s, 1H), 7.04 (s, 1H), 7. 17−7.33 (m, 10H); ^{13}C NMR δ 27.2, 38.9, 54.5, 66.3, 66.7, 67.7, 69.4, 72.9, 88.3, 91.3, 126.0−128.5 (several phenyl signals), 140.9, 144.2, 178.3 (C=O). Anal. Calcd for $C_{29}H_{31}FeNO_2$: C, 72.35; H, 6.49; N, 2.91. Found: C, 72.15; H, 6.61; N, 3.01.

(1*R*,4*R*,*Sp*)-1-[(1-Acetoxy)phenylmethyl]-2-[(1-dimethylamino)phenylmethyl]ferrocene, 8. The title compound was obtained by the reaction of **2a** (120 mg, 0.25 mmol) with excess aqueous dimethylamine. Yield 84 mg (0.18 mmol, 72%). Brown oil $[\alpha]^{25}_D = +29.7$ ($c = 0.091$, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.66 (s, 3H), 2.19 (s, 3H), 3.62 (s, 5H), 3.89 (s, 1H), 4.18−4.38 (m, 3H), 6.92 (s, 1H), 7.24−7.52 (m, 10H); ^{13}C NMR δ 21.6, 43.6, 66.2, 67.2, 68.0, 69.3, 69.7, 73.2, 87.3, 127−128 (several phenyl signals), 140.7, 144.3, 170.0. Anal. Calcd for $C_{28}H_{29}FeNO_2$: C, 71.95; H, 6.25; N, 3.00. Found: C, 71.56; H, 6.41; N, 3.22.

(1*R*,4*R*,*Sp*)-1-[(1-Acetoxy)phenylmethyl]-2-[(1-acetylamino)phenylmethyl]ferrocene 9. The title compound was obtained by treatment of **4a** (310 mg, 0.71 mmol) with excess acetic anhydride. Yield 340 mg (0.70 mmol, 99%). Yellow solid mp = 147−148 °C. $[\alpha]^{25}_D = +13.5$ ($c = 0.51$, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.59 (s, 3H), 2.22 (s, 3H), 3.95−4.35 (m, 3H), 4.11 (s, 5H), 5.93−5.98 (m, 2H), 6.79 (s, 1H), 7.12−7.32 (m, 10H); ^{13}C NMR δ 21.5, 22.8, 52.3, 67.1, 67.9, 69.3, 69.8, 72.2, 87.0, 88.3, 127.2−128.5 (several phenyl signals), 140.6,

(14) The choice of solvent strongly affected on the diastereoselectivity of the addition of Grignard reagent to the chiral *o*-aminoformylferrocene; the major isomer was the (1*R*,4*R*)-amino alcohol **1** in THF (82% de),[2b] while the major isomer was the (1*R*,4*S*)-amino alcohol in diethyl ether (71% de) (unpublished results). The chelation and nonchelation of amino and formyl group to Grignard reagent may be involved in stereoselectivity.

141.5, 168.5, 170.4. Anal. Calcd for $C_{28}H_{27}FeNO_3$: C, 69.86; H, 5.65; N, 2.91. Found: C, 70.15; H, 5.47; N, 3.16.

Hydrolysis of 2a in Aqueous Acetone. Compound **2a** (100 mg, 0.21 mmol) was placed in a 50-mL two-neck round-bottom flask and dissolved in acetone−water (10.0 mL/2.0 mL) with magnetic stirring. The mixture was stirred at room temperature for 18 h. After removal of most of the acetone by a rotary evaporator, the aqueous solution was extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed (brine), dried ($MgSO_4$), and filtered, and the solvent was removed by a rotary evaporator to leave a brown oil. ^{1}H NMR measurement revealed that the product contained (1*R*,4*R*,*Sp*)-1-[(1-acetoxy)phenylmethyl]-2-[(1-hydroxy)phenylmethyl]ferrocene **10** (75%) and **3** (25%). Pure **10** was isolated by column chromatography on silica gel (hexane−ethyl acetate = 5/1). Yield 66 mg (0.15 mmol, 71%). $[\alpha]^{25}_D = -34.9$ ($c = 0.106$, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.0 (br s, 1H), 2.21 (s, 3H), 4.0−4.4 (m, 4H), 4.11 (s, 5H), 5.65 (s, 1H), 7.06 (s, 1H), 7.2−7.3 (m, 10H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 21.5, 67.3, 67.8, 68.9, 69.7, 72.2, 72.5, 87.2, 90.2, 126.7−128.5 (several phenyl signals), 140.7, 142.3, 170.0 (C=O). Anal. Calcd for $C_{26}H_{24}FeO_3$: C, 70.92; H, 5.49. Found: C, 70.73; H, 5.54. The reaction for 7 days gave a mixture of **3** and the *meso*-diol **17**; distinguished ^{1}H NMR signals for **17**, 3.99 (s, Cp), 5.91 (s, CHO).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of 1,2-disubstituted ferrocene compounds, **1**, **2a**−**c**, **3**, **4a,b**, **7a,c**, **8**−**10**, **17**, **18**, **21** and (1*R*, 4*S*)-isomer of **1** and crystallographic data in CIF files for **1**, **2a**, **3**, **4a**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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