JOC The Journal of Organic Chemistry

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Stereochemistry of Substitution of the α-Dimethylamino Group by Dialkylzinc in Chiral Benzylferrocene

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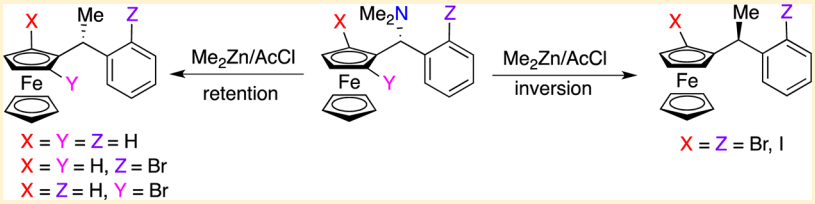
Supporting Information



ABSTRACT: The stereochemistry of the substitution of the α-dimethylamino group by dimethylzinc in the presence of acetyl chloride in the chiral benzylferrocene backbone was examined. The reaction with the benzylferrocene bearing an *o*-bromo substituent at both ferrocene and the phenyl ring proceeded with inversion of configuration, while the reaction with the benzylferrocene bearing an *o*-bromo substituent at either ferrocene or the phenyl ring proceeded with retention of configuration.

Thousands of ferrocenyl phosphine ligands, which are useful tools for metal-catalyzed asymmetric reactions, have been designed.[1] Substitution at the α-stereogenic center of chiral ferrocene is a common way of developing new chiral ferrocenyl-based ligands.[2] For example, pyrazole-containing ferrocenylphosphines **1** are prepared by substitution of the dimethylamino (or acetoxy) group by pyrazoles (Figure 1). The Josiphos ligand **2**,

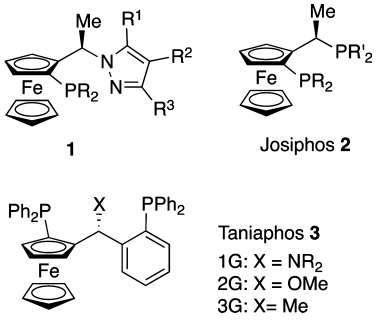


Figure 1. Chiral ferrocenyl phosphine ligands.

a widely accepted phosphine ligand, is also prepared by dimethylamino/phosphine exchange.[3] Substitution at the α-position usually proceeds with clear retention of configuration because of the neighboring-group effect of the ferrocenyl group.[4]

The Taniaphos ligands **3**, developed by Knochel et al., are efficient ligands for asymmetric synthesis[5] and are classified into three categories with different substituents at the α-stereogenic center; substituent X at the α-position is NR_2, MeO, or an alkyl group for the first-generation (1G), second-generation (2G), and third-generation (3G) ligands, respectively (Figure 1). The original methods for the synthesis of Taniaphos 3G include the substitution of the dimethylamino group by dialkylzinc reagents, where the stereochemical course was reported to be almost complete retention of configuration (90% de).[5b] However, when we carried out a separate preparation of Taniaphos 3G by the original method, i.e., substitution of the α-dimethylamino group of (R,R_p)-**7** with Me_2Zn in the presence of CH_3COCl, we found that the reaction proceeded with complete *inversion* of configuration to give the corresponding (S,R_p)-**8**. We were surprised at this result and re-examined the stereochemistry of substitution at the α-position by Me_2Zn in the series of chiral benzylferrocenes.

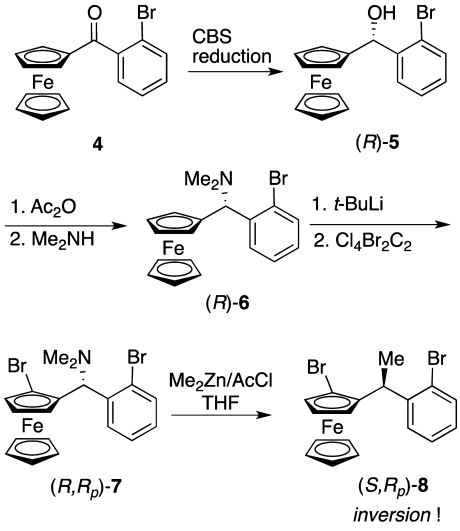
We first prepared (R,R_p)-**7** according to the literature procedure starting from (*o*-bromophenyl)ferrocenyl ketone **4** (Scheme 1)[5b] and confirmed its structure by X-ray analysis (see the Supporting Information). After the treatment of (R,R_p)-**7** with Me_2Zn in the presence of CH_3COCl in THF followed by the usual workup, the crude product was analyzed by ^1H NMR, which showed the presence of the corresponding α-methyl-substituted ferrocene **8** as a single isomer. The structure was confirmed by X-ray analysis to be configured (S,R_p) (see the Supporting Information). Thus, the substitution proceeded with complete *inversion* of configuration. This result contrasted sharply with the original report, which states that the reaction proceeds with retention of configuration.[5b]

Weissensteiner et al. recently reported some intriguing aspects of the stereochemistry of substitution at the α-position of chiral benzylferrocenes; the stereochemistry of substitution at the α-position depends on the *ortho* substituent at the phenyl/ferrocenyl groups.[6] For example, in the substitution of a methoxy group by diphenylphosphine in (R,R_p)-**9** (R = Et), the reaction proceeded with complete inversion to give (S,R_p)-**11**, while the

Received: June 12, 2012
Published: July 16, 2012

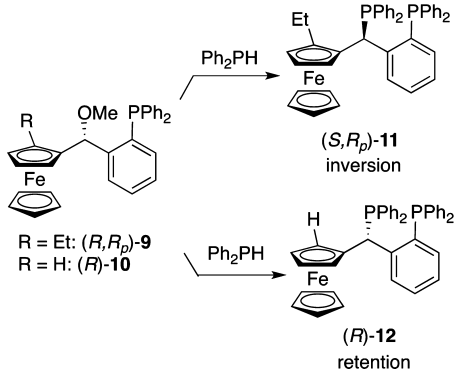
   dx.doi.org/10.1021/jo3012013 | J. Org. Chem. 2012, 77, 6638−6642

Scheme 1. Synthesis of (S,R_p)-1-Bromo-2-[1′-(*o*-bromophenyl)ethyl]ferrocene 8



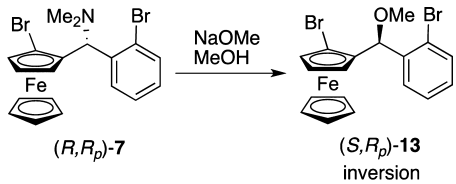
stereochemical outcome of the substitution in (R)-**10** (R = H) was complete retention of configuration to give (R)-**12** (Scheme 2).

Scheme 2. Substitution of α-methoxy group by phosphine



We also found that substitution of the dimethylamino group by NaOMe in (R,R_p)-7 proceeded with inversion of configuration (Scheme 3) to give (S,R_p)-**13**.[7] The stereochemical course in the amino/methyl exchange at the α-position of the substituted benzylferrocene can be rationalized by the substituent pattern.

Scheme 3. Substitution of α-Dimethylamino Group by Methoxide Ion



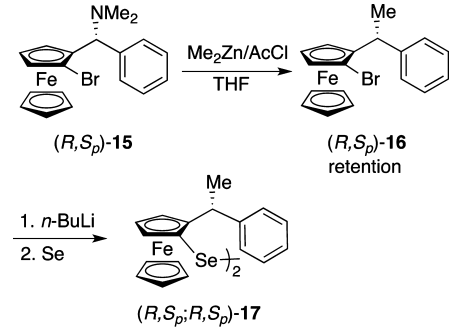
We then examined the influence of the substituent at the ferrocene and phenyl groups on the stereochemical course of the amino/methyl exchange reaction of benzylferrocene backbones.[8] Table 1 summarizes the stereochemistry in the amino/methyl exchange of the chiral benzylferrocene unit. The steric structure of the product was confirmed by X-ray analysis. The exchange at the phenyl bromo-substituted ferrocene (R)-**6** (Scheme 1)

Table 1. Summary of Stereochemistry in the Substitution of α-(Dimethylamino)benzylferrocene with Me_2Zn

R^1	R^2	R^3	starting compd	product chemistry	stereo	dr
H	H	Br	(R)-**6**	(R)-**14**	retention	>99/<1
H	Br	H	(R,S_p)-**15**	(R,S_p)-**16**	retention	>99/<1
H	H	H	(R)-**18**	(R)-**19**	retention	>99/<1
Br	H	Br	(R,R_p)-7	(S,R_p)-**8**	inversion	>99/<1
I	H	I	(R,R_p)-**20**	(S,R_p)-**21**	inversion	95/5

was readily revealed to proceed with retention of configuration to give (R)-**14**. Since the amino/methyl exchange product **16** from the Cp-bromo-substituted ferrocene **15**[9] was oil, its structure could not be determined by X-ray analysis. Thus, **16** was converted to the corresponding diselenide **17** by lithiation followed by treatment with selenium powder (Scheme 4).[10] A

Scheme 4. Preparation of Diselenide 17

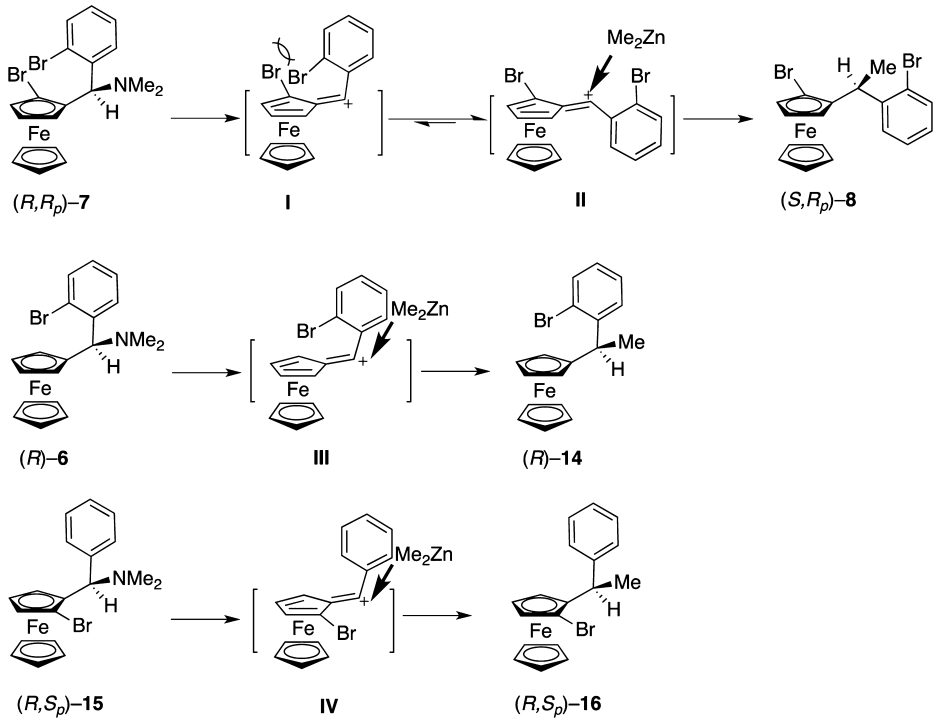


crystal of the diselenide **17** suitable for X-ray analysis was obtained, and the stereochemistry was revealed to be $(R,S_p;R,S_p)$, suggesting that the reaction occurred with retention of configuration (see the Supporting Information). We separately confirmed that the amino/methyl exchange with unsubstituted benzylferrocene (R)-**18** proceeded with retention of configuration to give (R)-**19**, although the stereochemical course of this reaction had already been reported.[11] The amino/methyl exchange in the corresponding diiodo-substituted ferrocene (R,R_p)-**20** proceeded with inversion of configuration contaminating with its diastereomer (dr = 95/5).

Stereochemistry of α-substitution of chiral ferrocene compounds examined here is consistent with Weissensteiner's work.[6] Thus, the stereochemistry of substitution of (R,R_p)-7 by Me_2Zn can be rationalized by Weissensteiner's mechanistic proposal (Scheme 5). In the first step, the α-dimethylamino group at the (R)-configured stereogenic center dissociates from the α-carbon leading to a carbocation intermediate **I** in which there is a significant steric hindrance between the two *ortho* substituents (*o*-Br at Cp and *o*-Br at Ph). Intermediate **I** can isomerize to the less sterically hindered (favorable) intermediate **II**. If the nucleophilic attack of Me_2Zn would occur from the above of the intermediate **II**, the stereogenic center of the product would be (S)-configured showing that the stereochemical course should be inversion of configuration. In the reaction with (R)-**6**, dissociation of the dimethylamino group should give a single carbocation intermediate **III**. The nucleophilic attack of Me_2Zn

dx.doi.org/10.1021/jo3012013 | J. Org. Chem. 2012, 77, 6638−6642

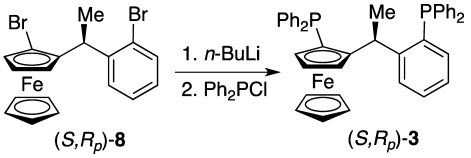
Scheme 5. Plausible Reaction Pathway



would occur from the above of the intermediate, and then the substitution should proceed with retention of configuration to give (R)-**14**. In the case of (R,S_p)-**15**, dissociation of the dimethylamino group would similarly take place to give the less hindered (favorable) intermediate **IV** which should give the retentive product (R,S_p)-**16**.

We finally prepared Taniaphos 3G by dilithiation followed by trapping with $ClPPh_2$ (Scheme 6). The stereochemistry was revealed to be the (S,R_p) configuration, showing that no isomerization took place at the stereogenic center of both central and planar chirality. The optical rotation of the diphosphine **3** was consistent with the reference value, although the stereochemistry of **3** was incorrectly proposed by Knochel et al. as (R,S_p).[12] The ligand ability of **3** was tested in the rhodium-catalyzed hydrogenation of alkene and revealed to be almost the same as the original ligand; methyl acetamide cinnamate; quantitative, 52% ee, *S*, dimethyl itaconate; 19% ee, *R*.[5]

Scheme 6. Preparation of Taniaphos 3G



In conclusion, Stereochemistry of substitution of the α-dimethylamino group by dimethylzinc in the presence of acetyl chloride in the series of benzylferrocene bearing an *ortho*-substitutent at ferrocene and the side-chain phenyl ring was examined. The reaction of the benzylferrocene bearing an *o*-bromo substituent at both ferrocene and the phenyl ring proceeds with inversion of configuration, while the reaction of the benzylferrocene bearing an *o*-bromo substituent at either ferrocene or the phenyl ring proceeds with retention of configuration.

EXPERIMENTAL SECTION

General Methods. The ^1H and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer as solutions in $CDCl_3$. The chemical shifts are reported in δ units downfield from the internal reference Me_4Si. High-resolution mass spectra (HRMS) were obtained on a TOF MS instrument with ESI source. All dry solvents were commercial products and used without further purification. The starting chiral ferrocenyl alcohol (R)-**5** and ferrocenyl amine (R)-**6** were prepared by the reported method.[5a,b] Chiral ferrocenyl amine (R)-**18** and its dimethylamino/methyl exchange product (R)-**19** were prepared according to the literature procedure.[11]

Preparation of 1-(R_p)-Bromo-2-[(R)-α-(*N*,*N*-dimethylamino)-(*o*-bromophenylmethyl)]ferrocene ((R,R_p)-7). The title compound was prepared by a slight modification of the literature procedure.[5a,b] In a 20 mL Schlenk tube containing a magnetic stirring bar were charged amine (R)-**6** (500 mg, 1.26 mmol) and dry diethyl ether (6.0 mL) under a slight pressure of nitrogen. The flask was cooled in a dry ice/methanol bath, and a pentane solution of *t*-BuLi (1.59 mol/L, 2.76 mL, 4.42 mmol) was then added slowly by using a syringe through the septum with magnetic stirring. The dry ice bath was removed, and the solution was allowed to warm to room temperature and stirred for 1 h. A diethyl ether (3.0 mL) solution of $C_2Br_2Cl_4$ (910 mg, 2.78 mmol) was injected into the mixture at −78 °C, and the mixture was then allowed to warm to room temperature and stirred for 1 h. After hydrolysis and usual workup, the crude product was purified by column chromatography on silica gel (hexane/diethyl ether/triethylamine = 20/1/1) to give the pure (R,R_p)-7 (430 mg, 1.03 mmol, 82% yield). Orange solid: mp 84 °C; $[\alpha]^{20}_D$ = +121.3 (c = 0.71, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 6H), 4.12 (s, 5H), 4.16 (m, 1 H), 4.35 (m, 1H), 4.45 (m, 1H), 5.03 (s, 1H), 7.02−7.08 (m, 1 H), 7.15−7.26 (m, 2H), 7.57 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 44.4, 65.3, 67.2, 67.5, 70.0, 71.7, 77.3, 90.2, 126.2, 127.1, 128.2, 131.0, 132.4, 141.0; HRMS (ESI) calcd for $C_{19}H_{19}Br_2FeN$ 475.9312 (M^+ + H), found 475.9327. Crystals suitable for X-ray analysis were obtained by recrystallization from $CHCl_3$−hexane (CCDC 883437).

Reaction of α-(Dimethylamino)benzylferrocene with Me_2Zn. The following provides a typical experimental procedure for the reaction of α-(dimethylamino)benzylferrocenes with Me_2Zn.[11] In a 20 mL

dx.doi.org/10.1021/jo3012013 | J. Org. Chem. 2012, 77, 6638−6642

Schlenk tube containing a magnetic stirring bar were charged (R,R_p)-**7** (503 mg, 1.05 mmol) and dry diethyl ether (6.0 mL) under a slight pressure of nitrogen. Me_2Zn (1 mol/L in hexane, 1.7 mL, 4.2 mmol) was added dropwise to the solution at −78 °C, followed by CH_3COCl (0.12 mL, 1.68 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. After hydrolysis and usual workup, the crude product was purified by flash chromatography (hexane/ethyl acetate = 20/1) to give (S,R_p)-**8** (371 mg, 0.83 mmol): yield 79%; orange solid; mp 129−130 °C; $[\alpha]^{20}_D$ = +80.6 (c = 0.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (d, 3H, J = 7.1 Hz), 3.98 (s, 5H), 3.99 (m, 1H), 4.05 (m, 1H), 4.40 (m, 1H), 4.57 (q, 1H, J = 7.2 Hz), 7.12 (t, 1H, J = 7.8 Hz), 7.34 (t, 1H, J = 7.8 Hz), 7.49 (d, 1H, J = 7.8 Hz), 7.64 (d, 1 H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 23.8, 37.1, 64.7, 66.0, 69.8, 71.0, 79.2, 91.4, 124.2, 127.4, 127.9, 129.0, 132.90, 144.9; HRMS (ESI) calcd for $C_{18}H_{16}Br_2Fe$ 445.8968 (M^+), found 445.8985. Crystals suitable for the X-ray analysis were obtained by recrystallization from CH_2Cl_2−hexane, CCDC 883461.

(*R*)-[α-(*o*-Bromophenyl)ethyl]ferrocene ((*R*)-14). The title compound was prepared from (*R*)-**6** by a procedure similar to that described above: yield 73%; orange solid; mp 59−60 °C; $[\alpha]^{28}_D$ = +140.372 (c = 0.13 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.54 (d, J = 7.1 Hz), 4.05 (m, 1H), 4.10 (m, 1H), 4.14 (m, 1H), 3.92 (s, 5H), 4.26 (m, 1H), 4.37 (q, 1H, J = 7.1 Hz), 6.9−6.99 (m, 1H), 7.13 (t, 1H, J = 8.0 Hz), 7.49 (d, 1H, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 20.8, 38.5, 66.6, 66.8, 67.9, 68.1, 68.7, 93.2, 123.4, 127.3, 127.5, 128.5, 132.4, 146.9; HRMS (ESI) calcd for $C_{18}H_{17}BrFe$ 367.9863 (M^+), found 367.9859. Crystals suitable for the X-ray analysis were obtained by recrystallization from diethyl ether, CCDC 883466.

1-(S_p)-Bromo-2-(1′(*R*)-phenylethyl)ferrocene ((*R,S*$_p$)-16). The title compound was prepared from (R,S_p)−**15**[8] by a procedure similar to that described above: yield 78%; orange oil; $[\alpha]^{26}_D$ = +48.4 (c = 0.13, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (d, J = 7.1 Hz), 3.85 (m, 1H), 3.92 (s, 5H), 3.94 (q, 1H, J = 7.2 Hz), 4.00 (m, 1H), 4.41 (m, 1H), 7.26−7.32 (m, 1H), 7.38−7.47 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 23.4, 38.9, 65.0, 65.5, 69.6, 70.9, 78.7, 93.1, 126.5, 128.1, 128.1, 145.1; HRMS (ESI) calcd for $C_{18}H_{17}BrFe$ 367.9863 (M^+), found 367.9864. This compound was converted to the corresponding diselenide **17** to determine its stereochemistry (see below).

1-(R_p)-Iodo-2-[1′(*S*)-(*o*-iodophenyl)ethyl]ferrocene ((*S,R*$_p$)-21). The title compound was prepared from (R_p)-1-iodo-2-[(*R*)-α-*N*,*N*-dimethylamino)-*o*-iodophenylmethyl]ferrocene **20**[7] by procedure similar to that described above: yield 95%; orange solid: mp 88−89 °C; $[\alpha]^{25}_D$ = +80.4 (c = 0.14 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (d, J = 7.14, 2H), 3.92 (s, 5H), 4.08 (m, 1H), 4.18 (m, 1H), 4.32 (q, J = 7.14, 1H), 4.42 (m, 1H), 6.95−7.00 (m, 1H), 7.37−7.49 (m, 2H), 7.94−7.97 (m, 1H); distinct signals 1.43 (d, J = 7.1 Hz), 3.85 (s); ^{13}C NMR ($CDCl_3$) δ 24.8, 44.4, 64.5, 68.9, 71.5, 74.2, 93.9, 101.6, 128.1, 128.2, 128.3, 139.7, 148.0, 171.5; HRMS (ESI) calcd for $C_{18}H_{16}FeI_2$ 541.8691 (M^+), found 541.8683. Crystals suitable for the X-ray analysis were obtained by recrystallization from CH_2Cl_2−hexane, CCDC 885599.

1-(R_p)-Diphenylphosphanyl-2-[1′(*S*)-(*o*-diphenylphosphanyl-phenyl)ethyl]ferrocene ((*S,R*$_p$)-3) (Taniaphos 3G). The title compound was prepared by lithiation of (S,R_p)-**8** followed by trapping with Ph_2PCl according to the literature procedure:[5a,b] yield 72%; orange solid; mp 89−90 °C; $[\alpha]^{25}_D$ = +352.4 (c = 0.33, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (d, 3H, J = 7.1 Hz), 3.77 (s, 5H), 3.79 (m, 1 H), 4.22 (m, 1H), 4.33 (m, 1H), 5.02 (m, 1 H), 6.9−6.95 (m, 1H), 7.09 (t, 1H, J = 7.3 Hz), 7.20−7.43 (m, 20H), 7.41−7.65 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 36.3 (dd, J = 25.0, 9.7 Hz), 69.4 (m), 69.5, 69.7, 69.7, 70.8 (d, J = 4.3 Hz), 75.9 (d, J = 12.1 Hz) 99.7 (d, J = 25.4 Hz), 25.2 (d, J = 5.4 Hz) 126.2, 127.6−140.7 (m), 151.1 (d, J = 23.5 Hz); ^{31}P NMR ($CDCl_3$) δ −12.9 (d, J = 18.4 Hz), −22.4 (d, J = 18.4 Hz); HRMS (ESI) calcd for $C_{42}H_{36}FeP_2$ 658.1642 (M^+), found 658.1645. Crystals suitable for the X-ray analysis were obtained by recrystallization from benzene−pentane, CCDC 883462.

Preparation of Bis-1-(S_p)-[1′-(*R*)-(Phenylethyl)ferrocenyl] Diselenide ((*R,S*$_p$;*R,S*$_p$)-17). In a 20 mL Schlenk tube containing a magnetic stirring bar were charged (R,S_p)-**16** (135 mg, 0.37 mmol) and dry diethyl ether (4.0 mL) under a slight pressure of nitrogen. The tube was cooled in an ice bath, and a hexane solution of *n*-BuLi (1.62 mol/L, 0.28 mL, 0.46 mmol) was then added using a syringe through the septum with magnetic stirring. After the mixture was stirred for 1 h, selenium powder (43 mg, 0.55 mmol) was added all at once and the solution was allowed to warm to room temperature and stirred for 3 h. The reaction was quenched with water, and oxygen was bubbled through the solution for 1 h. The solution was filtered through a Celite pad and extracted with ethyl acetate (20 mL × 3). The combined extracts were washed (brine), dried (Mg_2SO_4), and filtered, and the solvent was evaporated to leave a reddish brown residue. Purification of the residue by column chromatography (silica gel, hexane/ethyl acetate =20/1) afforded diselenide ($R,S_p;R,S_p$)-**17** (176 mg, 0.24 mmol): yield 65%; red solid; mp 81 °C; $[\alpha]^{28}_D$ = −263.8 (c = 0.14, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.54 (d, 6H, J = 7.0 Hz), 3.83 (s, 10H), 4.06−4.09 (m, 4H), 4.22 (m, 2H), 4.34 (m, 2H), 7.26−7.46 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 22.6, 31.6, 68.2, 69.3, 69.7, 73.3, 75.6, 98.3, 126.3, 128.1, 128.2, 145.8. Anal. Calcd for $C_{36}H_{34}Fe_2Se_2$: C, 58.73; H, 4.65. Found: C, 58.46; H, 4.88. Crystals suitable for the X-ray analysis were obtained by recrystallization from benzene−hexane, CCDC 883467.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra (PDF) for ferrocene compounds (**3**, **7**, **8**, **16**, **17**, and **21**); crystallographic data for **3**, **7**, **8**, **14**, **17**, **19** (CCDC 883468), **20** (CCDC 885600), and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We wish to thank Professor Yoshiaki Nishibayashi and Dr. Yoshiaki Tanabe, Tokyo University, for the X-ray diffraction analysis of the chiral ferrocene compounds. This study was supported financially by a Grant-in-Aid for Scientific Research (No. 22550044) from the Japan Society for the Promotion of Science (JSPS).

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(5) The original synthetic scheme includes an error in the stereochemistry of *ortho*-lithiation of ferrocene, and the compound **7** was incorrectly drawn as (R,S_p)-configured. It is updated to (R,R_p)-configured in the corrigendum by the author. (a) Ireland, T.; Grossheimann, G.; Wieser-Jeunesse, C.; Knochel, P. *Angew. Chem., Int.*

Ed. **1999**, *38*, 3212; **2008**, *47*, 3666 (corrigendum). (b) Ireland, T.; Tappe, K.; Grossheimann, G.; Knochel, P. *Chem.—Eur. J.* **2002**, *8*, 843; **2008**, *14*, 3509 (corrigendum).

(6) Schuecker, R.; Weissensteiner, W.; Mereiter, K.; Lotz, M.; Spindler, F. *Organometallics* **2010**, *29*, 6443 The combination of the central and the planar chirality can affect the stereochemistry of α-substitution reaction. The Weissensteiner paper suggests that the stereo course of α-substitution of the S,R_p (or R,S_p) isomer should be complete retention, while the corresponding R,R_p (or S,S_p) isomer favors inversion stereochemistry.

(7) Fukuzawa, S.-i.; Yamamoto, M.; Kikuchi, S. *J. Org. Chem.* **2007**, *72*, 1514.

(8) We tried to prepare (R,S_p) isomer (R^1 = H, R^2 = R^3 = Br in Table 1) of the dibromoferrocene **7** by dilithiation of (*R*)-**18** followed by trapping with bromine; however, we were not able to prepare it because the method would give (R,R_p)-**7**. Fukuzawa, S.-i.; Yamamoto, M.; Hosaka, M.; Kikuchi. *Eur. J. Org. Chem.* **2007**, 5540.

(9) Tappe, K.; Knochel, P. *Tetrahedron: Asymmetry* **2004**, *15*, 91. The (R,R_p) isomer of **3** is prepared and revealed to be an efficient ligand to give the hydrogenation product with high enantioselectivities.

(10) (a) Nishibayashi, Y.; Segawa, K.; Singh, J. D.; Fukuzawa, S.-I.; Ohe, K.; Uemura, S. *Organometallics* **1996**, *15*, 370. (b) Fukuzawa, S.-I.; Takahashi, K.; Kato, H.; Yamazaki, H. *J. Org. Chem.* **1997**, *62*, 7711.

(11) Lotz, M.; Ireland, T.; Perea, J. J. A.; Knochel, P. *Tetrahedron:Asymmetry* **1999**, *10*, 1839.

(12) There are two errors in the synthetic scheme of **3** as shown by Knochel et al.; first, in the stereochemistry of *ortho*-lithiation of (*R*)-**6** followed by trapping with bromine, the dibromoferrocene (*R,Rp*)-**7** is incorrectly drawn as (*R,Sp*), and second, the stereochemistry of α-substitution of the dimethylamino group by Me_2Zn is incorrectly assigned to retention. As the result, they incorrectly assign the stereochemistry of (*S,Rp*)-**8** to (*R,Sp*) and, thus, incorrectly propose the stereochemistry of **3** as (*R,Sp*).

dx.doi.org/10.1021/jo3012013 | *J. Org. Chem.* 2012, 77, 6638−6642