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Synthesis of chiral primary 1-ferrocenylalkylamines via highly diastereoselective addition of organolithium compounds to ferrocenecarboxaldehyde imine derived from (*S*)-2-methoxy-1-phenylethylamine

Tsutomu Fukuda, Akihiro Takehara, Naoto Haniu and Masatomo Iwao*

Department of Applied Chemistry, Faculty of Engineering, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan

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Abstract

The imine **3** derived from ferrocenecarboxaldehyde **1** and (*S*)-2-methoxy-1-phenylethylamine **2** was reacted with several organolithium compounds to give 1,2-addition products **4** in good yields with excellent diastereoselectivities (>98% de). The adducts **4** were readily converted to the corresponding primary 1-ferrocenylalkylamines **5** by hydrogenolysis or stereoretentive substitutions without racemization.

1. Introduction

Primary 1-ferrocenylalkylamines are used as chiral auxiliaries in some asymmetric syntheses, such as the Ugi four-component condensation reaction,[1] and the synthesis of benzophenanthridine alkaloids (+)- and (−)-corynoline.[2] Although the utilization of primary 1-ferrocenylalkylamines as the ligands in transition metal-catalyzed asymmetric synthesis has remained rather unexplored compared with that of the corresponding tertiary amines,[3] the potential of these compounds as new types of ligands has been shown recently by Knochel in copper(I)-catalyzed allylation of diorganozinc compounds.[4] For the preparation of chiral primary 1-ferrocenylalkylamines, the conventional resolution technique has been employed.[1] Recently, however, some practically useful asymmetric syntheses have also been developed.[5] For example, Enders reported diastereoselective additions of organolithium compounds to ferrocenecarboxaldehyde–SAMP–hydrazone.[6] Reductive cleavage of the resultant hydrazine N–N bond produced chiral primary 1-ferrocenylalkylamines having modest to excellent enantiomeric excesses. Brocard

* Corresponding author. Fax: +81-95-843-7313; e-mail: iwao@net.nagasaki-u.ac.jp

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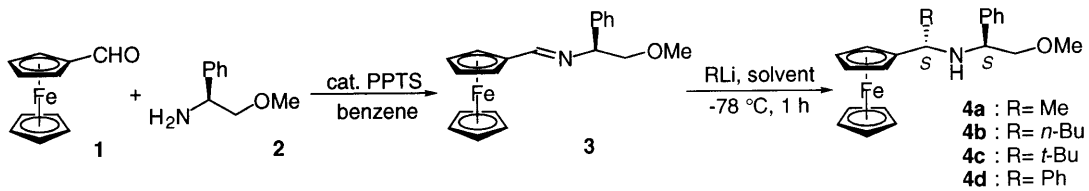
employed ferrocenecarboxaldehyde imines derived from valinol and phenylglycinol for a similar diastereoselective addition reaction.[7] On the other hand, Soai reported enantioselective addition of dialkylzinc reagents to ferrocenyldiphenylphosphinylimine in the presence of chiral 2-aminoalcohols.[8] As another approach, Reeves described enantioselective CBS-reduction of acylferrocenes to produce chiral alcohols,[9] which were successfully converted to the corresponding amines via stereoretentive substitution reactions.[4,10] Herein, we wish to report an enantioselective synthesis of chiral primary 1-ferrocenylalkylamines via highly diastereoselective additions of organolithium compounds to a chiral ferrocenecarboxaldehyde imine **3**.[11]

2. Results and discussion

The imine **3** was readily prepared by the reaction of ferrocenecarboxaldehyde **1** with (*S*)-2-methoxy-1-phenylethylamine **2**[12] in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) in an essentially quantitative yield. The crude **3** was used directly for the next reaction due to its instability during chromatographic purification. The results of the reactions of the imine **3** with 1.5 equiv. of organolithium compounds are summarized in Table 1. In general, the reactions with alkyllithium reagents went smoothly in THF at −78°C (*n*-BuLi, *t*-BuLi) or at −78°C to room temperature (MeLi) to give the corresponding 1,2-addition products **4a**–**c** in high yields (>90%) and excellent diastereoselectivities (>98% de) (entries 1–3).[13] On the other hand, the reaction of **3** with phenyllithium was found to be sluggish in THF (entry 4). However, this problem was easily overcome by using ether as a solvent (entry 5). The (*S*,*S*) stereochemistry of the addition products **4a**–**d** was determined after cleavage of the chiral auxiliary (vide infra).

Table 1
Diastereoselective 1,2-addition of imine **3**

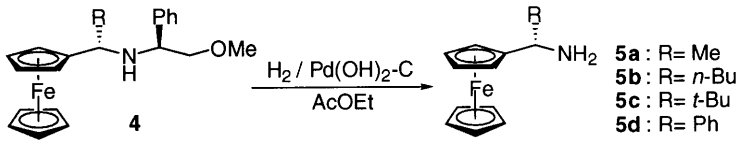


Entry	RLi	Solvent	Product	Yield (%)[a]	% de[b]
1	MeLi	THF	**4a**	96[c]	>98
2	*n*-BuLi	THF	**4b**	100	>98
3	*t*-BuLi	THF	**4c**	95	>98
4	PhLi	THF	**4d**	23	>98
5	PhLi	Ether	**4d**	88	>98

[a] Isolated yield.
[b] Determined by ^{1}H NMR analysis.
[c] The reaction mixture was warmed to room temperature.

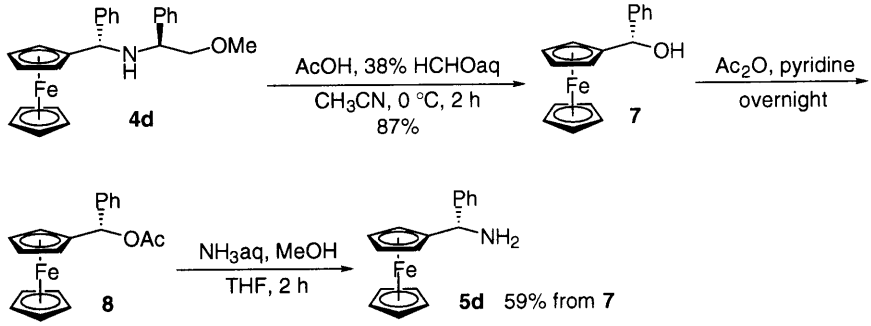
Removal of the methyl phenylethyl ether moiety of **4a–c** was readily accomplished by hydrogenolysis over Pearlman's catalyst[14] under atmospheric pressure to give the corresponding chiral 1-ferrocenylalkylamines **5a–c** in good yields (Table 2). The hydrogenolysis of **4d**, however, did not produce the desired α-ferrocenylbenzylamine **5d**, but afforded only benzylferrocene **6**. This indicated that the hydrogenolysis proceeds much faster at the ferrocenylbenzyl carbon compared to the normal benzylic position. The conversion of **4d** to **5d**, however, could be carried out in a multistep sequence using stereoretentive substitution reactions (Scheme 1).[15] The hydrolysis of **4d** in a mixture of acetic acid, formaldehyde, and acetonitrile at 0°C for 2 h produced the alcohol **7** in 87% yield.[16] This compound was converted to the unstable acetate **8** which, without purification, was transformed to the amine **5d** by treatment with aqueous ammonia in a mixture of methanol and THF at ambient temperature for 2 h in 59% yield for two steps.[15]

Table 2
Hydrogenolysis of 1-ferrocenylalkylamine derivatives **4**



Entry	R	Substrate	Product	Yield (%)[a]
1	Me	**4a**	**5a**	78
2	*n*-Bu	**4b**	**5b**	87
3	*t*-Bu	**4c**	**5c**	91
4	Ph	**4d**	**5d**	0

[a] Isolated yield.

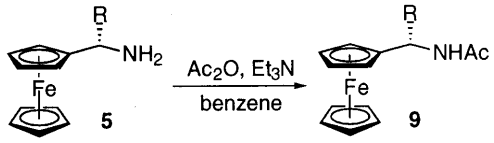


Scheme 1. Preparation of (*S*)-α-ferrocenylbenzylamine **5d**

The enantiomeric excess of the 1-ferrocenylalkylamines **5a–d** thus synthesized was determined by HPLC analyses over chiral stationary phase (Daicel Chiralpak AS or AD) after converting them to the acetamide derivatives **9a–d** (Table 3). The enantiomeric excess of each compound was found to be >98%, which indicated essentially no racemization took place during removal

of the chiral auxiliary. In addition, these results reinforced the very high stereoselectivity in the addition of organolithium compounds to the imine **3**. The absolute configurations of **9a–d** were determined to be (*S*) by comparison of their specific rotations with the reported values.[6] Thus, the relative configurations of the addition products **4a–d** are (*S*,*S*) as indicated above.

Table 3
Acetylation of 1-ferrocenylalkylamine derivatives **5**



Entry	R	Substrate	Product	Yield (%)[a]	% ee
1	Me	**5a**	**9a**	92	>99[b]
2	*n*-Bu	**5b**	**9b**	80	>99[b]
3	*t*-Bu	**5c**	**9c**	94	>99[c]
4	Ph	**5d**	**9d**	63	98[c]

[a] Isolated yield.
[b] Determined by HPLC analysis (Daicel Chiralpak AS).
[c] Determined by HPLC analysis (Daicel Chiralpak AD).

The stereoselectivity of the addition reaction may be accounted for by a chelation-controlled mechanism.[12a,17] A plausible transition structure **10** is shown in Fig. 1. The lithium of an open dimer[18] of an organolithium compound coordinates with N and O of the auxiliary group to produce a rigid five-membered chelate. Then, the alkyl group of the non-coordinated end attacks the C=N bond from the less congested *si*-face via a six-centered transition state[18,19] to give (*S*,*S*)-product **4**. In this transition state model, the bulky ferrocenyl group must take a *syn* orientation to the phenyl group to allow the attack of the alkyl group. Even though taking such an orientation, the distance between the ferrocenyl group and the phenyl group is too large to result in any repulsive interaction.

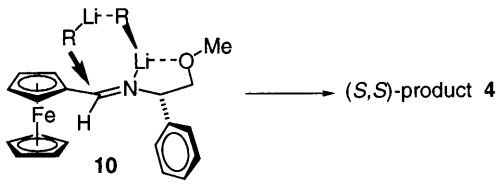


Figure 1. Asymmetric induction mechanism

3. Conclusion

We have developed a useful method for the synthesis of enantiomerically pure primary 1-ferrocenylalkylamines **5a–d** via highly stereoselective addition of organolithium compounds to the imine **3**. The utility of these amines as the ligands in transition metal-catalyzed asymmetric synthesis is under investigation in our laboratories.

4. Experimental

4.1. General

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were obtained with a Perkin–Elmer System 2000 instrument. ^{1}H NMR spectra were recorded at 200 MHz on a Varian Gemini-200 instrument or at 400 MHz on a JEOL JMS GX-400 instrument. All signals were expressed as ppm downfield from tetramethylsilane used as an internal standard (δ value in C_6D_6 or $CDCl_3$). High resolution mass spectra were recorded on a JEOL JMS-DX303 instrument. HPLC analysis of enantiomeric excess was carried out using Shimadzu LC-6A equipped with an appropriate optically active column, as described in the footnote of Table 3. Optical rotations were measured on a JASCO DPI-1000 digital polarimeter at ambient temperature. Column chromatography was conducted on silica gel 60, 70–230 mesh ASTM (E. Merck), unless otherwise stated. Flash chromatography was conducted on silica gel 60, 230–400 mesh ASTM (E. Merck). Solvents were dried (Na–benzophenone ketyl for ether and THF) and distilled shortly before use. Reactions using organolithium compounds were carried out under an atmosphere of nitrogen or argon if necessary. MeLi was purchased from Kanto Chemical Co., Inc. *n*-BuLi, *t*-BuLi and PhLi were purchased from Aldrich Chemical Co., Inc. All organolithium compounds were used after titration. Ferrocenecarboxaldehyde **1**[20] and (*S*)-2-methoxy-1-phenylethylamine **2**[21] were synthesized according to the literature procedures.

4.2. (S)-N-*Ferrocenylmethylidene-2-methoxy-1-phenylethylamine* **3**

(*S*)-2-Methoxy-1-phenylethylamine **2** (1.00 g, 6.61 mmol) was added to a solution of ferrocenecarboxaldehyde **1** (1.28 g, 6.00 mmol) and catalytic amount of PPTS in dry benzene (24 mL). After being stirred for 2 h at room temperature, the resulting mixture was evaporated. The residue was heated in vacuo at 70°C to remove the unreacted amine **2**. After azeotropic treatment with benzene, the product was dried in vacuo to give the imine **3** as a brown solid. This crude product was found to be essentially pure from ^{1}H NMR analysis and used for the next reaction without further purification; IR (KBr): 3084, 2982, 2924, 2878, 1643, 1491, 1451, 1371, 1323, 1303, 1246, 1195, 1105, 1060, 1044, 1024, 998, 981, 959, 910, 846, 817, 758, 701 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): δ 3.13 (s, 3H), 3.54 (dd, J=3.7 and 9.2 Hz, 1H), 3.71 (t, J=9.2 Hz, 1H), 4.05 (s, 5H), 4.07–4.11 (m, 2H), 4.45 (dd, J=3.7 and 9.2 Hz, 1H), 4.53 (quint, J=1.1 Hz, 1H), 4.82 (quint, J=1.1 Hz, 1H), 7.11 (tt, J=1.5 and 7.3 Hz, 1H), 7.23 (t, J=7.3 Hz, 2H), 7.56 (d, J=7.3 Hz, 2H), 8.09 (s, 1H); $[\alpha]_D^{27}$ −189 (*c* 1.05, C_6H_6). HREIMS *m*/*z*. Calcd for $C_{20}H_{21}FeNO$ (M^+): 347.0973. Found 347.0972.

4.3. 1,2-*Addition of organolithium compounds to the imine* **3**. *General procedure*

The crude imine **3** prepared from 6.00 mmol of **1** as described above was dissolved in dry THF (60 mL). (In the reaction of phenyllithium, dry ether (60 mL) was used as a solvent.) To this solution was added dropwise a solution of organolithium compound (9.0 mmol) at −78°C. After being stirred for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl at the same temperature. (In the reaction of methyllithium, the mixture was quenched after being warmed to room temperature.) The product was extracted with ether and the extract was

washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography over silica gel using the following eluents: hexane–ethyl acetate = 5:1 for **4a**,**b**; hexane–ethyl acetate = 10:1 for **4c**; hexane–ethyl acetate = 5:1, containing 1% triethylamine for **4d**. Yields after chromatography are shown in Table 1.

4.3.1. N-*[(S)-2-Methoxy-1-phenylethyl]-(S)-1-ferrocenylethylamine* ***4a***

Orange oil; IR (neat): 3342, 3093, 2968, 2927, 2888, 2824, 1493, 1456, 1368, 1308, 1194, 1107, 1026, 1001, 970, 915, 892, 817, 758, 702 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ 1.29 (d, J = 6.2 Hz, 3H), 1.35 (br s, 1H), 3.07 (s, 3H), 3.35 (dd, J = 4.4 and 8.8 Hz, 1H), 3.40 (t, J = 8.8 Hz, 1H), 3.46 (q, J = 6.2 Hz, 1H), 3.96–3.98 (m, 1H), 3.98–4.01 (m, 1H), 4.07 (s, 5H), 4.12 (quint, J = 1.1 Hz, 1H), 4.22 (dd, J = 4.4 and 8.8 Hz, 1H), 4.34 (quint, J = 1.1 Hz, 1H), 7.12 (tt, J = 1.5 and 7.7 Hz, 1H), 7.23 (t, J = 7.7 Hz, 2H), 7.48 (dd, J = 1.5 and 7.7 Hz, 2H); $[\alpha]_D^{27}$ +63.4 (c 1.04, $CHCl_3$). HREIMS m/z. Calcd for $C_{21}H_{25}FeNO$ (M^+): 363.1286. Found 363.1284.

4.3.2. N-*[(S)-2-Methoxy-1-phenylethyl]-(S)-1-ferrocenylpentylamine* ***4b***

Orange oil; IR (neat): 3347, 3093, 3027, 2955, 2928, 2859, 2824, 1493, 1456, 1379, 1353, 1324, 1230, 1194, 1106, 1041, 1025, 1001, 970, 908, 816, 759, 702 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ 0.88 (t, J = 7.3 Hz, 3H), 1.20–1.48 (m, 5H), 1.59–1.68 (m, 1H), 1.70–1.81 (m, 1H), 3.09 (s, 3H), 3.45–3.52 (m, 3H), 3.94–3.98 (m, 2H), 4.03 (quint, J = 1.1 Hz, 1H), 4.09 (s, 5H), 4.11 (t, J = 5.9 Hz, 1H), 4.30 (quint, J = 1.1 Hz, 1H), 7.12 (tt, J = 1.5 and 7.7 Hz, 1H), 7.24 (t, J = 7.7 Hz, 2H), 7.49 (dd, J = 1.5 and 7.7 Hz, 2H); $[\alpha]_D^{24}$ +48.1 (c 0.930, C_6H_6). HREIMS m/z. Calcd for $C_{24}H_{31}FeNO$ (M^+): 405.1755. Found 405.1786.

4.3.3. N-*[(S)-2-Methoxy-1-phenylethyl]-(S)-1-ferrocenyl-2,2-dimethylpropylamine* ***4c***

Orange oil; IR (neat): 3347, 3087, 3029, 2953, 2824, 1480, 1456, 1392, 1361, 1228, 1192, 1107, 1027, 1002, 818, 762, 702 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ 0.95 (s, 9H), 2.05 (br s, 1H), 3.06 (s, 3H), 3.34 (s, 1H), 3.61 (dd, J = 5.1 and 9.2 Hz, 1H), 3.65 (dd, J = 4.4 and 9.2 Hz, 1H), 3.88–3.91 (m, 2H), 3.91–3.97 (m, 1H), 4.04–4.06 (m, 1H), 4.06 (s, 5H), 4.62 (t, J = 5.1 Hz, 1H), 7.11–7.15 (m, 1H), 7.28 (t, J = 7.7 Hz, 2H), 7.61 (dd, J = 1.1 and 7.7 Hz, 2H); $[\alpha]_D^{25}$ +8.62 (c 0.985, C_6H_6). HREIMS m/z. Calcd for $C_{24}H_{31}FeNO$ (M^+): 405.1755. Found 405.1787.

4.3.4. N-*[(S)-2-Methoxy-1-phenylethyl]-(S)-α-ferrocenylbenzylamine* ***4d***

Orange oil; IR (neat): 3351, 3085, 3062, 3027, 2982, 2924, 2888, 2853, 1601, 1494, 1456, 1385, 1354, 1194, 1106, 1026, 1002, 969, 931, 819, 761, 701 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ 1.35 (br s, 1H), 3.04 (s, 3H), 3.28 (dd, J = 4.0 and 9.2 Hz, 1H), 3.42 (t, J = 9.2 Hz, 1H), 3.90 (dd, J = 4.0 and 9.2 Hz, 1H), 3.92–3.94 (m, 1H), 3.94–3.96 (m, 1H), 4.06 (quint, J = 1.1 Hz, 1H), 4.09 (s, 5H), 4.20 (quint, J = 1.1 Hz, 1H), 4.47 (s, 1H), 7.08–7.25 (m, 6H), 7.32 (d, J = 7.7 Hz, 2H), 7.40 (d, J = 7.7 Hz, 2H); $[\alpha]_D^{26}$ +109 (c 0.995, $CHCl_3$). HREIMS m/z. Calcd for $C_{26}H_{27}FeNO$ (M^+): 425.1442. Found 425.1435.

4.4. Hydrogenolysis of 1-ferrocenylalkylamine derivatives ***4****. General procedure*

The amine **4** (5.74 mmol) and $Pd(OH)_2$ on carbon (1.04 g) were dissolved in ethyl acetate (104 mL). The mixture was stirred at room temperature under a hydrogen atmosphere. After being stirred for the following times [**4a**: 23 h, **4b**: 3 h, **4c**: 4 h, **4d**: 17 h], the mixture was passed through a pad of Celite. After evaporation, the residue was purified by flash chromatography

over Chromatorex NH-DM1020 silica gel using the following eluents: hexane–ethyl acetate = 3:1–0:1 for **5a**; hexane–ethyl acetate = 5:1 for **5b**,**c**. Yields after chromatography are shown in Table 2.

*4.4.1. (S)-1-Ferrocenylethylamine **5a***

Orange oil; IR (KBr): 3458, 3079, 2975, 2921, 1613, 1568, 1533, 1434, 1371, 1350, 1249, 1154, 1106, 1087, 1060, 1025, 1000, 805 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ 1.10 (br s, 2H), 1.21 (d, $J = 6.2$ Hz, 3H), 3.61 (q, $J = 6.2$ Hz, 1H), 3.93–3.96 (m, 2H), 3.99 (s, 5H), 4.00–4.02 (m, 1H), 4.06–4.08 (m, 1H); $[\alpha]_D^{26}$ +26.7 (*c* 1.04, C_6H_6). HREIMS *m*/*z*. Calcd for $C_{12}H_{15}FeN$ (M^+): 229.0554. Found 229.0555.

*4.4.2. (S)-1-Ferrocenylpentylamine **5b***

Orange oil; IR (neat): 3376, 3094, 2956, 2929, 2858, 1466, 1411, 1380, 1106, 1023, 1001, 817 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ 0.88 (t, $J = 7.3$ Hz, 3H), 0.98 (br s, 2H), 1.20–1.59 (m, 6H), 3.49 (dd, $J = 5.1$ and 7.7 Hz, 1H), 3.95 (t, $J = 1.8$ Hz, 2H), 4.00 (q, $J = 1.8$ Hz, 1H), 4.01 (s, 5H), 4.18 (q, $J = 1.8$ Hz, 1H); $[\alpha]_D^{26}$ +41.2 (*c* 1.13, C_6H_6). HREIMS *m*/*z*. Calcd for $C_{15}H_{21}FeN$ (M^+): 271.1023. Found 271.1012.

*4.4.3. (S)-1-Ferrocenyl-2,2-dimethylpropylamine **5c***

Orange needles (ether–hexane). This compound sublimed at 100–105°C in a sealed capillary. IR (KBr): 3358, 2962, 1479, 1387, 1361, 1235, 1104, 1075, 1024, 999, 918, 868, 813, 761 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ 0.88 (s, 9H), 1.00 (br s, 2H), 3.22 (s, 1H), 3.90–3.94 (m, 2H), 3.94–3.98 (m, 1H), 4.00 (s, 5H), 4.23–4.25 (m, 1H); $[\alpha]_D^{25}$ +113 (*c* 0.860, C_6H_6) {lit.[1] $[\alpha]_D^{20}$ −112.8°C (*c* 1, C_6H_6): (*R*)-isomer}. HREIMS *m*/*z*. Calcd for $C_{15}H_{21}FeN$ (M^+): 271.1023. Found 271.1003.

*4.4.4. Benzylferrocene **6***

Orange plates (pentane); mp 75.5–76.0°C (lit.[22] 70–74°C); IR (KBr): 3020, 1601, 1492, 1449, 1428, 1392, 1323, 1285, 1224, 1151, 1103, 1071, 1022, 999, 926, 858, 820, 754, 722 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ 3.53 (s, 2H), 3.93 (t, $J = 1.5$ Hz, 2H), 3.95 (t, $J = 1.5$ Hz, 2H), 3.98 (s, 5H), 7.02–7.10 (m, 2H), 7.10–7.21 (m, 3H); HREIMS *m*/*z*. Calcd for $C_{17}H_{16}Fe$ (M^+): 276.0601. Found 276.0599.

*4.5. (S)-α-Ferrocenylbenzylamine **5d***

This compound was prepared in three steps from the amine **4d**. A solution of **4d** (91.1 mg, 0.214 mmol) in acetonitrile (1.0 mL) was added to a solution of acetic acid (1.0 mL) and aqueous formaldehyde (38% solution in water, 1.0 mL) in acetonitrile (1.0 mL) at 0°C. After being stirred for 2 h at the same temperature, the mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with ether. The extract was washed successively with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was subjected to column chromatography over silica gel (hexane–ethyl acetate = 10:1, containing 1% triethylamine) to give (*S*)-α-ferrocenylbenzylalcohol (**7**) (54.2 mg, 87%) as orange oil; ^1H NMR (200 MHz, $CDCl_3$): δ 2.50 (d, $J = 3.2$ Hz, 1H), 4.13–4.23 (m, 4H), 4.21 (s, 5H), 5.45 (d, $J = 3.2$ Hz, 1H), 7.17–7.42 (m, 5H); $[\alpha]_D^{26}$ +77.9 (*c* 1.12, C_6H_6) {lit.[9] $[\alpha]_D^{20}$ −85 (*c* 1, C_6H_6): (*R*)-isomer (>95% ee)}.

To a solution of (*S*)-α-ferrocenylbenzylalcohol (54.2 mg, 0.186 mmol) in pyridine (1.0 mL) was added acetic anhydride (88 μL, 0.95 mmol) at room temperature. The mixture was stirred

for 16 h and concentrated. The residue was dried in vacuo at 40°C to give (*S*)-α-ferrocenylbenzyl acetate (**8**). This product was used for the next reaction without further purification; ^{1}H NMR (200 MHz, C_6D_6): δ 1.68 (s, 3H), 3.89–4.00 (m, 3H), 3.97 (s, 5H), 4.36 (quint, J=1.2 Hz, 1H), 7.00 (s, 1H), 7.02–7.15 (m, 3H), 7.41–7.49 (m, 2H).

The mixture of 28% aqueous ammonia (1.0 mL) and methyl alcohol (1.0 mL) was added to a solution of (*S*)-α-ferrocenylbenzyl acetate in THF (1.0 mL) at room temperature. After being stirred for 1.5 h at the same temperature, methyl alcohol and THF were removed by evaporation. The residual solution was extracted with ether, washed successively with water and brine, dried over Na_2SO_4, and concentrated. The residue was subjected to column chromatography over silica gel (hexane–ethyl acetate=5:1, containing 1% triethylamine) to give (*S*)-α-ferrocenylbenzylamine (**5d**) (32.0 mg, 59%) as orange oil; IR (neat): 3376, 3086, 3027, 2926, 2852, 1601, 1494, 1456, 1412, 1394, 1381, 1348, 1289, 1232, 1187, 1106, 1025, 1001, 820, 701 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): δ 1.35 (br s, 2H), 3.88–3.91 (m, 1H), 3.92–3.94 (m, 1H), 3.96–3.98 (m, 1H), 3.99 (s, 5H), 4.27–4.30 (m, 1H), 4.70 (s, 1H), 7.07 (tt, J=1.5 and 7.3 Hz, 1H), 7.10–7.20 (m, 2H), 7.39 (dd, J=1.5 and 8.4 Hz, 2H); $[\alpha]_D^{25}$ +15.4 (*c* 1.13, C_6H_6). HREIMS m/z. Calcd for $C_{17}H_{17}FeN$ (M^+): 291.0710. Found 291.0732.

*4.6. Acetylation of 1-ferrocenylalkylamine derivatives **5**. General procedure*

The amine **5** (0.17 mmol) and triethylamine (71 μL, 0.51 mmol) was dissolved in dry benzene (2.0 mL). To this solution was added acetic anhydride (48 μL, 0.51 mmol) at room temperature. After being stirred for 1 h, the mixture was concentrated. The residue was subjected to column chromatography over Chromatorex NH-DM1020 silica gel (hexane–ethyl acetate=1:1) for **9a**–**c** or over silica gel (hexane–ethyl acetate=1:1, containing 1% triethylamine) for **9d**. Yields after chromatography are shown in Table 3.

*4.6.1. (S)-N-(1-Ferrocenylethyl)acetamide **9a***

Orange plates (ether–hexane); mp 112.0–113.0°C; IR (KBr): 3304, 3095, 2966, 2926, 1648, 1536, 1369, 1302, 1283, 1235, 1134, 1105, 1031, 1000, 965, 809, 738, 600 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (d, J=7.0 Hz, 3H), 1.97 (s, 3H), 4.12–4.16 (m, 3H), 4.17 (s, 5H), 4.19–4.22 (m, 1H), 4.89 (dq, J=7.0 and 8.4 Hz, 1H), 5.66 (br s, 1H); HPLC (Daicel Chiralpak AS, hexane–*i*-PrOH=1:1): >99% ee; $[\alpha]_D^{25}$ +73.5 (*c* 1.01, C_6H_6) {lit.[6b] $[\alpha]_D^{22}$ −83.7 (*c* 1.0, C_6H_6): (*R*)-isomer (95% ee)}. HREIMS m/z. Calcd for $C_{14}H_{17}FeNO$ (M^+): 271.0660. Found 271.0655.

*4.6.2. (S)-N-(1-Ferrocenylpentyl)acetamide **9b***

Orange needles (ether–hexane); mp 90.5–92.5°C; IR (KBr): 3303, 3079, 2959, 2927, 2857, 1639, 1551, 1467, 1374, 1300, 1134, 1107, 1046, 1026, 1002, 960, 819, 752, 709, 613, 597, cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): δ 0.90 (t, J=7.3 Hz, 3H), 1.21–1.51 (m, 5H), 1.66 (s, 3H), 1.69–1.79 (m, 1H), 3.93–3.99 (m, 3H), 4.07 (s, 5H), 4.09 (quint, J=1.1 Hz, 1H), 5.09 (dt, J=4.4 and 9.2 Hz, 1H), 5.14 (br d, J=9.2 Hz, 1H); HPLC (Daicel Chiralpak AS, hexane–*i*-PrOH=7:3): >99% ee; $[\alpha]_D^{27}$ +40.3 (*c* 1.38, C_6H_6) {lit.[6b] $[\alpha]_D^{22}$ −44.8 (*c* 1.0, C_6H_6): (*R*)-isomer (95% ee)}. HREIMS m/z. Calcd for $C_{17}H_{23}FeNO$ (M^+): 313.1129. Found 313.1130.

*4.6.3. (S)-N-(1-Ferrocenyl-2,2-dimethylpropyl)acetamide **9c***

Orange needles (CH_2Cl_2–hexane). This compound sublimed at 160–165°C in a sealed capillary; IR (KBr): 3299, 3107, 2972, 1634, 1559, 1367, 1300, 1234, 1106, 1031, 1001, 832, 811, 773,

740, 603 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.81 (s, 9H), 2.16 (s, 3H), 3.89 (t, $J=1.1$ Hz, 1H), 4.10 (quint, $J=1.1$ Hz, 1H), 4.11–4.15 (m, 1H), 4.13 (s, 5H), 4.19 (quint, $J=1.1$ Hz, 1H), 4.65 (d, $J=10.3$ Hz, 1H), 5.77 (br d, $J=10.3$ Hz, 1H); HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH = 9:1): >99% ee; $[\alpha]_D^{28}$ −99.2 (*c* 0.870, $CHCl_3$) {lit.[6a] $[\alpha]_D^{22}$ +83.6 (*c* 1.0, $CHCl_3$): (*R*)-isomer (85% ee)}. HREIMS *m*/*z*. Calcd for $C_{17}H_{23}FeNO$ (M^+): 313.1129. Found 313.1132.

*4.6.4. (*S*)-*N*-(α-Ferrocenylbenzyl)acetamide* ***9d***

Orange needles (CH_2Cl_2–hexane); mp 171.5–173.0°C; IR (KBr): 3280, 3062, 1636, 1550, 1494, 1447, 1371, 1306, 1237, 1107, 1024, 1004, 972, 823, 776, 731, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.06 (s, 3H), 4.03 (s, 1H), 4.07 (s, 1H), 4.15 (s, 5H), 4.16–4.20 (m, 2H), 5.94 (d, $J=8.4$ Hz, 1H), 6.15 (br d, $J=8.4$ Hz, 1H), 7.23–7.28 (m, 1H), 7.29–7.36 (m, 4H); HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH = 9:1): 98% ee; $[\alpha]_D^{25}$ +37.3 (*c* 1.23, $CHCl_3$) {lit.[6b] $[\alpha]_D^{22}$ −35.1 (*c* 0.25, $CHCl_3$): (*R*)-isomer (76% ee)}. HREIMS *m*/*z*. Calcd for $C_{19}H_{19}FeNO$ (M^+): 333.0816. Found 333.0816.

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