SYNTHESIS OF NEW CHIRAL 1,2-DISUBSTITUTED FERROCENES

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Synthesis of six chiral 1,2-disubstituted ferrocene derivatives is described starting from (*S*)-{[2-(methoxymethyl)pyrrolidin-1-yl]methyl}ferrocene (**2**) and {[*N*-((1*R*,2*S*)-methoxy-1-methyl-2-phenethyl)-*N*-methylamino]methyl}ferrocene (**3**). Oxidation of the (*N*-substituted aminomethyl)ferrocenes with active MnO_2 furnished the corresponding 2-substituted ferrocenecarbaldehydes.

Keywords: Ferrocenes; Planar chirality; Diastereoselective reactions; Ferrocenecarbaldehydes; Pyrrolidines; Oxidations.

The most frequently used method for the synthesis of 1,2-disubstituted ferrocene derivatives is based on *ortho*-lithiation of a ferrocene ring, bearing an appropriate *ortho*-directing group. As (dimethylamino)methyl is a common *ortho*-directing group, (dimethylamino)methylferrocene served as the starting material for the synthesis of achiral 2-[(dimethylamino)methyl]ferrocenecarbaldehyde[1]. This method was improved by Brocard *et al.*[2] and also used in the synthesis of achiral 2-[1-(dimethylamino)ethyl]ferrocenecarbaldehyde[3]. Stereoselective syntheses of 1,2-disubstituted ferrocene derivatives are based on the pioneering work of Ugi *et al.*[4] Enantiomerically pure (*R*)-1-[1-(dimethylamino)ethyl]ferrocene was employed as the starting material and several (R,S_p)-1-[1-(dimethylamino)ethyl]-2-substituted ferrocene derivatives were prepared, including (R,S_p)-2-[1-(dimethylamino)ethyl]-ferrocenecarbaldehyde. Another frequently used starting material for the stereoselective synthesis of planar chiral 1,2-disubstituded ferrocene derivatives is (*R*)-ferrocenyl-*p*-tolyl sulfoxide[5–7]. Its *ortho*-metallation with *n*-BuLi and subsequent quenching with electrophiles furnished several chiral ferrocene derivatives with 95–98% ee.

Other methods for the synthesis of chiral 1,2-disubstituted ferrocene derivatives are based on chiral ferrocenyloxazolines[8–10], {[*N*-((1*R*,2*S*)-methoxy-1-methyl-2-phenethyl)-*N*-methylamino]methyl}ferrocene[11,12], and (*S*)-{[2-(methoxymethyl)pyrrolidin-1-yl]methyl}ferrocene[13–15]. Several

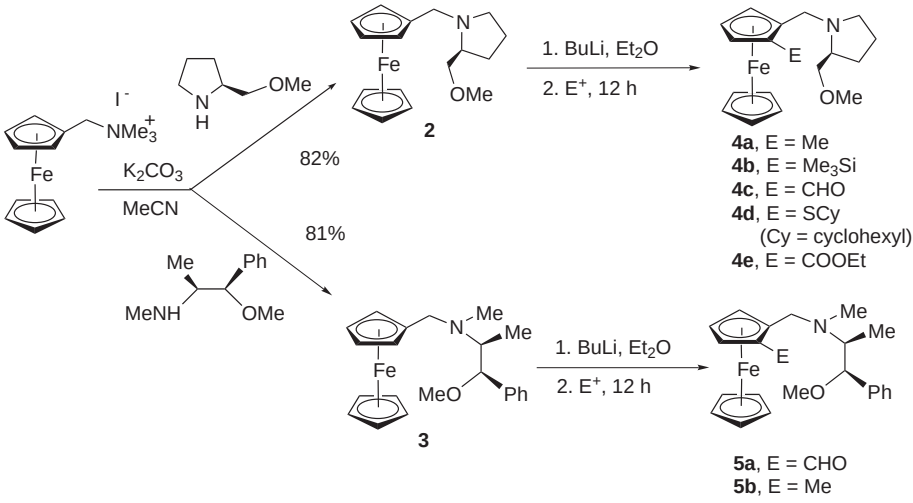
functional groups were introduced in this way into position 2 of ferrocene, with the exception of the formyl group. A very promising method for the synthesis of chiral 2-substituted ferrocenecarbaldehydes was devised by Kagan *et al.*[16,17]. The method is based on the synthesis of ferrocenecarbaldehyde acetals with (*R*)- or (*S*)-butane-1,2,4-triol, followed by *ortho*-metallation and quenching with suitable electrophiles. The following groups were introduced into position 2: Me_3Si, Bu_3Sn, PPh_2, I, Br, COOMe, tosyl, $B(OH)_2$, OH and Me. 2-Acylferrocenecarbaldehydes can be prepared either by Ender's SAMP/RAMP methodology or the Brocard's oxidative approach[3]. In the former, acylferrocenes are converted into their hydrazones by the reaction with (*S*)- or (*R*)-1-amino-2-methoxymethylpyrrolidine[18,19]. The hydrazones are *ortho*-metalated with *n*-BuLi followed by quenching with DMF, and deprotection of the acyl group is the final operation. The latter possibility is the Brocard's oxidative approach[3], where the chiral 1-[1-(dimethylamino)ethyl]ferrocenes are *ortho*-metalated with *n*-BuLi, the anions subsequently quenched with DMF and the resultant chiral 1-(dimethylamino)-ethyl-2-formylferrocenes oxidised by active MnO_2.

The main aim of this work was to explore the applicability of this methodology of the synthesis of chiral 1,2-disubstituted ferrocenes based on {[*N*-((1*R*,2*S*)-methoxy-1-methyl-2-phenethyl)-*N*-methylamino]methyl}ferrocene (**3**)[11,12], and (*S*)-{[2-(methoxymethyl)pyrrolidin-1-yl]methyl}ferrocene (**2**)[13,14] to the synthesis of new chiral derivatives. Another aim was to examine the possibility of oxidative transformation of the alkylamino moiety into the formyl group, which would lead to new chiral 2-substituted ferrocenecarbaldehydes.

RESULTS AND DISCUSSION

The starting amines **2** and **3** were smoothly prepared without any problems according to the published procedure[11–13]. According to literature reports[11–13], *sec*- or *tert*-butyllithium should have been used for their metallation, but we checked both *n*-butyllithium and *sec*-butyllithium as the metallation agents (Scheme 1, Table I).

The results given in Table I show that *n*-butyllithium (method *A*) is better than *sec*-butyllithium (method *B*) for the metallation of **2**, because it allowed us to work at –30 °C and gave good yields (56–92%) of the products with high de (95–97%). On the other hand, in the metallation of **3**, it is necessary to work with *sec*-butyllitthium at –70 °C (method *B*): the use of *n*-butylllithium (method *A*) resulted in low de of the products (11%) even though the yield was good (72%).



SCHEME 1

TABLE I
Ortho-substitutions of ferrocenylamines **2** and **3**

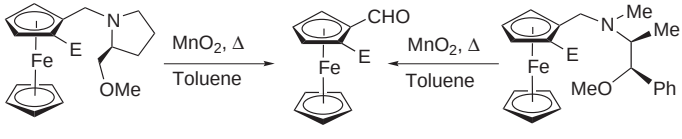
Entry	Substrate	R	Method[a]	Yield, %[b]	de, %[c]	Product[d]
1	(*S*)-**2**	Me	*B*	37.3	99	(S,R_p)-**4a**
2	(*S*)-**2**	Me	*A*	64.1	97	(S,R_p)-**4a**
3	(*S*)-**2**	Me_3Si	*A*	67.3[e]	97	(S,S_p)-**4b**
4	(*S*)-**2**	CHO	*A*	83.0	94	(S,S_p)-**4c**
5	(*S*)-**2**	SCy [e]	*A*	55.9	96	(S,S_p)-**4d**
6	(*S*)-**2**	COOEt	*A*	73.9	91	(S,S_p)-**4e**
7	(*S*)-**2**	COOEt	*B*	68.3	72	(S,S_p)-**4e**
8	(1*R*,2*S*)-**3**	CHO	*A*	72.0	11	(1*R*,2*S*,R_p)-**5a**
9	(1*R*,2*S*)-**3**	CHO	*B*	69.8	96	(1*R*,2*S*,S_p)-**5a**
10	(1*R*,2*S*)-**3**	Me	*B*	91.6	97	(1*R*,2*S*,R_p)-**5b**
11	(1*R*,2*S*)-**3**	SH	*B*	0[g]	–	–

[a] *n*-BuLi was used as metallation agent in method *A* and *sec*-BuLi in method *B*. [b] Isolated yield of diastereomeric mixture. [c] By ^{1}H NMR, see Experimental. [d] Configuration according to the literature. [e] Literature[13] gives 88% yield, 93% de. [f] Cy = cyclohexyl. [g] Conversion was 42%, it was not possible to analyze the product mixture.

Metallation with *sec*-butyllithium resulted in 96–97% de of the products. Through the metallation of **2** and subsequent quenching with methyl iodide, trimethylsilyl chloride, DMF, dicyclohexyl disulfide and ethyl chloroformate, we prepared derivatives with Me, TMS, CHO, SCy (Cy = cyclohexyl) and COOEt group as the substituents. The attempt to prepare the thiol derivative failed, as the product was extremely air-sensitive, and a complex mixture of products was formed.

Chiral 2-substituted ferrocenecarbaldehydes are useful intermediates for the production of chiral amino alcohols, which can be used as catalysts in R_2Zn addition to the carbonyl group of aldehydes. As there is just a few papers, describing the preparation of chiral 2-substituted ferrocenecarbaldehydes[6,7,17,18], we decided to examine the possibility of the transformation of 2-substituted amine derivatives **4a**–**4e**, **5a**, **5b** into the corresponding 2-substituted ferrocenecarbaldehydes **7a**–**7c** *via* oxidation.

The oxidation was performed with freshly prepared[20] active MnO_2 (Scheme 2), and the procedure was tested on simple amines **2** and **3**. The oxidation proceeded smoothly and, after 24 h, ferrocenecarbaldehyde was isolated in 78% yield. No attempts were made to recover the chiral auxilliaries. The results of the oxidations yielding chiral 2-substituted ferrocenecarbaldehydes (Table II) proved that this is a feasible route towards their preparation.



2, E = H
4a, E = Me
4b, E = Me_3Si
4d, E = SCy (Cy = cyclohexyl)

6, E = H
7a, E = Me
7b, E = Me_3Si
7c, E = SCy (Cy = cyclohexyl)

3, E = H
5b, E = Me

SCHEME 2

TABLE II
Oxidations of ferrocenylamines **2**–**5**

Entry	Substrate	Reaction time, h	Yields, %	Product
1	(*S*)-**2**	18	77.9	**6**
2	(1*R*,2*S*)-**3**	24	91.4	**6**
3	(S,R_p)-**4a**	40	59.2	(R_p)-**7a**
4	(S,S_p)-**4b**	40	54.0	(S_p)-**7b**
5	(S,S_p)-**4d**	20	49.0	(S_p)-**7c**
6	(1*R*,2*S*,R_p)-**5b**	20	83.7	(R_p)-**7a**

In conclusion, we have demonstrated that *n*-BuLi can be used as the metallation agent for the metallation of ferrocenylamines, and 2-substituted ferrocenylamine derivatives can be oxidised without loss of de into the corresponding chiral 2-substituted ferrocenecarbaldehydes by the Brocard's method[3]. This can be used as an alternative to Kagan's method[16,17].

EXPERIMENTAL

General Methods

Melting points were determined on a Kofler melting point apparatus and are uncorrected. ^{1}H (200 MHz) and ^{13}C (75 MHz) NMR spectra were recorded at room temperature in $CDCl_3$ on a Varian Gemini 2000 spectrometer. Chemical shifts (δ-scale) are reported in ppm relative to tetramethylsilane as the internal standard, coupling constants (*J*) are given in Hz. IR spectra (wavenumbers in cm^{-1}) were recorded in $CHCl_3$ as a solvent on a Perkin Elmer 781 spectrometer. UV-VIS spectra were recorded in methanol on a Hewlett Packard 8452A spectrometer (λ, nm). Optical rotations were measured on a Perkin Elmer 241 polarimeter at 20 °C in ethanol; $[\alpha]_D$ values given in 10^{-1} deg cm^2 g^{-1}. The diastereomeric excess of amines was determined using ^{1}H NMR on the basis of the integral ratio of the following chemical shifts: **4a** and **5b** δ of the CH_3 group, **4b** δ of the $SiMe_3$ group, **4c** and **5a** δ of the CHO group, **4d** δ of the CH_3 from the ethyl group and **4d** δ of the OCH_3 group. All reactions requiring inert conditions were carried out under nitrogen. Diethyl ether was dried and distilled from sodium/benzophenone ketyl under nitrogen, acetonitrile was distilled from calcium hydride and toluene was distilled over sodium under nitrogen before use. Ferrocenylmethyl-*N*,*N*,*N*-trimethylammonium iodide was prepared by Kindsay's method[21]. Active MnO_2 was prepared prior to use according to the literature procedure[20]. (1*R*,2*S*)-1-Methoxy-*N*-methyl-1-phenylpropan-2-amine was prepared according to ref.[22] Chromatographic separations were performed either on silica gel (Merck 60) or alumina (Lachema, activity II–III). The chemicals were purchased from Aldrich or Merck.

Preparation of Derivatives **2** and **3**. General Procedure[12,13]

A mixture of (ferrocenylmethyltrimethyl)ammonium iodide (6.00 g, 15.6 mmol), an amine (16.2 mmol) and K_2CO_3 (4.34 g, 31.4 mmol) in acetonitrile (200 ml) was heated at reflux under nitrogen for 2 or 4 days. After filtration, the solvent was removed and the residue stirred with a mixture of Et_2O (200 ml), water (100 ml) and 85% H_3PO_4 (20 ml) for 5 min. The water layer was washed with diethyl ether, alkalized with solid Na_2CO_3, and extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated. The product was purified by chromatography on a short alumina column (hexane).

(S)-{[2-(Methoxymethyl)pyrrolidin-1-yl]methyl}ferrocene (**2**). (*S*)-**2** was obtained as an orange oil after 2 days (4.0 g; 82%), which is in accord with ref.[13]. ^{1}H NMR ($CDCl_3$): 1.54–1.73 m, 3 H ($NCH_2C\mathbf{H}_2C\mathbf{H}_2$); 1.81 m, 1 H ($NCH_2C\mathbf{H}_2$); 2.25 ddd, 1 H, ^2J = 9.4, ^3J = 9.2, 7.1 (NCH_2); 2.62 m, 1 H (NCH); 2.93 ddd, 1 H, ^2J = 9.4, ^3J = 7.0, 1.8 (NCH_2); 3.23 dd, 1 H, ^2J = 9.4, ^3J = 6.4 (OCH_2); 3.34 s, 3 H (OCH_3); 3.35 dd, 1 H, ^2J = 9.4, ^3J = 4.9 (OCH_2); 3.41 d, 1 H, ^2J = 13.1

($FcCH_2$); 3.75 d, 1 H, ^2J = 13.1 ($FcCH_2$); 4.09 m, 2 H (H_β); 4.11 s, 5 H (C_5H_5); 4.16 m, 1 H ($H_{\alpha1}$); 4.18 m, 1 H ($H_{\alpha2}$). $[\alpha]_D$ –58.7 (589), –61.3 (578), –69.5 (546) (*c* 0.62, EtOH).

{[N-((1R,2S)-Methoxy-1-methyl-2-phenethyl)-N-methylamino]methyl}ferrocene (**3**). (1*R*,2*S*)-**3** was obtained as a yellow solid after 4 days (4.8 g; 81%). M.p. 44–46 °C, in accord with ref.[11]. ^{1}H NMR ($CDCl_3$): 1.00 d, 3 H, ^3J = 6.8 (CHC**H**$_3$); 2.25 s, 3 H (NCH_3); 2.82 dq, 1 H, ^3J = 5.1, 6.8 (NCH); 3.25 s, 3 H (OCH_3); 3.41 d, 1 H, ^2J = 12.9 (CH_2); 3.50 d, 1 H, ^2J = 12.9 (CH_2); 4.07 m, 4 H (C_5H_4); 4.08 s, 5 H (C_5H_5); 4.29 d, 1 H, ^3J = 5.1 (C**H**Ph); 7.20–7.24 m, 3 H (Ph); 7.27–7.34 m, 2 H (Ph). $[\alpha]_D$ –13.5 (589), –13.7 (578), –14.4 (546) (*c* 0.54, EtOH).

Preparation of Compounds **4a**–**4e** and **5a**, **5b**

Method A. To a solution of amine 2 or 3 (200 mg, 0.64 mmol) in anhydrous Et_2O (2 ml) was added dropwise 1.6 M solution of *n*-BuLi (0.45 ml, 0.71 mmol, 1.1 equiv.) under nitrogen at –78 °C. The reaction mixture was stirred at –30 °C for 2.5 h and then at 20 °C for 2 h. The mixture was cooled to –55 °C and an electrophile (0.71 mmol, 1.1 equiv.) was added dropwise. The mixture was allowed to warm to room temperature over 12 h. After the reaction was quenched with aqueous $NaHCO_3$, the organic layer was separated and the water layer extracted with Et_2O. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated. The crude product was purified by chromatography.

Method B. The same as method *A*; 1.3 M solution of *sec*-BuLi was used instead of *n*-BuLi, the mixture was stirred at –78 °C for 1.5 h and then at –30 °C for 2 h. Electrophiles were added at –78 °C.

(S,R$_p$)-1-{[2-(Methoxymethyl)pyrrolidin-1-yl]methyl}-2-methylferrocene (**4a**). (*S*,*R*$_p$)-**4a** was obtained as an orange oil after chromatography on silica with isohexane/Et_2O (3:1). Method *A* with MeI as the electrophile gave the product in 64% yield (>99% de); method *B* in 37% yield (97% de). ^{1}H NMR ($CDCl_3$): 1.50–1.72 m, 3 H ($NCH_2C\mathbf{H}_2C\mathbf{H}_2$); 1.83 m, 1 H ($NCH_2C\mathbf{H}_2$); 2.00 s, 3 H (FcC**H**$_3$); 2.18 ddd, 1 H, ^2J = 9.4, ^3J = 9.3, 7.3 (NCH_2); 2.67 m, 1 H (NCH); 2.95 ddd, 1 H, ^2J = 9.4, ^3J = 7.8, 2.0 (NCH_2); 3.26 dd, 1 H, ^2J = 9.4, ^3J = 6.4 (OCH_2); 3.37 s, 3 H (OCH_3); 3.31 d, 1 H, ^2J = 12.9 (FcC**H**$_2$); 3.40 dd, 1 H, ^2J = 9.4, ^3J = 4.5 (OCH_2); 3.93 d, 1 H, ^2J = 12.9 (FcC**H**$_2$); 3.96 m, 1 H ($H_{\alpha1}$); 4.01 s, 5 H (C_5H_5); 4.04 m, 2 H (H_β); 4.08 m, 1 H ($H_{\alpha2}$). ^{13}C NMR ($CDCl_3$): 13.6 (Fc**C**H$_3$), 22.9 ($NCH_2\mathbf{C}H_2$), 28.8 ($NCH_2CH_2\mathbf{C}H_2$), 52.5 (Fc**C**H$_2$), 54.5 (NCH_2), 59.3 (OCH_3), 62.2 (NCH), 65.7 ($CH_{\alpha1}$), 69.2 (C_5H_5), 69.78 ($CH_{\alpha2}$), 69.83 (CH_β), 76.9 (C_i), 77.2 (CH_2O), 84.1 (C_i). IR ($CHCl_3$): 2810 (w), 2430 (w), 1470 (m), 1230 (s), 1120 (s, C–O–C), 1010 (w), 830 (m). UV VIS, λ (log ε): 206 (3.41). For $C_{18}H_{25}FeNO$ (326.5) calculated: 66.07% C, 7.70% H, 4.28% N; found: 65.79% C, 7.80% H, 4.08% N. $[\alpha]_D$ –34.6 (*c* 0.615, EtOH).

(S,S$_p$)-1-{[2-(Methoxymethyl)pyrrolidin-1-yl]methyl}-2-(trimethylsilyl)ferrocene (**4b**). (*S*,*S*$_p$)-**4b** was obtained by method *A* with Me_3SiCl as the electrophile, chromatography on silica with isohexane/Et_2O (1:1) gave the product as an orange oil in accord with ref.[13] (67%, 97% de). ^{1}H NMR ($CDCl_3$): 0.28 s, 9 H ($Si(CH_3)_3$); 1.46–1.64 m, 3 H ($NCH_2C\mathbf{H}_2C\mathbf{H}_2$); 1.86 m, 1 H ($NCH_2C\mathbf{H}_2$); 2.01 m, 1 H ($NCH_2$); 2.57 m, 1 H (NCH); 2.71 m, 1 H (NCH_2); 3.07 d, 1 H, ^2J = 12.6 (FcC**H**$_2$); 3.23 dd, 1 H, ^2J = 9.0, ^3J = 6.3 (OCH_2); 3.36 s, 3 H (OCH_3); 3.47 dd, 1 H, ^2J = 9.0, ^3J = 5.1 (OCH_2); 4.01 d, 1 H, ^2J = 12.0 (FcC**H**$_2$); 4.03 m, 1 H ($H_{\alpha1}$); 4.08 s, 5 H (C_5H_5); 4.21 m, 2 H (H_β); 4.27 m, 1 H ($H_{\alpha2}$). IR ($CHCl_3$): 2800 (w), 2420 (w), 1260 (s), 1120 (m, C–O–C), 850 (s). UV VIS, λ (log ε): 208 (3.59). For $C_{20}H_{31}FeNOSi$ (388.6) calculated:

62.32% C, 8.11% H, 3.63% N; found: 62.40% C, 8.29% H, 3.46% N. $[\alpha]_D$ –41.0 (*c* 0.485, EtOH).

(S,S$_p$)-2-{[2-(Methoxymethyl)pyrrolidin-1-yl]methyl}ferrocene-1-carbaldehyde (**4c**). (*S*,*S*$_p$)-**4c** was obtained by method *A* with DMF as the electrophile, chromatography on alumina with isohexane/Et_2O (2:1) gave the product as a red oil (83%, 94% de). ^{1}H NMR ($CDCl_3$): 1.51–1.72 m, 3 H ($NCH_2C\mathbf{H}_2C\mathbf{H}_2$); 1.85 m, 1 H ($NCH_2C\mathbf{H}_2$); 2.19 m, 1 H ($NCH_2$); 2.70 m, 1 H (NCH); 2.96 m, 1 H (NCH_2); 3.30 dd, 1 H, ^2J = 9.0, ^3J = 5.4 (OCH_2); 3.38 d, 1 H, ^2J = 12,2 (Fc$C\mathbf{H}_2$); 3.39 s, 3 H (OCH_3); 3.46 dd, 1 H, ^2J = 9.0, ^3J = 5.7 (OCH_2); 4.22 s, 5 H (C_5H_5); 4.37 (d, 1 H, ^2J = 12.2 (Fc$C\mathbf{H}_2$); 4.53 m, 1 H ($H_{\alpha1}$); 4.58 m, 2 H (H_β); 4.79 m, 1 H ($H_{\alpha2}$); 10.14 s, 1 H (CHO). ^{13}C NMR ($CDCl_3$): 23.0 ($NCH_2\mathbf{C}H_2$), 28.68 ($NCH_2CH_2\mathbf{C}H_2$), 52.2 (Fc$\mathbf{C}H_2$), 54.6 (NCH_2), 59.3 (OCH_3), 62.4 (NCH), 69.9 ($CH_{\alpha1}$), 70.3 (C_5H_5), 71.8 ($CH_{\alpha2}$), 75.8 (CH_β), 77.0 (C_i), 77.2 (CH_2O), 77.9 (C_i), 193.9 (CHO). IR ($CHCl_3$): 2420 (w), 1680 (s, C=O), 1230 (s), 760 (m). UV VIS, λ (log ε): 202 (3.43). For $C_{18}H_{23}FeNO_2$ (340.4) calculated: 63.36% C, 6.79% H, 4.10% N; found: 63.28% C, 6.85% H, 4.01% N. $[\alpha]_D$ –229.7 (589), –262.1 (578), –267.2 (546) (*c* 0.195, EtOH).

(S,S$_p$)-1-(Cyclohexylsulfanyl)-2-{[2-(methoxymethyl)pyrrolidin-1-yl]methyl}ferrocene (**4d**). (*S*,*S*$_p$)-**4d** was obtained by method *A* with biscyclohexyl disulfide, chromatography on alumina with isohexane/Et_2O (1:1) gave the product as yellow crystals (56%, 96% de). M.p. 40–45 °C. ^{1}H NMR ($CDCl_3$): 1.07–1.30 m, 4 H (**Cyclohexyl**); 1.55–1.80 m, 8 H (**Cyclohexyl** + $NCH_2CH_2C\mathbf{H}_2$); 1.91 m, 2 H ($NCH_2C\mathbf{H}_2$); 2.11 m, 1 H (NCH_2); 2.65 m, 1 H (NCH); 2.86 m, 1 H (NCH_2); 2.93 m, 1 H (SCH); 3.11 d, 1 H, ^2J = 12.3 (Fc$C\mathbf{H}_2$); 3.18 dd, 1 H, ^2J = 9.0, ^3J = 7.8 (OCH_2); 3.39 s, 3 H (OCH_3); 3.59 dd, 1 H, ^2J = 9.0, ^3J = 4.2 (OCH_2); 4.09 s, 5 H (C_5H_5); 4.12 m, 1 H (H_β); 4.17 d, 1 H, ^2J = 12.3 (Fc$C\mathbf{H}_2$); 4.27 m, 2 H (H_α). ^{13}C NMR ($CDCl_3$): 23.1 ($NCH_2\mathbf{C}H_2$), 26.1 (**Cyclohexyl**), 26.6 ($NCH_2CH_2\mathbf{C}H_2$), 29.4 (**Cyclohexyl**), 33.1 (**Cyclohexyl**), 34.1 (**Cyclohexyl**), 47.8 (SCH), 53.1 (Fc$\mathbf{C}H_2$), 54.4 (NCH_2), 59.3 (OCH_3), 63.3 (NCH), 67.5 ($CH_{\alpha1}$), 70.1 (C_5H_5), 71.4 ($CH_{\alpha2}$), 75.7 (CH_β), 77.0 (C_i), 77.2 (CH_2O), 78.7 (C_i). IR ($CHCl_3$): 2800 (m, O–CH_3), 2430 (w), 1460 (s), 1230 (s), 1120 (s), 1010 (m), 830 (m). UV VIS, λ (log ε): 208 (3.64). For $C_{23}H_{33}FeNOS$ (426.6) calculated: 64.63% C, 7.78% H, 3.28% N; found: 64.70% C, 7.84% H, 3.04% N. $[\alpha]_D$ +3.37 (*c* 0.51, EtOH).

Ethyl (S,S$_p$)-2-{[2-(methoxymethyl)pyrrolidin-1-yl}methyl]ferrocene-1-carboxylate (**4e**). (*S*,*S*$_p$)-**4e** was obtained with ethyl chloroformate after chromatography on alumina with isohexane/Et_2O (3:1) as a red oil. Method *A* gave the product in 74% yield (91% de); method *B* in 68% yield (72% de). ^{1}H NMR ($CDCl_3$): 1.37 t, 3 H, ^3J = 7.2 ($CH_2C\mathbf{H}_3$); 1.57–1.77 m, 3 H ($NCH_2CH_2C\mathbf{H}_2$); 1.86 m, 1 H ($NCH_2C\mathbf{H}_2$); 2.24 m, 1 H ($NC\mathbf{H}_2$); 2.72 m, 1 H (NCH); 3.06 m, 1 H (NCH_2); 3.26 dd, 1 H, ^2J = 9.0, ^3J = 7.2 (OCH_2); 3.36 d, 1 H, ^2J = 12.2 (Fc$C\mathbf{H}_2$); 3.37 s, 3 H (OCH_3); 3.53 dd, 1 H, ^2J = 9.0, ^3J = 4.5 (OCH_2); 4.14 s, 5 H (C_5H_5); 4.28 q, 2 H, ^3J = 7.2 ($C\mathbf{H}_2CH_3$); 4.32 m, 1 H ($H_{\alpha1}$); 4.47 m, 1 H (H_β); 4.53 d, 1 H, ^2J = 12.2 (Fc$C\mathbf{H}_2$); 4.79 m, 1 H ($H_{\alpha2}$). ^{13}C NMR ($CDCl_3$): 14.9 ($CH_2\mathbf{C}H_3$), 22.9 ($NCH_2\mathbf{C}H_2$), 28.8 ($NCH_2CH_2\mathbf{C}H_2$), 52.1 (Fc$\mathbf{C}H_2$), 54.4 (NCH_2), 59.3 (OCH_3), 60.1 ($\mathbf{C}H_2CH_3$), 62.2 (NCH), 70.0 ($CH_{\alpha1}$), 70.5 (C_5H_5), 71.4 (CH_β), 74.7 ($CH_{\alpha2}$), 76.2 (C_i), 77.2 (CH_2O), 77.7 (C_i), 172.0 (COO). IR ($CHCl_3$): 2420 (w), 1720 (m, C=O), 1230 (s), 780 (m). UV VIS, λ (log ε): 209 (3.40). For $C_{20}H_{27}FeNO$ (352.5) calculated: 62.35% C, 7.06% H, 3.64% N; found: 62.14% C, 7.04% H, 3.24% N. $[\alpha]_D$ –92.5 (589), –99.3 (578), –123.5 (546) (*c* 0.575, EtOH).

(1R,2S,S$_p$)-{N-[(2-Methoxy-1-methyl-2-phenethyl)-N-methylamino]methyl}ferrocene-1-carbaldehyde (**5a**). (1*R*,2*S*,*S*$_p$)-**5a** was obtained with DMF as the electrophile after chromatography on alumina with isohexane/Et_2O (3:1) as a red oil. Method *A* gave the product in 72% yield (11% de); method *B* in 70% yield (96% de). ^{1}H NMR ($CDCl_3$): 1.06 d, 3 H, ^3J = 6.7 (CHC$\mathbf{H}_3$);

2.18 s, 3 H (NCH_3); 2.82 dq, 1 H, ^3J = 5.6, 6.7 (NCH); 3.23 s, 3 H (OCH_3); 3.48 d, 1 H, ^2J = 12.9 (CH_2); 3.84 d, 1 H, ^2J = 12.9 (CH_2); 4.18 s + d, 6 H (C**H**Ph + C_5H_5); 4.42 m, 1 H ($H_{\alpha1}$); 4.47 m, 1 H (H_β); 4.73 m, 1 H ($H_{\alpha2}$); 7.16–7.35 m, 5 H (Ph); 9.83 s, 1 H (CHO). ^{13}C NMR ($CDCl_3$): 8.9 (CH**C**H_3), 36.9 (NCH_3), 52.5 (CH_2), 56.9 (OCH_3), 63.8 (NCH), 69.1 ($CH_{\alpha1}$), 70.3 (C_5H_5), 71.6 (CH_β), 75.7 ($CH_{\alpha2}$), 77.2 (C_i), 77.8 (C_i), 86.0 (**C**HPh), 127.2 + 127.4 + 128.3 (Ph), 141.5 (C_5H_5), 193.7 (CHO). IR ($CHCl_3$): 2420 (m), 1690 (s, C=O), 1230 (s), 820 (s). UV VIS, λ (log ε): 204 (3.51). For $C_{23}H_{27}FeNO_2$ (404.5) calculated: 68.16% C, 6.71% H, 3.46% N; found: 68.05% C, 6.81% H, 3.07% N. $[\alpha]_D$ –233 (589), –261 (578), –353 (546) (*c* 0.165, EtOH).

(1R,2S,R$_p$)-{N-[(2-Methoxy-1-methyl-2-phenethyl)-N-methylamino]methyl}-1-methylferrocene (**5b**). (1*R*,2*S*,*R*$_p$)-**5b** was obtained with MeI as electrophile as an orange oil by method *B*, chromatography on alumina with isohexane/Et_2O (1:1) (92%, 97% de). ^{1}H NMR ($CDCl_3$): 1.05 d, 3 H, ^3J = 6.6 (CHC**H**$_3$); 1.77 s, 3 H (FcC**H**$_3$); 2.15 s, 3 H (NCH_3); 2.82 dq, 1 H, ^3J = 6.0, 6.6 (NCH); 3.23 s, 3 H (OCH_3); 3.34 d, 1 H, ^2J = 12.6 (CH_2); 3.49 d, 1 H, ^2J = 12.6 (CH_2); 3.90 m, 1 H ($H_{\alpha1}$); 3.94 m, 1 H (H_β); 3.97 s + d, 6 H (C**H**Ph + C_5H_5); 4.19 m, 1 H ($H_{\alpha2}$); 7.20–7.25 m, 3 H (Ph); 7.28–7.33 m, 2 H (Ph). ^{13}C NMR ($CDCl_3$): 8.7 (CH**C**H_3), 13.4 (**C**H_3Fc), 37.1 (NCH_3), 52.8 (CH_2), 56.9 (OCH_3), 63.4 (NCH), 68.7 ($CH_{\alpha1}$), 69.2 (C_5H_5), 69.6 (CH_β), 70.0 ($CH_{\alpha2}$), 77.2 (C_i), 77.8 (C_i), 84.3 (**C**HPh), 127.2 + 127.3 + 128.2 (Ph), 141.7 (C_i). IR ($CHCl_3$): 2420 (w), 1470 (w), 1230 (s), 1100 (m, C–O–C), 780 (s). UV VIS, λ (log ε): 206 (3.67). For $C_{23}H_{29}FeNO$ (390.5) calculated: 70.59% C, 7.47% H, 3.58% N; found: 70.80% C, 7.91% H, 3.20% N. $[\alpha]_D$ –25.1 (589), –27.1 (578), –36.7 (546) (*c* 0.54, EtOH).

Oxidation of Amines. General Method[3]

To a solution of ferrocenylmethylamine (32 mmol) in anhydrous toluene (5 ml) was added active MnO_2 (3.2 mmol, 10 equiv.). The mixture was heated at reflux under nitrogen for 18–40 h and the progress of the reaction was monitored by TLC. After the reaction mixture was cooled down to room temperature, the unreacted MnO_2 was filtered off, the solvent removed by evaporation and the residue purified by chromatography on alumina using isohexane/diethyl ether (4:1–2:1) as the eluent.

Ferrocenecarbaldehyde (**6**). Compound **6** was obtained in 18 h from (*S*)-**2** as red crystals (78%) and in 24 h from (1*R*,2*S*)-**3** (91%). M.p. 121–123 °C; ref.[25] gives 124.5 °C. ^{1}H NMR ($CDCl_3$): 4.28 s, 5 H (C_5H_5); 4.61 m, 2 H (H_β); 4.80 m, 2 H (H_α); 9.96 s, 1 H (CHO).

(R$_p$)-2-Methylferrocene-1-carbaldehyde **7a**. (*R*$_p$)-**7a** was obtained in 40 h from **4a** as red crystals (59%) after chromatography on silica with isohexane/Et_2O (3:1) and in 20 h from **5b** (84%). M.p. 40–42 °C, in accord with ref.[17]. ^{1}H NMR ($CDCl_3$): 2.26 s, 3 H (CH_3); 4.20 s, 5 H (C_5H_5); 4.46 m, 1 H ($H_{\alpha2}$); 4.50 m, 1 H (H_β); 4.70 m, 1 H ($H_{\alpha1}$); 10.10 s, 1 H (CHO). ^{13}C NMR ($CDCl_3$): 29.7 (CH_3), 69.5 (C_5H_3), 70.2 (C_5H_5), 71.0 (C_5H_3), 75.0 (C_5H_3), 77.0 (C_i), 87.1 (C_i), 193.9 (CHO). IR ($CHCl_3$): 2420 (w), 1680 (s, C=O), 1440 (m), 1220 (m), 1040 (w), 840 (m), 750 (s). UV VIS, λ (log ε): 202 (3.24). For $C_{12}H_{12}FeO$ (227.3) calculated: 63.20% C, 5.30% H; found: 63.17% C, 5.42% H. $[\alpha]_D$ 146 (589), 169 (578), 160 (546) (*c* 0.10, EtOH); ref.[20] gives $[\alpha]_D$ +147.8 ± 8 (*c* 0.76, EtOH).

(S$_p$)-2-(Trimetylsilyl)ferrocene-1-carbaldehyde **7b**. (*S*$_p$)-**7b** was obtained in 40 h from (*S*,*S*$_p$)-**4b**. Chromatography on silica with isohexane/Et_2O (6:1) gave the product as red crystals (54%). M.p. 60–65 °C, in accord with ref.[17]. ^{1}H NMR ($CDCl_3$): 0.32 s, 9 H ($Si(CH_3)_3$); 4.26 s, 5 H (C_5H_5); 4.53 m, 1 H ($H_{\alpha1}$); 4.72 m, 1 H (H_β); 4.99 m, 1 H ($H_{\alpha2}$); 10.03 s, 1 H (CHO). ^{13}C NMR ($CDCl_3$): 0.003 ($Si(CH_3)_3$), 69.2 (C_5H_5), 73.2 (C_5H_3), 74.3 (C_5H_3), 74.6 (C_i), 79.3

(C_5H_3), 77.0 (C_i), 193.9 (CHO). IR ($CHCl_3$): 2420 (w), 1680 (s, C=O), 1440 (m), 1260 (s), 1050 (w), 840 (s, C–Si). UV VIS, λ (log ε): 204 (3.38). For $C_{14}H_{18}FeOSi$ (289.4) calculated: 58.75% C, 6.34% H; found: 58.45% C, 6.20% H. $[\alpha]_D$ –133.3 (*c* 0.09, EtOH); ref.[21] gives $[\alpha]_D$ +194 (*c* 0.28, EtOH); (R_p).

(S_p)-2-(Cyclohexylsulfanyl)ferrocene-1-carbaldehyde **7c**. (S_p)-**7c** was obtained in 20 h from (S,S_p)-**4d**. Chromatography on silica with isohexane/Et_2O (4:1) gave the product as red crystals (49%). M.p. 40–45 °C. ^{1}H NMR ($CDCl_3$): 1.22 m, 2 H (CH_2); 1.59 m, 4 H (CH_2); 1.71 m, 2 H (CH_2); 1.85 m, 2 H (CH_2); 2.59 m, 1 H (CH); 4.28 s, 5 H (C_5H_5); 4.66 t, 1 H, ^3J = 2.5 (H_β); 4.69 dd, 1 H, ^3J = 2.5, 1.6 ($H_{\alpha1}$); 4.96 m, 1 H, ^3J = 2.5, 1.6 ($H_{\alpha2}$); 10.26 s, 1 H (CHO). ^{13}C NMR ($CDCl_3$): 25.7, 26.1, 33.5 (CH_2), 49.2 (CH), 68.9 (C_5H_3), 71.3 (C_5H_5), 73.1 (C_5H_3), 77.0 (**Cyclohexyl**), 80.7 (C_5H_3), 82.0 (**Cyclohexyl**), 194.8 (CHO). IR ($CHCl_3$): 2660 (m), 2400 (w), 1670 (s, C=O), 1420 (m), 1220 (s), 1000 (w), 780 (s). UV VIS, λ (log ε): 202 (3.50). For $C_{17}H_{20}FeOS$ (327.5) calculated: 62.20% C, 6.14% H; found: 61.59% C, 5.77% H. $[\alpha]_D$ 769.7 (589), 887.9 (578), 1193.9 (546) (*c* 0.165, EtOH).

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