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Enantioselective Synthesis of New C_2-Symmetric Ferrocenylalkylamines via Sonochemical Amination of 1-Ferrocenylalkyl Acetates

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Abstract: The synthesis of four new C_2-symmetric ferrocenylalkylamines, (*R,R*)-bis(1-ferrocenyl-ethyl)-amine (**5**), (*R,R*)-*N,N'*-bis-(1-ferrocenyl-ethyl)-ethane-1,2-diamine (**6**), (*R,R*)-2,6-diferrocenyl-piperidine (**7a**), and (*R,R*)-2,5-diferrocenyl-pyrrolidine (**7b**) is described. The syntheses are based on the enantioselective, oxaza-borolidine catalyzed borane reduction of acylferrocenes followed by S_n1 amination, which can be accelerated by ultrasound, as shown for the preparation of (*R*)-1-ferrocenyl-ethylamine (**15**) in greatly improved yield.
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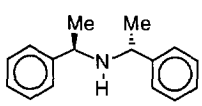
Introduction

C_2-symmetric amines and diamines have proven their great potential for enantioselective synthesis and catalysis as chiral bases, ligands or auxiliary groups[1,2]. As prominent examples, the lithium amides derived from **1**[3] and **2**[4] have been used for enantioselective deprotonations[5]. Other applications involve the use of C_2-symmetric pyrrolidines of type **3** as chiral catalysts or auxiliaries[1b,6]. Only very few chiral piperidines of type **4**, however, have ever been prepared in optically active form[7].



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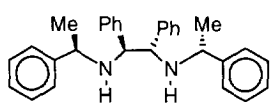

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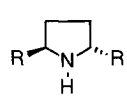

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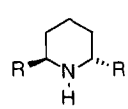

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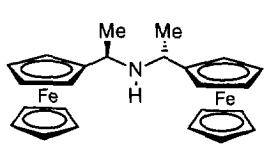
The chemistry of ferrocene offers a number of unique chemical and stereochemical opportunities, and the ferrocene substructure has become a frequently used motive for the design of chiral reagents and catalysts in recent years[8]. Though, only a few chiral C_2-symmetric amines containing the ferrocene moiety have been described[9]. As part of a programme directed towards the development of new chiral reagents and catalysts, we here report on the short and stereoselective synthesis of the four new compounds **5**[10], **6**, **7a** and **7b**.



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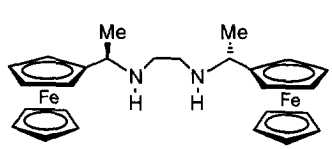

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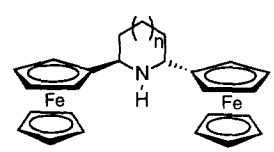
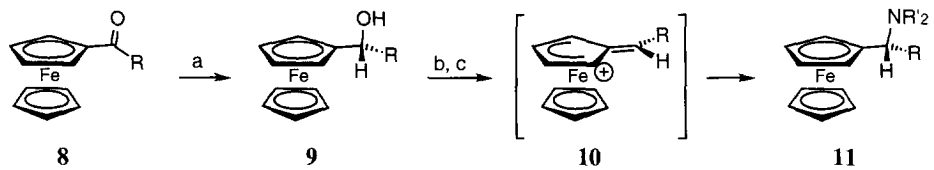


7a: n = 1
7b: n = 0

The general strategy for the preparation of nonracemic 1-ferrocenylalkylamines is shown in Scheme 1. Starting from an acylferrocene derivative **8**, enantioselective reduction leads to an alcohol **9** which is then converted to an amine **11** via O-acetylation and nucleophilic substitution[11]. It is important to note that nucleophilic substitution reactions in α-position of ferrocene derivatives generally occur in an S_N1 fashion with *complete retention of configuration* and proceed via configurationally stable cationic intermediates of type **10** (the iron participates as a neighboring group)[11,12].

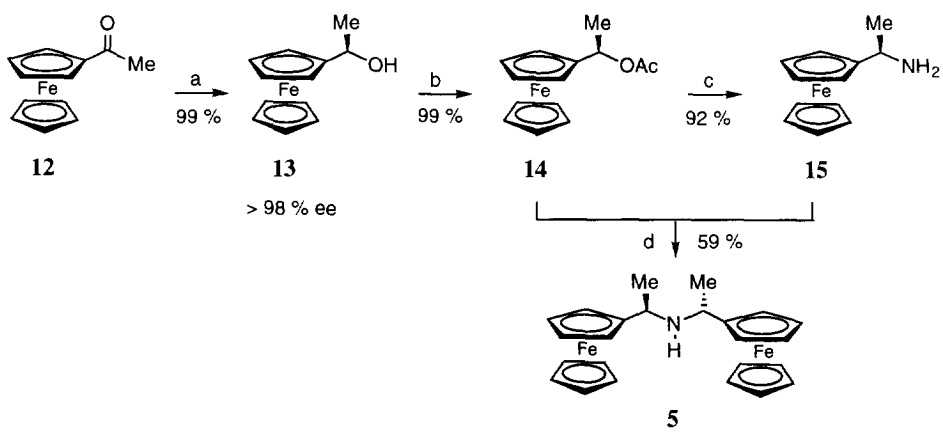
As one of the most useful methods for the enantioselective reduction of prochiral ketones, we employed the oxazaborolidine catalyzed borane reduction (CBS reduction)[13]. The CBS method was first applied to acyl ferrocenes by Wright[14] and later by Hayashi[15], Knochel[16], and Richards[17].



Scheme 1: General procedure for the synthesis of chiral ferrocenylalkylamines of type **11**: a) catalytic enantioselective reduction; b) Ac_2O, Et_3N; c) HNR'_2, Δ.

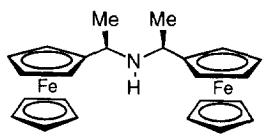
Results and Discussion

The synthesis of the optically active amine **5** is shown in Scheme 2. Firstly, (*R*)-1-ferrocenylethanol (**13**) was obtained in high yield from commercially available acetylferrocene (**12**) by enantioselective reduction with borane-dimethyl sulfide at 0 °C in THF in the presence of 20 mol % of (*S*)-2-methyl-5,5-diphenyl-3,4-propano-1,3,2-oxazaborolidine[14,18]. The enantiomeric purity of crude **13**, determined by HPLC, was 98 % ee and could be further enhanced (> 99 % ee) by a single recrystallization from hexane[19]. When only 10 mol % of the catalyst were employed, the enantiomeric purity of **13** dropped to 83 % ee.



Scheme 2: Synthesis of **5**: a) 1 eq. BH_3-SMe_2, THF, 20 mol % (*S*)-2-methyl-5,5-diphenyl-3,4-propano-1,3,2-oxazaborolidine, 0 °C, 1 h; b) Ac_2O, Et_3N, cat. DMAP, 20 °C, 17 h; c) conc. aq. NH_3, DMF, high intensity ultrasound, 0 °C, 9 h; d) CH_3CN, cat. DMAP, reflux, 30 h.

Acetylation (Ac_2O, Et_3N, cat. DMAP) of **13** then afforded the acetate **14**[11]. The conversion of **14** to (*R*)-1-ferrocenylethylamine (**15**) was initially accomplished in 45 % yield by treatment with aqueous ammonia in methanol following the procedure of Ugi[11] who reported a comparable low yield (40 %). *Nevertheless, the yield of* **15** *could be greatly enhanced (up to 92 %) by reacting* **14** *with aqueous ammonia in DMF under sonochemical conditions (0 °C, 9 h)*[20]. At higher concentration, the sonochemical reaction of **14** with ammonia (5 g of **14** in 30 ml DMF and 50 ml conc. aq. NH_3) at 0 °C for 8 h afforded **15** (75 %) together with significant amounts of **5** (19 %). The latter (desired) compound was prepared in better yield (59 %) by refluxing a 1:1-mixture of **14** and **15** in acetonitrile for 30 h. As expected, **5** was formed as the pure (*R,R*)-diastereomer[21]. In a control experiment, where the racemic building blocks *rac*-**14** and *rac*-**15** were treated in the same manner, a 1:1 mixture of *rac*-**5** and its *meso* diastereomer **16** was formed.



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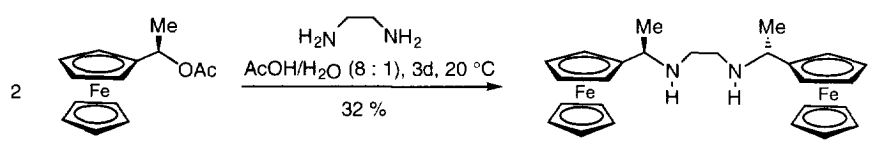
The synthesis of diamine **6** (Scheme 3) was best accomplished in a one-pot procedure by reacting **14** with 0.4 eq. of ethane-1,2-diamine for 72 h in an acetic acid / water (8:1) mixture[22]. It should be noted that these conditions are not equally well suited for related alkylations of other amines. For instance, treatment of **14** with methyl amine under similar conditions afforded the substitution product only in low (16 %) yield. The attempt to use sonochemical conditions (see above) opened an alternative, albeit less efficient access to **6**. In this case, reaction of **14** with 5 equivalents of ethane-1,2-diamine (MeOH / H_2O = 6:1; 50 °C, ultrasound) first afforded the monoalkylated diamine, which was then sonicated together with an other portion of **14** (2.5 eq.) providing **6** in 18 % overall yield.

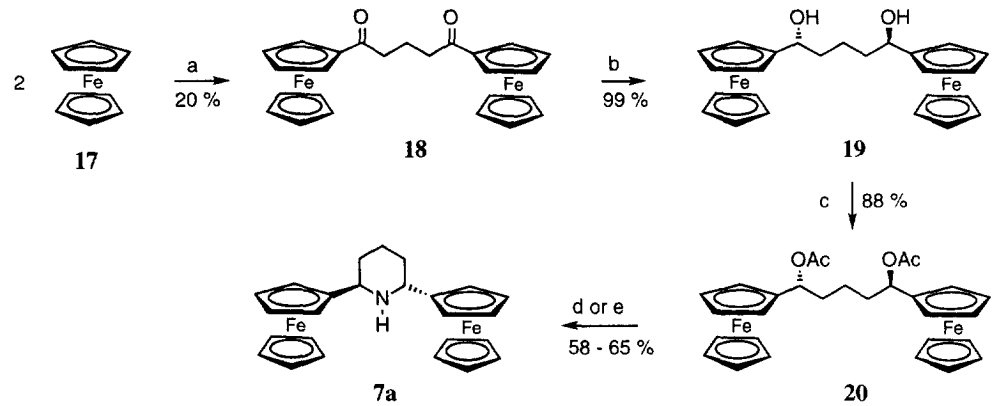


14 **6**

Scheme 3: Synthesis of **6**:

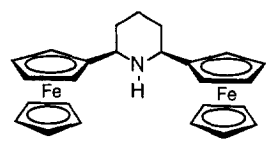
The synthesis of the C_2-symmetric piperidine derivative **7a** (Scheme 4) started with ferrocene (**17**) which was treated with glutaryl dichloride (0.5 equiv.) in the presence of $AlCl_3$ to provide the diketone **18**. Enantioselective reduction of **18** under the CBS conditions afforded the diol **19** which in turn was bis-acetylated to give the cyclization precursor **20**. Refluxing this compound in DMF in the presence of aqueous ammonia for several days afforded the desired C_2-symmetric amine **7a** in 58 % yield. The use of

ultrasound for the amination of **20** (DMF, 0 °C) resulted in much shorter reaction times (7-10 h) and improved yields of **7a** (65 %).



Scheme 4: Synthesis of **7a**: a) glutaryl dichloride, $AlCl_3$, CH_2Cl_2, 16 h, 20 °C; b) 1.2 eq. BH_3-SMe_2, THF, 13 mol % (*S*)-2-methyl-5,5-diphenyl-3,4-propano-1,3,2-oxazaborolidine, 0 °C, 1 h; c) Ac_2O, Et_3N, cat. DMAP, 20 °C, 12 h; d) conc. aq. NH_3, DMF, reflux, 4 d; e) conc. aq. NH_3, DMF, high intensity ultrasound, 0 °C, 7 - 10 h.

When **18** was reduced with sodium borohydride and the resulting 1:1 mixture of diastereomeric alcohols was acetylated and heated with ammonia as before, the two separable diastereomers *rac*-**7a** and the *meso*-compound **21** (1:1) were obtained. In the non-racemic series (see above) **7a** was isolated as the pure *trans*-diastereomer besides only small amounts of **21**. This proves the stereospecifity of the amination step and indicates a high enantiomeric purity of the product. The absolute configuration of **7a** was assigned based on the expected stereochemical outcome of the CBS reduction[13] of **18**.



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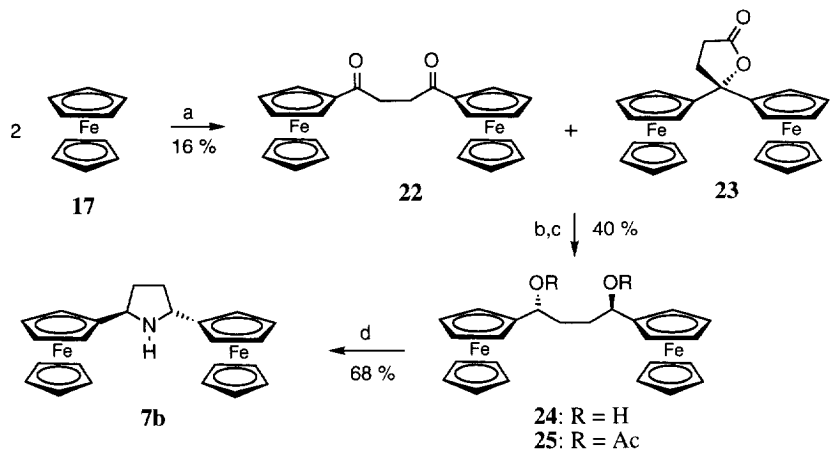
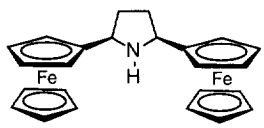
The synthesis of the pyrrolidine derivative **7b**, the lower homologue of **7a**, following the same general strategy turned out to be much more difficult as expected (Scheme 5). Friedel-Crafts acylation of ferrocene with succinyl dichloride (0.5 equiv.) in the presence of $AlCl_3$ only furnished a 1:1-mixture of the diketone **22** and the isomeric lactone **23** in very low yield. When this mixture was subjected to the usual CBS conditions, however, the desired diol **24** could be isolated in 42 % yield besides unchanged **23** after chromatographic separation. Acetylation of **24** under the usual conditions then afforded the diacetate **25**, which on treatment with ammonia under sonochemical conditions (DMF, 0 °C, 9 h) cleanly furnished the chiral pyrrolidine derivative **7b** in 68 % yield, which (in contrast to **7a**) proved to be rather acid-sensitive (decomposition).



Scheme 5: Synthesis of **7b**: a) succinyl dichloride, $AlCl_3$, CH_2Cl_2, 12 h, 20 °C; b) 1.2 eq. BH_3-SMe_2, THF, 13 mol % (*S*)-2-methyl-5,5-diphenyl-3,4-propano-1,3,2-oxazaborolidine, 0 °C, 1 h; c) Ac_2O, Et_3N, cat. DMAP, 20 °C, 12 h; d) conc. aq. NH_3, DMF, high intensity ultrasound, 0 °C, 9 h.

As a side-product, significant amounts (15 %) of the *meso*-diastereoisomer **26** were isolated ($[\alpha]_D = 0°$), which indicates the selectivity of the CBS-reduction of the diketone **22** being lower than in the case of **18**. Nevertheless, due to the fact that two carbonyl groups are (more or less independently) reduced, the enantiomeric excess of the product (**24**) can be estimated to be > 90 % ee.



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Conclusion

The synthetic routes described herein open a short and enantioselective access to the new C_2-symmetric ferrocenylalkylamines **5**, **6**, **7a** and **7b**. It was found that the amination of 1-ferrocenylalkyl acetates with ammonia is best performed sonochemically in DMF / H_2O mixtures at 0 °C. In addition, 1-ferrocenylethylamine (**15**), for which a highly improved (sonochemical) preparation protocol was developed, represents an interesting chiral primary amine related to the well known and often used α–phenylethylamine[23]. Because the oxazaborolidine catalyst employed in the chirogenic steps is available in both enantiomeric forms, the compounds described here (and possibly a number of related ferrocenylalkylamines) can be prepared in any desired absolute configuration. We are optimistic that the work described herein will prove its value for the future development of new chiral reagents or catalysts[24].

EXPERIMENTAL

General Methods: Melting points were measured with a *Büchi 510* apparatus and are uncorrected. FT-IR spectra were recorded with a *Nicolet* Magna FT-IR spectrometer usually using the ATR (attenuated total reflectance) technique. Wavenumbers are quoted in cm^{-1}, abbreviations are: s, strong; m, medium; w, weak and br, broad. NMR spectra were recorded on a Bruker AM 270 or AM 400 spectrometer. All NMR recordings were referenced to the $CHCl_3$ resonances (7.26 and 77.0 ppm). ^1H NMR: splitting patterns abbreviations are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; ψ, pseudo. ^{13}C NMR: multiplicities were determined via DEPT, abbreviations are: q, CH_3; t, CH_2; d, CH; s, quaternary carbons. High resolution mass spectra (HRMS) were obtained with a *Varian* MAT 711 instrument (70 eV). Elemental analyses were performed on a *Perkin-Elmer* CHNO/S-Analysator 2400 II or a *Heraeus* CHN-Rapid instrument. Unless otherwise indicated, optical rotations were measured in $CHCl_3$ (freshly filtered through *ICN* Aluminia B) on a *Perkin-Elmer* 241 polarimeter at 20 °C. Analytical thin layer chromatography (TLC) was performed using Merck Silica 60 F 254 glass plates; the chromatograms were visualized under ultraviolet light and/or by staining with a cerium reagent (prepared by dissolving 2 g of phosphomolybdic acid, 1g cerium(IV)sulfate and 10 ml conc. sulfuric acid in 90 ml H_2O) followed by heating. Flash chromatography[25] was performed using Merck Silica 60 (230 - 400 mesh). The optical purity of alcohol **13** was routinely determined by analytical HPLC on a *Daicel* Chiralcel OJ-column (i-PrOH / hexane = 15:85). Anhydrous THF was freshly distilled from sodium/benzophenone in an argon atmosphere. Methyl tert.-butyl ether is abbreviated as MTBE. Sonochemical transformations were carried out using a Branson Sonifier 250.

(R)-1-Ferrocenylethanol (**13**): All operations were performed in a flame-dried Schlenk-type reaction vessel in an argon atmosphere. A stirred solution of 3.63 g (*S*)-2-methyl-5,5-diphenyl-3,4-propano-1,3,2-oxazaborolidine[18] (13.1 mmol; prepared in the same flask by refluxing a 1:1 mixture of (*S*)-diphenylprolinol and methyl boronic acid in toluene for 65 h under azeotropic removal of water followed by complete removal of the solvent in vacuo) in 20 ml THF was cooled to 0° C and 6.6 ml (13.2 mmol) of a borane-Me_2S solution (2 M in THF) were added. After 5 min, a solution of acetylferrocene (**12**) (15.00 g; 65.76 mmol) in 210 ml THF and, separately, a borane-Me_2S solution (26.4 ml, 52.8 mmol; 2 M in THF) were simultaneously added slowly over a period of 1 h at 0° C. The reaction mixture was then allowed to stir for 1 h at 0° C before it was cautiously quenched with ca. 10 ml MeOH. The solution was concentrated under reduced pressure and the residue purified by flash chromatography (EtOAc/hexane 1:3) to afford 14.97 g (99%) of **13** as an orange solid. The optical purity of this material was 98 % ee (HPLC). An analytical sample was recrystallized from hot hexane to afford orange crystals of >99% ee (HPLC). mp.: 73-74 °C (ref.[11]: 72-73 °C). $[\alpha]_{589}^{20}$ = -28.2 (c = 1.02; C_6H_6) (ref.[11]: $[\alpha]_{589}^{25}$ = -30.5 (c = 1.1; C_6H_6)). TLC: hexane / EtOAc (3:1). ^1H NMR (270 MHz, $CDCl_3$): δ = 1.45 (d, 3H, J = 6.5 Hz), 1.85 (d, 1H, J = 4.5Hz), 4.12 - 4.33 (m, 9H), 4.56 (dq, 1H, J = 4.5 / 6.5 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 23.7 (q), 65.5 (d), 66.0 (d), 66.1 (d), 67.8 (d), 67.9 (d), 68.2 (d), 94.7 (s). IR (ATR): $\tilde{\nu}$ = 3353 (s, br), 3098, 3086, 2973, 2960, 2922 (m), 2870, 1700, 1646 (w), 1456, 1432, 1410, 1377, 1364, 1309, 1234, 1203 (m), 1105, 1093, 1071, 1036, 1023, 1011, 1002 (s), 923 (w), 876 (m), 865, 813 (s), 724 (w). MS (%): 230 (100), 212 (20), 186 (7), 165 (10), 147 (44), 138 (91), 121 (22), 91 (13), 56 (11). HRMS: 230.0394 as calcd for $C_{12}H_{14}FeO$. The racemic compound *rac*-**12** was prepared in analogy to ref.[26] as follows: 8.5 g (223.4 mmol) $NaBH_4$ were added to a stirred solution of 10 g

(43.8 mmol) acetylferrocene (**12**) in 350 ml ethanol / dioxane (4:1). After 2 h at room temperature, the orange mixture was diluted with 500 ml water and extracted with MTBE. The combined organic layers were washed with water and brine, dried with $MgSO_4$, filtered and concentrated in vacuo to yield 9.97 g (98 %) of *rac*-**13** as an orange solid (mp.: 75 °C ; ref.[27]: 78 °C).

(R)-1-Ferrocenylethyl acetate (**14**)**:** Following the procedure of Ugi[11], 2.6 ml (27.6 mmol) Ac_2O and a catalytic amount of DMAP were added to a stirred solution of 1.26 g (5.48 mmol) (*R*)-1-ferrocenylethanol (**13**) in 10 ml of freshly distilled triethylamine. After stirring for 17 h at room temperature, the orange solution was partitioned between water and EtOAc. The combined organic layers were washed with brine and dried with Na_2SO_4. The oily residue obtained after solvent evaporation was crystallized from hot hexane to give 1.495 g (99 %) of the pure acetate **14** as orange plates; mp.: 71 °C (ref.[11]: 70-71 °C). $[\alpha]_{589}^{20}$ = -61.3 (c = 0.95; C_6H_6). TLC: hexane / EtOAc (3:1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 1.56 (d, 3H, J = 6.5 Hz), 2.03 (s, 3H), 4.12 - 4.19 (m, 7H), 4.21 - 4.25 (m, 1H), 4.25 - 4.28 (m, 1H), 5.84 (q, 1H, J = 6.5 Hz). IR (ATR): $\tilde{\nu}$ = 3095 (w), 2983, 2938 (w), 1731 (s), 1369 (m), 1236 (s), 1040, 1024, 1002, 829, 819 (m). HRMS: 272.0500 as calcd for $C_{14}H_{16}FeO_2$. Anal. calcd for $C_{14}H_{16}FeO_2$: C, 61.79; H, 5.93; found: C, 62.02; H, 5.99.

(R)-1-Ferrocenylethylamine (**15**)**:** To a solution of (*R*)-1-ferrocenylethyl acetate (**14**) (400 mg; 1.47 mmol) in 10 ml DMF was added 30 ml concentrated aq. NH_3. The mixture was placed in an ice/water bath and sonicated for 9 h (10 ml of aq. NH_3 was added after 4 h). The orange mixture was partitioned between MTBE and 2 N HCl. The aqueous layer was brought to pH > 9 with 2 N NaOH and extracted twice with MTBE. The combined organic layers were washed with brine and dried with K_2CO_3. The crude product was purified by flash chromatography (EtOAc first, then MeOH) to yield 307 mg (92 %) of **15** as a dark orange oil. $[\alpha]_{589}^{20}$ = -22.1 (c = 3.3; EtOH); ref.[11]: $[\alpha]_{589}^{20}$ = -14.5 (69 % ee). ^{1}H NMR: (270 MHz, $CDCl_3$) δ = 1.35 (d, 3H, J = 6.5 Hz), 1.74 (br, 2H), 3.80 (q, 1H, J = 6.5 Hz), 4.08 - 4.24 (m, 9H). IR (ATR): $\tilde{\nu}$ = 3094 (m), 2968, 2928, 2865 (m), 1662 (s), 1444, 1367, 1224 (m), 1105 (s), 1019, 1000 (m), 815 (s). HRMS: 229.0554 as calcd for $C_{12}H_{15}FeN$.

(R,R)-Bis(1-ferrocenylethyl)amine (**5**)**:** To a stirred solution of 318 mg (1.17 mmol) (*R*)-1-ferrocenylethyl acetate (**14**) and 270 mg (1.17 mmol) (*R*)-1-ferrocenylethylamine (**15**) in 20 ml acetonitrile was added a catalytic amount of DMAP and the orange solution was refluxed for 30 h. The cooled reaction mixture was extracted with MTBE and 2 N HCl. The layers were separated and the aqueous layers were treated with 2 N NaOH and extracted with MTBE. The combined organic layers were washed with brine and dried with K_2CO_3. The filtered solution was concentrated and the residue purified by flash chromatography (EtOAc first, then MeOH) to yield 304 mg (59 %) of **5** as an orange solid (mp.: 98 °C). $[\alpha]_{589}^{20}$ = - 65 (c = 0.31; $CHCl_3$). ^{1}H NMR: (400 MHz, $CDCl_3$): δ = 1.35 (d, 6H, J = 6.5 Hz), 1.52 (br, 1H), 3.66 (q, 2H, J = 6.5 Hz), 4.10 - 4.22 (m, 18H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.2 (q), 48.9 (d), 65.8 (d), 67.1 (d), 67.2 (d), 67.3 (d), 68.4 (d), 94.7 (s). IR (ATR): $\tilde{\nu}$ = 3093 (m), 2963, 2925 (m), 2863 (w), 1734, 1456, 1437, 1366 (w), 1105 (s), 1000 (m), 816 (s). HRMS: 441.0842 as calcd for $C_{24}H_{27}Fe_2N$. Anal. calcd for $C_{24}H_{27}Fe_2N$: C, 65.34; H, 6.17; N, 3.17; found: C, 65.28; H, 6.19; N, 3.19. When the racemic starting materials (*rac*-**14** and *rac*-**15**) were treated employing the same procedure, a 1:1-mixture of two diastereomers (*rac*-**5** and the *meso isomer* **16**) was obtained in 42 % yield (mp.: 65 °C). ^{1}H NMR: (270 MHz, $CDCl_3$): δ = 1.36 (d, 3H, J = 6.5 Hz), 1.41 (d, 3H, J = 6.5 Hz), 1.55 (b, 1H), 3.57 (q, 1H, J = 6.5

Hz), 3.67 (q, 1H, J = 6.5 Hz), 4.01 - 4.24 (m, 18H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.2 (q), 22.6 (q), 48.9 (d), 49.1 (d), 65.5 (d), 65.8 (d), 66.9 (d), 67.1 (d), 67.2 (d), 67.3 (d), 67.5 (d), 68.3 (d), 68.4 (d), 93.8 (s). IR (ATR): $\tilde{\nu}$ = 3093 (m), 2964 (m), 2927, 2865 (w), 1451, 1436, 1367 (m), 1105 (s), 1024, 1000 (m), 817 (s). HRMS: 441.0842 as calcd for $C_{24}H_{27}Fe_2N$. Anal. calcd for $C_{24}H_{27}Fe_2N$: C, 65.34; H, 6.17; N, 3.17; found: C, 65.191; H, 6.18; N, 3.26.

(R,R)-N,N'-Bis-(1-ferrocenyl-ethyl)-ethane-1,2-diamine (**6**): To 83 mg (1.38 mmol) of freshly destilled ethane-1,2-diamine in 0.5 ml water was slowly added a solution of 903 mg (3.31 mmol) (*R*)-1-ferrocenylethyl acetate **14** in 4.0 ml of acetic acid. The mixture was stirred for 3 d, then treated with aq. NaOH (until pH > 8) and extracted with CH_2Cl_2. The combined organic layers were dried with K_2CO_3 and the solvent was removed in vacuo. The crude product was purified by double flash chromatography: (1): Al_2O_3-N (EtOAc first, then MeOH); (2.): silica gel (EtOAc first, then AcOH / MeOH (1:10)). The residue obtained by concentrating the product fractions in vacuo was treated with aq. NaOH, extracted with CH_2Cl_2 and dried with K_2CO_3. The solvent was removed in vacuo again to give 218 mg (32%) of **6** as a dark orange oil. $[\alpha]_{589}^{20}$ = –61.6 (c = 0.12; $CHCl_3$). TLC: MeOH / EtOAc (1:1). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.38 (d, 3H, J = 6.5 Hz), 1.67 (br s, 1H), 2.61 - 2.81 (m, 2H), 3.52 (q, 1H, J = 6.5), 4.05 - 4.27 (m, 9H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 21.7 (q), 47.1 (t), 52.2 (d), 65.8 (d), 67.2 (d), 67.2 (d), 67.3 (d), 68.4 (d), 93.7 (s). IR (ATR): $\tilde{\nu}$ = 3317 (w, br), 3092 (m), 2966 (s), 2927, 2816 (m), 1733 (w), 1672, 1635 (w), 1449 (m), 1411, 1396 (w), 1366, 1301, 1232 (m), 1105 (s), 1057, 1042, 1023 (m), 1000 (s), 904 (w), 817 (s), 751 (m). MS (%): 484 (12), 271 (24), 213 (100), 121 (24). HRMS: 484.1255 as calcd for $C_{26}H_{32}Fe_2N_2$.

1,5-Diferrocenyl-1,5-pentanedione (**18**)**:** A stirred solution of 5 g (27 mmol) ferrocene (**17**) and 1.85 ml (14.5 mmol) glutaryl dichloride in 80 ml CH_2Cl_2 was cooled to 0 °C and 3.6 g (27 mmol) $AlCl_3$ was added in small portions and the solution was allowed to stir for 16 h at room temperature. The mixture was then cooled to 0° C, quenched by dropwise addition of water and, after removing the ice bath, treated with a 10 % aq. solution of $Na_2S_2O_4$ for 20 min. The layers were separated and the aqueous layer extracted with CH_2Cl_2. The combined organic layers were washed with 2N NaOH and brine, dried with K_2CO_3, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (hexane : EtOAc = 5:1) to give 1.35 g (20 %) of **18** as an orange solid (mp.: 125 - 127 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.13 (Ψquint., 2H, J = 7 Hz), 2.85 (t, 4H, J = 7 Hz), 4.21 (s, 10H), 4.51 (t, 4H, J = 2 Hz), 4.83 (t, 4H, J = 2 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 19.4 (t), 38.8 (t), 69.3 (d), 69.8 (d), 72.2 (d), 78.9 (s), 204.3 (s). IR (ATR): $\tilde{\nu}$ = 3096 (w), 2933, 2893 (w), 1664 (s), 1454 (m), 1411, 1379, 1282, 1247, 1106, 1079, 1049, 1026, 1002, 886, 823 (w). HRMS: 468.0475 as calcd for $C_{25}H_{24}Fe_2O_2$. Anal. calcd for $C_{25}H_{24}Fe_2O_2$: C, 64.14; H, 5.17; found: C, 63.92; H, 5.38.

(R,R)-1,5-Diferrocenyl-1,5-pentanediol (**19**)**:** According to the procedure already described for the preparation of **13** (see above) 1,5-diferrocenyl-1,5-pentanedione (**18**) (618 mg; 1.32 mmol) was reduced with borane-Me_2S (1.2 eq.) in the presence of (*S*)-2-methyl-5,5-diphenyl-3,4-propano-1,3,2-oxazaborolidine (13 mol %) to afford the alcohol **19**. The crude product (99 % yield), which could be directly employed for the next step (preparation of **20**; see below), was purified by flash chromatography (hexane / EtOAc = 3:1) to yield 468 mg (75 %) of **19** as an orange solid (mp.: 114/115 °C). $[\alpha]_{589}^{20}$ = -36.8 (c = 0.44; $CHCl_3$). ^{1}H NMR: (400 MHz, $CDCl_3$): δ = 1.45 - 1.77 (m, 6H), 1.96 (d, 2H, J = 3.5 Hz), 4.05 - 4.27 (m, 18H), 4.28 - 4.35 (m, 2H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 22.5 (t), 37.9 (t), 65.2 (d), 67.3 (d), 67.8 (d), 67.9 (d),

68.3 (d), 69.5 (d), 94.5 (s). IR (ATR): $\tilde{\nu}$ = 3552 (w), 3397, 3092, 2927, 2861 (m), 1653, 1457 (w), 1411, 1385, 1314, 1234 (m), 1105 (s), 1079, 1040 (m), 1022, 1000 (s), 937, 896 (w), 818 (s). HRMS: 472.0788 as calcd for $C_{25}H_{28}Fe_2O_2$. Anal. calcd for $C_{25}H_{28}Fe_2O_2$: C, 63.59; H, 5.98; found: C, 63.74; H, 5.96. When the same starting material (**18**) was reduced using $NaBH_4$ in EtOH / dioxane (4:1), an isomeric mixture (*rac*-**19** and its *meso* diastereoisomer) was obtained in 99 % yield (mp.: 112 - 114 °C). The ^1H NMR, ^{13}C NMR and IR data of this material were identical to those of pure **19**.

(R,R)-1,5-Diferrocenyl-1,5-bisacetoxypentane (**20**)**:** To a stirred solution of the diol **19** (1.13 g; 2.41 mmol) in 40 ml triethylamine were added 0.75 ml (7.5 mmol) Ac_2O and a catalytic amount of DMAP. The mixture was stirred for 12 h at room temperature and then partitioned between water and MTBE. The organic layers were washed with brine, dried with K_2CO_3 and the solvent was removed in vacuo. According to ^1H NMR and TLC (hexane / EtOAc = 3:1) the crude product (**20**; orange oil) was sufficiantly pure to be directly used for the next transformation. Yield: 1.18 g (88 %). $[\alpha]_{589}^{20}$ = -17.1 (c = 0.55; $CHCl_3$). ^1H NMR: (270 MHz, $CDCl_3$) δ = 1.31 - 1.50 (m, 2H), 1.88 (Ψq, 4H, J = 7 Hz), 2.10 (s, 6H), 4.10 - 4.20 (m, 16H), 4.25 (m, 2H), 5.83 (t, 2H, 7 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 21.2 (q), 21.8 (t), 34.6 (t), 66.4 (d), 67.5 (d), 67.7 (d), 68.0 (d), 68.9 (d), 71.7 (d), 87.8 (s), 170.5 (s). IR (ATR): $\tilde{\nu}$ = 3094 (w), 2952, 2926, 2855 (w), 1731 (s), 1457, 1437, 1412 (w), 1371 (m), 1237 (s), 1106, 1044, 1023, 1002, 819 (m). HRMS: 556.0999 calcd for $C_{29}H_{32}Fe_2O_4$; found: 556.1006.

(R,R)-2,6-Diferrocenylpiperidine (**7a**); *Method A***:** A mixture of the diacetate **20** (1.1 g; 1.97 mmol), 40 ml DMF and 10 ml concentrated aq. NH_3 was refluxed for 4 d. The mixture was partitioned between MTBE and 2 N HCl. The aqueous layer was treated with 2 N aq. NaOH and extracted with MTBE. The combined organic layers were washed with brine, dried with K_2CO_3 and evaporated. The residue was then purified by flash chromatography (EtOAc) to afford 518 mg of diastereomerically pure **7a** (58 %) as an orange solid (mp.: 144 - 146 °C). $[\alpha]_{589}^{20}$ = -111.8 (c = 0.69; $CHCl_3$). ^1H NMR: (270 MHz, $CDCl_3$): δ = 1.64 - 1.75 (m, 4H), 1.76 - 2.05 (m, 3H, incl. NH), 3.85 - 3.94 (m, 2H), 4.09 - 4.17 (m, 10H), 4.21 (m, 4H), 4.27 (m, 4H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 21.6 (t), 31.8 (t), 51.2 (d), 66.6 (d), 67.3 (d), 67.4 (d), 68.5 (d), 92.7 (s). IR (ATR): $\tilde{\nu}$ = 3092 (w), 2931 (m), 2862, 2851, 1456 (w), 1437, 1430 (m), 1411 (w), 1314 (m), 1303 (w), 1105 (s), 1054, 1039, 1024 (w), 999 (m), 817 (s). HRMS: 453.0842 calcd for $C_{25}H_{27}Fe_2N$; found: 453.0843. Anal. calcd for $C_{25}H_{27}Fe_2N$: C, 66.26; H, 6.01; N, 3.09; found: C, 66.26; H, 6.02; N, 3.13. When 500 mg of a 1:1 mixture of the diastereomeric diacetates (*rac*-**20** and its *meso* isomer) were treated with NH_3 as decribed above, a mixture of the two diastereomeric 2,6-diferrocenylpiperidines *rac*-**7a** and the *meso* isomer **21** was obtained. Separation by flash chromatography (EtOAc) afforded 114 mg (23 %) of the meso-product (semicrystalline solid) **21** and 105 mg (22%) of *rac*-**7a** (orange solid; mp.: 108 - 109 °C). Data for **21**: ^1H NMR: (400 MHz, $CDCl_3$) δ = 1.28 - 1.43 (m, 2H), 1.49 - 1.60 (m, 1H), 1.82 - 1.94 (m, 3H), 2.05 (br, 1H, NH), 3.56 (ψd, 2H), 4.08 - 4.14 (m, 4H), 4.17 (s, 10H), 4.21 (m, 2H), 4.28 (m, 2H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 25.5 (t), 33.9 (t), 56.9 (d), 66.0 (d), 66.2 (d), 67.2 (d), 67.3 (d), 68.3 (d), 93.4 (s). IR (ATR): $\tilde{\nu}$ = 3092 (w), 2928 (m), 2850, 2787, 1437 (w), 1426, 1420 (m), 1323 (w), 1299 (m), 1105 (s), 1053, 1021 (w), 999 (m), 937, 910 (w), 816 (s). HRMS: 453.0842 as calcd for $C_{25}H_{27}Fe_2N$.

(R,R)-2,6-Diferrocenylpiperidine (**7a**); *Method B***:** To a solution of the diacetate **20** (2.06 g; 3.71 mmol) in 50 ml DMF was added 50 ml concentrated aq. NH_3. The mixture was placed in an ice/water bath and

sonicated for 9 h (a total of 20 ml aq. NH_3 and 15 ml DMF were added portionwise every 2 h). The orange mixture was partitioned between MTBE and 2 N HCl. The aqueous layer was brought to pH > 9 with 2 N NaOH and extracted twice with MTBE. The combined organic layers were washed with brine and dried with K_2CO_3. The crude product was purified by flash chromatography (hexane / EtOAc = 1:1) to yield 1.092 g (65 %) of **7a** as an orange solid. The characteristic data (TLC, ^1H NMR, MS) were identical with those of **7a** prepared by method A (see above). $[\alpha]_{589}^{20}$ = -106.3 (c = 0.59; $CHCl_3$).

1,4-Diferrocenyl-1,4-butanedione (**22**)**:** A stirred solution of 10 g (54.0 mmol) ferrocene (**17**) and 3.19 ml (29.0 mmol) succinyl dichloride in 100 ml CH_2Cl_2 was cooled to 0 °C and 7.2 g (54.0 mmol) of $AlCl_3$ were added in small portions. The mixture was stirred for 12 h at room temperature, recooled to 0 °C and carefully hydrolyzed with ca. 50 ml ice-water. The cooling bath was removed and, after adding 10 ml of a solution of 10 % aqueous $Na_2S_2O_4$, stirring was continued for 20 min. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2. The combined organic layers were washed with 2N NaOH, brine and dried with K_2CO_3. After filtration and concentration the solution in vacuo, the crude product was flash-chromatographed (hexane : EtOAc = 3:1) to give 2.08 g (16 %) of an orange solid, which proved to be an unseparable mixture of **22** and the isomeric compound 3,3-diferrocenyl-γ-butyrolactone **23** (ratio ca. 1:1) which was directly used for the next step (CBS reduction). Data of the mixture: **22**: ^1H NMR (270 MHz, $CDCl_3$): δ = 3.18 (s, 4H), 4.29 (s, 10H), 4.53 (ψt, 4H, J = 2 Hz), 4.87 (ψt, 4H, J = 2 Hz); **23**: 2.90 (s, 4H), 4.03 - 4.07 (m, 2H), 4.12 - 4.24 (m, 16H).

(R,R)-1,4-Diferrocenyl-1,4-butanediol (**24**)**:** The above mixture of **22** and **23** (2.08 g; 4.58 mmol) was treated as described above for the preparation of **19** to afford the alcohol **24**. The crude product was purified by flash chromatography (hexane / EtOAc = 3:1) to give 882 mg (42 % yield) of **24** as an orange solid (mp.: 112 - 115 °C). $[\alpha]_{589}^{20}$ = -23.2 (c = 0.32). ^1H NMR (270 MHz, $CDCl_3$): δ = 1.66 - 1.95 (m, 4H), 2.15 - 2.25 (br, 1H), 2.25 - 2.37 (br, 1H), 4.10 - 4.33 (m, 18H), 4.33 - 4.46 (m, 2H). IR (ATR): $\tilde{\nu}$ = 3546 (w), 3390 (m, br), 3092, 2922 (m), 2858 (w), 1411, 1387 (m), 1313, 1236 (w), 1105 (s), 1041, 1023 (m), 1000, 817 (s). HRMS: calcd for $C_{24}H_{26}Fe_2O_2$: 458.0632; found: 458.0637. Anal. calcd for $C_{24}H_{26}Fe_2O_2$: C, 62.92; H, 5.72; found: C, 63.21; H, 5.83.

(R,R)-1,4-Diferrocenyl-1,4-bisacetoxybutane (**25**)**:** The diol **24** (448 mg; 0.97 mmol) was treated with acetic anhydride (as described above for the preparation of **20**) to afford the acetate **25** as an orange solid (mp.: 104 - 106 °C). Yield: 508 mg (96 %). $[\alpha]_{589}^{20}$ = -22.0 (c = 0.43). ^1H NMR (270 MHz, $CDCl_3$): δ = 1.86 - 1.95 (m, 4H), 2.12 (s, 6H), 4.10 - 4.31 (m, 18H), 5.73 - 5.86 (m, 2H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 21.3 (q), 31.4 (t), 66.5 (d), 67.4 (d), 67.7 (d), 68.1 (d), 68.7 (d), 71.6 (d), 87.7 (s), 170.5 (s). IR (ATR): $\tilde{\nu}$ = 3094 (w), 2932 (w), 1730 (s), 1434, 1412 (w), 1370 (m), 1234 (s), 1106, 1041, 1021, 1002 (m), 949, 915 (w), 818 (m). HRMS: calcd for $C_{28}H_{30}Fe_2O_4$: 542.0843; found: 542.0844.

(R,R)-2,5-Diferrocenylpyrrolidine (**7b**)**:** A solution of the diacetate **25** (400 mg; 0.73 mmol) in 10 ml DMF and 30 ml aqueous ammonia and sonified for 7 h to afford **7b** as an orange solid. Yield: 276 mg (68 %) (mp.: 88 - 89 °C). $[\alpha]_{589}^{20}$ = -35.4 (c = 0.30). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.79 - 1.92 (m, 2H), 2.22 - 2.32 (m, 2H), 2.35 - 2.64 (br, 1H), 4.10 - 4.25 (m, 20H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 33.6 (t), 56.9 (d), 66.3 (d), 67.0 (d), 67.6 (d), 67.7 (d), 68.4 (d), 92.4 (s). IR (ATR): $\tilde{\nu}$ = 3091, 2956, 2866, 1707, 1640, 1411, 1386, 1311, 1235 (w), 1105 (s), 1043, 1022 (w), 1000 (m), 904 (w), 815 (s). HRMS: calcd for $C_{24}H_{25}Fe_2N$: 439.0686; found: 439.0692.

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21. The fact that the product was obtained as a pure diastereomer directly proves the high enantiomeric purity (> 98 % ee) of the starting material(s) and the product.
22. For the use of AcOH as solvent for substitution reactions of ferrocenyl derivatives, see: Barbaro, P.; Togni, A. *Organometallics* **1995**, *14*, 3570.
23. As an example, H[CHIRAMT] is an interesting chiral ligand based on α-phenylethylamine, see: a) Villacorta, G. M.; Rao, C. P.; Lippard, S. J. *J. Am. Chem. Soc.* **1988**, *110*, 3275; b) ; Ahn, K.-H.; Klassen, R. B.; Lippard, S. J. *Organometallics* **1990**, *9*, 3178.
24. While the chirality of the ferrocene derivatives described in this paper is solely based on *centers* of chirality, it might be possible to transform these compounds into ferrocene derivatives possessing additionally planes of chirality (e.g. via diastereoselective deprotonation / alkylation)[8a].
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