Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 1621–1628

TETRAHEDRON: *ASYMMETRY*

Asymmetric synthesis of ferrocenylazido alcohols and their derivatization to novel chiral ferrocenyl-thiazoline ligands with C_2-symmetry

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Received 27 May 2002; accepted 29 July 2002

Abstract—The synthesis of previously unreported chiral ferrocenyl-thiazoline ligands is described. (*R*)-2-Azido-1-ferrocenylethanol **3** and (*R*,*R*)-1,1′-bis(2-azido-1-hydroxyethyl)ferrocene **10**, available by enantioselective borane reduction of α-azidoacetyl ferrocene **1** and 1,1′-bis(2-azidoacetyl)ferrocene **2**, respectively, were converted into the corresponding ferrocenyl thiazolines by a three-step sequence involving catalytic hydrogenation, acylation and cyclization promoted by Lawesson's reagent. New chiral ferrocene-thiazolines with C_2-symmetry were obtained either from (*R*)-2-azido-1-ferrocenylethanol **3** and diacyl chlorides or from (*R*,*R*)-1,1′-bis(2-azido-1-hydroxyethyl)ferrocene **10** and monoacyl chlorides.

1. Introduction

Chiral oxazoline and bis-oxazoline ligands have found widespread use in metal-catalyzed asymmetric reactions.[1] The concept of ferrocene acting as a three-dimensional metal-containing phenyl equivalent has recently prompted the synthesis and applications of chiral ferrocenyl-oxazoline ligands containing both planar and central elements of chirality.[2] However, despite the fact that the electronic and steric effects resulting from the replacement of the oxygen with sulfur could change the behavior of the chelating heterocycle towards metals, the synthesis of chiral thiazolines has barely been studied. To the best of our knowledge there have been only four reports on the preparation of chiral thiazoline analogues of known oxazoline ligands,[3] and we know of no reported examples dealing with the synthesis of chiral ferrocenyl-thiazoline ligands.

We have been interested in the possibilities offered by chiral metal-containing building blocks for the synthesis of new catalysts and materials. In this context, we recently reported that α-azidoacetylferrocene **1** can be readily prepared from acetylferrocene trimethylsilylenol ether by bromination followed by halogen-azido substitution using polymeric quaternary ammonium azide.[4] Likewise, 1,1′-bis(α-azidoacetyl)ferrocene **2** was prepared starting from 1,1′-bis(acetyl)ferrocene.[5]

We wish to report herein the enantioselective conversion of **1** and **2** into the corresponding β-azido alcohols **3** and **10** and β-amino alcohols **4** and **11**, which may themselves act as ligands for transition-metal catalyzed reactions, or may be used as direct precursors of chiral aziridines[6] or chiral oxazolines.[7] However, they have also proved to be valuable starting materials for further elaboration in the preparation of previously unreported chiral ferrocenyl-thiazolines, which lead to a broad range of new potential ligands.

2. Results

For the asymmetric reduction of the α-azidoacetyl ferrocene **1**, the procedure developed by Corey and Itsuno was chosen because it has shown broad utility with a number of substrates during the last decade.[8] Although, the oxazaborolidine-catalyzed asymmetric borane reduction of prochiral 2-azidoacetophenones to give optically active 2-azido-1-phenylethanol has been described,[9] previous attempts to reduce ferrocenyl ketones enantioselectively were restricted to acylated[10] or α-halo acylated systems.[11]

Initially, the enantioselective borane reduction of **1** was carried out using the Corey–Bakshi–Shibata (CBS) cat-

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0957-4166/02/$ - see front matter
PII: S0957-4166(02)00441-X

alyst,[12] (*R*)-2-azido-1-ferrocenylethanol **3** being obtained in 95% yield using 30 mol% of the catalyst. The ee, as determined by chiral HPLC, was 94% and the absolute configuration assigned to **3** was deduced taking into account previous results found in similar enantioselective catalytic reductions on related carbonyl compounds such as acylferrocenes[10] and α-chloroacetylferrocene.[11] In addition, catalytic hydrogenation of **3** provided the known compound (*R*)-2-amino-1-ferrocenylethanol **4** in 83% yield. Comparison of its specific rotation value to that previously reported[13] confirmed the absolute configuration proposed and the high enantiomeric excess reveals that the hydrogenation proceeds with excellent stereochemical integrity.

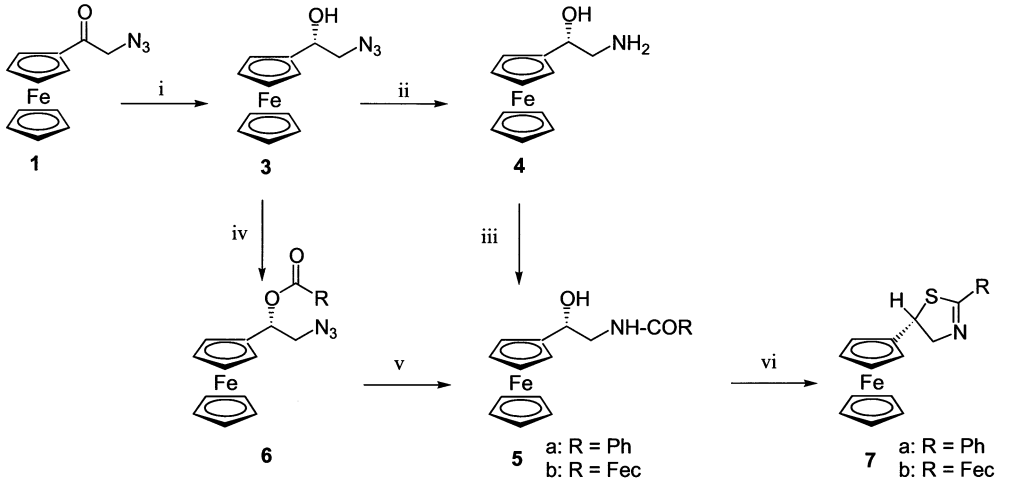
Acylation of **4** with benzoyl chloride or chlorocarbonyl ferrocene in THF in the presence of Et_3N at room temperature afforded the chiral β-hydroxyamides **5a** and **5b** in 95 and 70% yield, respectively. These compounds can also be prepared from **3** by the following sequence: pretreatment of **3** with *n*-BuLi in THF at −78°C followed by addition of the corresponding acyl chloride at the same temperature gave the 2-azido ester **6** which undergo tributylphosphine-promoted *O*→*N* acyl transfer at room temperature to give **5**, albeit in low chemical yields and enantiomeric purities.

The conversion **6**→**5** represents the first chiral version of the recently termed 'Staudinger ligation' which allows the chemoselective formation of amide-linked products from azides and alkoxycarbonyl-linked triarylphosphines.[14] In the present case, the ester group situated adjacent to the azido functionality traps the iminophosphorane in an intramolecular fashion, resulting formation of the β-hydroxyamide **5** and triphenylphosphine oxide after hydrolysis.

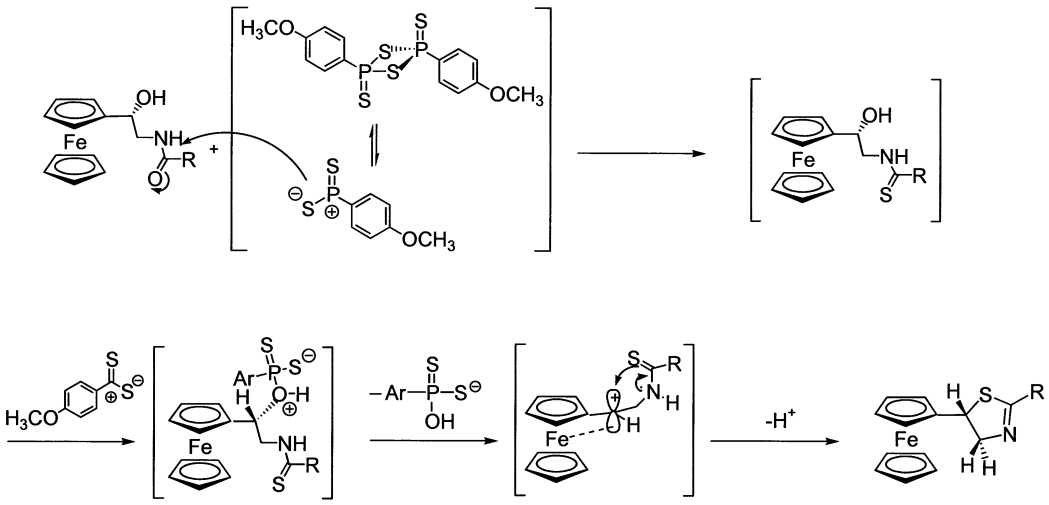
When β-hydroxyamides **5** were submitted to reaction with an excess of Lawesson's reagent [*p*-MeOPhPS$_2$]$_2$ (LR) in refluxing THF the corresponding ferrocenylthiazolines **7** were obtained in yields ranging from 65 to 84% (Scheme 1).

It is known that for the efficient intramolecular cyclization of β-hydroxyamides to 2-thiazolines, a powerful hydroxyl activating reagent, e.g. diethylamidosulfur trifluoride (SF_3NEt_2, DAST), is needed.[15] However, for the conversion **5**→**7** no activation of the hydroxyl function is needed prior to the cyclization step. This fact could be due to the strong tendency of heteroatomic substituents in the α position of the ferrocenyl moiety to undergo replacement by other donor functionalities and the dual behavior of LR as both sulfurating and hydroxyl-activating reagent, as outlined in Scheme 2.

We were able to obtain the crystal structure of compound **7b** by X-ray diffraction (Fig. 1). Crystallographic data are given in Section 4, and selected structural parameters are collected in Fig. 1. The (*R*)-absolute configuration was determined by refining the Flack enantiopole parameter x[16] and confirms the expected stereochemical outcome of the nucleophilic displacement of α-heterosubstituted ferrocenes which takes place with full retention of configuration.[17] The distances Fe···RC (RC = centroid rings) (1.650–1.654 Å) are very close to the value of 1.66 Å in ferrocene.[18] All Cp rings are planar and they are arranged in an ecliptic position. The Fe atoms are located symmetrically between the rings with Fe–C distances between 2.033 and 2.060 Å. The interplanar angles between the thiazoline ring [C(21), C(22), N, C(23), S] and the corresponding ferrocene ring are 79.6° [C(1), C(2), C(3), C(4), C(5)] and 25.5° [C(16), C(17), C(18), C(19), C(20)], respectively. The atoms C(22), N, C(23) and S are coplanar (mean deviation from the plane 0.002 Å), the C(21) is 0.2089 Å out of this plane. The C(19)–C(23) bond length [1.471(6) Å], is normal [C–C ring mean value of 93 C–thiazoline ring compounds from CCDC is 1.477 Å], and the angles C(23)–S–C(21) [90.5(2)°] and C(23)–N–C(22) [113.4(3)°] are also normal [mean value of 93 C–thiazoline ring compounds from CCDC is 89.331° (angle C–S–C) and 113.056° (angle C–N–C)]. While the chirality of compounds **7** is solely based on one stereogenic center, it might be possible to transform



Scheme 1. *Reagents and conditions*: (i) $BH_3{\cdot}SMe_2$, CBS, THF, 0°C; (ii) H_2, Pd/C, EtOH, rt; (iii) R-COCl, CH_2Cl_2; Et_3N, rt; (iv) *n*-BuLi, THF, −78°C then R-COCl; (v) *n*-Bu_3P, THF, rt; (vi) LR (2 equiv.), THF, reflux.



Scheme 2.

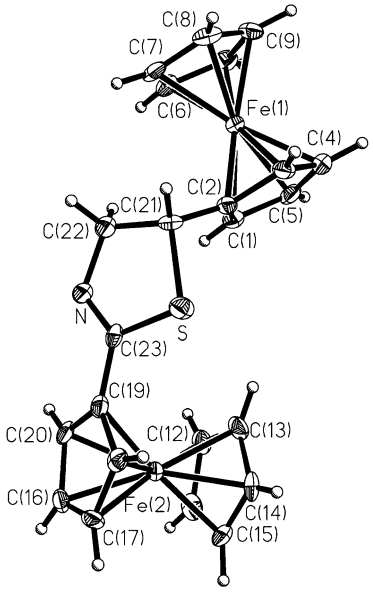


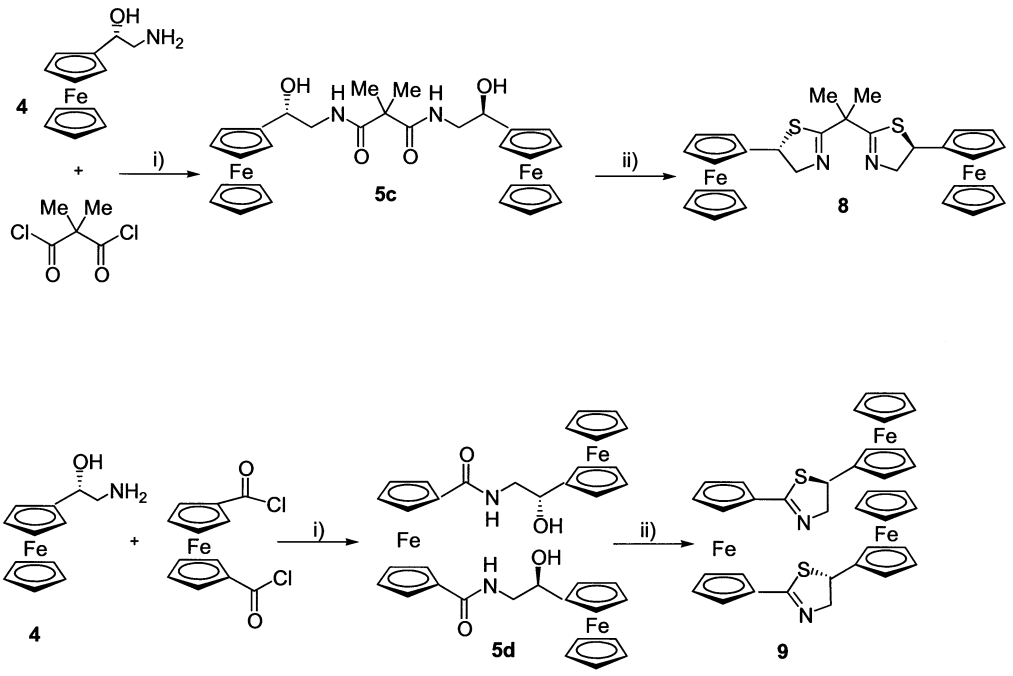
Figure 1. Thermal ellipsoid plot (50% probability level) of **7b**. Selected bond lengths (Å) and angles (°): Fe(1)–C(2) 2.043(4), Fe(1)–C(8) 2.044(4), Fe(1)–C(1) 2.046(4), Fe(1)–C(4) 2.047(4), Fe(1)–C(10) 2.051(4), Fe(1)–C(6) 2.053(4), Fe(1)–C(5) 2.060(4), Fe(2)–C(19) 2.039(4), N–C(23) 1.268(5), N–C(22) 1.456(5), S–C(23) 1.781(4), S–C(21) 1.858(4), C(2)–C(21) 1.491(5), C(19)–C(23) 1.471(6), C(21)–C(22) 1.548(5); C(23)–N–C(22) 113.4(3), C(23)–S–C(21) 90.5(2), C(21)–C(2)–Fe(1) 125.2(3), C(23)–C(19)–Fe(2) 125.5(3), C(2)–C(21)–S 110.7(3), C22–C(21)–S 103.9(3), N–C(22)–C(21) 113.0(3), N–C(23)–C(19) 123.0(4), N–C(23)–S 117.9(3), C(19)–C(23)–S 119.1(3).

these compounds into ferrocenyl-thiazolines possessing additional planes of chirality (e.g. via diastereoselective deprotonation/alkylation).[19]

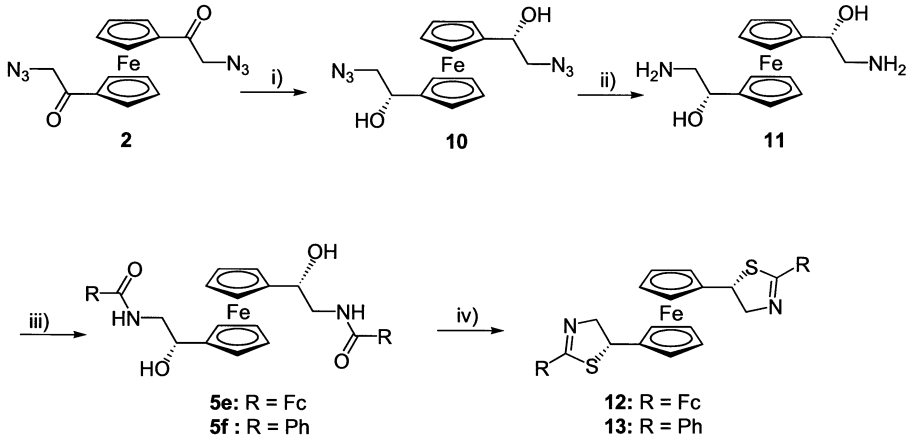
The methodology was then extended to novel C_2-symmetric bis-thiazolines bearing two or three ferrocene moieties. Thus, bis(β-hydroxyamide) **5c**, readily available in 87% yield from the reaction of (*R*)-2-amino-1-ferrocenyl ethanol **4** with dimethyl malonyl chloride, underwent cyclization under the influence of Lawesson's reagent to give the C_2-symmetric bidentate bis(ferrocenyl-thiazoline) **8** in modest yield (30%). On the other hand, the 1,1′-bis(β-hydroxyamide)ferrocene **5d**, available in 71% yield from (*R*)-2-amino-1-ferrocenyl ethanol and 1,1′-ferrocene-dicarbonyl dichloride, underwent cyclization under the same conditions to give 1,1′-bis(ferrocenylthiazo-linyl)ferrocene **9**, bearing a C_2-symmetrical ferrocene framework, in 40% yield (Scheme 3).

Our approach also allows facile preparation of the isomeric C_2-symmetrical ferrocenyl-thiazoline **12** bearing three ferrocene moieties. Thus, the reduction of 1,1′-bis(α-azidoacetyl)ferrocene **2** can be performed with 60% mol of the CBS-oxazaborolidine and 2 equiv. of borane[20] in dichloromethane providing the 1,1′-disubstituted ferrocenyl azido alcohol **10** in 92% yield with a diastereomeric ratio *dl*:*meso* of 90:10. The enantiomeric purity, determined by chiral HPLC, was higher than 95% ee. When the reduction was carried out in THF the yield was low due to the poor solubility of **2** in THF and the reaction was less diastereoselective (80:20). The separation of the *meso*-diastereomer from the desired C_2-symmetrical diol **10** was done by simple recrystallization. The (*R*,*R*) absolute configuration assigned to **10** was deduced taking into account the previous result found in the enantioselective catalytic reduction on related compound **1**.

Catalytic hydrogenation of **10** provided the 1,1′-disubstituted ferrocenyl amino alcohol **11** in 82% yield, which, on reaction with chlorocarbonyl ferrocene or benzoyl chloride in THF in the presence of Et_3N at room temperature afforded the chiral β-hydroxyamides **5e** and **5f** in 87 and 57% yield, respectively. Further treatment with Lawesson's reagent provided the C_2-symmetric bis-thiazolines **12** and **13** in 60 and 45% yield, respectively (Scheme 4).



Scheme 3. *Reagents and conditions*: (i) Et_3N, THF; (ii) LR, THF, reflux.



Scheme 4. *Reagents and conditions*: (i) CBS oxazaborolidine/THF, 0°C and then $BH_3{\cdot}SMe_2$, THF; (ii) H_2/Pd–C, EtOH; (iii) 2R-COCl, Et_3N, THF; (iv) LR, THF, reflux.

3. Conclusions

The present approach to the previously unreported chiral thiazolines enables the design of novel bidentate C_2 symmetric molecules by tuning the size and shape of the spacer and also the nature of the substituent held by the thiazoline stereogenic center. In addition, as the oxazaborolidine catalyst employed in the chirogenic step is available in both enantiomeric forms, the compounds described here (and possibly a number of related ferrocene-thiazolines) can be prepared in any desired absolute configuration. This type of compound opens up access to new ligands for application as chiral modifiers in asymmetric catalysis.

4. Experimental

4.1. General

All reactions were carried out under N_2, using anhydrous solvents that were dried using routine procedures. Column chromatography was performed with the use of a column of dimensions 60×4.5 cm and of silica gel (60 Å C.C. 70–200 μm, sds) as the stationary phase. All melting points were determined on a Kofler hot-plate melting point apparatus and are uncorrected. IR spectra were determined on a Nicolet Impact 400 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC200 (200 MHz) or a Varian Unity 300

(300 MHz). Chemical shifts refer to signals of tetramethylsilane in the case of ^1H and ^{13}C spectra. The EI mass spectra were recorded on a Fisons AUTOSPEC 500 VG spectrometer. Microanalyses were performed on a Perkin–Elmer 240C instrument. Ee and de of the products were determined by HPLC fitted with a Cyclobond 2000 column and using *n*-hexane/*i*-PrOH (97/3) as eluent.

4.2. General procedure for the preparation of β-azido alcohols, 3 and 10

To a solution of (*S*)-CBS-oxazaborolidine (1 M in toluene) in anhydrous THF cooled at 0°C and under nitrogen, a solution of BH_3–THF (1 M in THF) was added. Then, a solution of the appropriate α-azidoacetylferrocene **1** or **2** in dry THF or CH_2Cl_2 (5 mL) and BH_3–SMe_2 (2 M in THF), in the same solvent were slowly added over a period of 20 min. After the addition, the reaction mixture was stirred for 10 min, quenched cautiously with methanol (10 mL) and later with a saturated solution of NH_4Cl (20 mL), and then extracted with CH_2Cl_2 (4×15 mL). The organic layers were dried over Na_2SO_4, the solvent evaporated under reduced pressure and the residue chromatographed on a silica gel column using CH_2Cl_2/EtOAc (20:1) as eluent. The pure compounds were recrystallized from ether/pentane (5:1).

4.2.1. (*R*)-2-Azido-1-ferrocenylethanol, 3. Prepared according to the general procedure, starting from α-azidoacetylferrocene **1** (1.52 g, 5.65 mmol), and using (*S*)-CBS-oxazaborolidine (1.69 mmol, 1 M in toluene, 1.69 mL) in anhydrous THF (5 mL), BH_3–THF (1.13 mmol; 1 M in THF, 1.13 mL) and BH_3–SMe_2 (6.21 mmol; 3.1 mL), in the same solvent (2 mL); yield = 95%; $[\alpha]_D = -77$ (*c* 1.35, $CHCl_3$), ee = 94%); mp 37–39°C; IR (Nujol) 3435, 2102, 1448, 1415, 1401, 1312, 1259, 1070, 1033, 822 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.23 (s, 1H), 3.39 (d, 2H, $J = 4.0$ Hz), 4.21 (s, 8H), 4.27 (s, 1H), 4.54 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 57.27 (CH_2), 65.69 (CH, Cp), 67.28 (CH, Cp), 68.51 (2×CH, Cp), 68.61 (5×CH, Cp), 69.52 (CH-OH), 89.88 (q, Cp); EIMS *m*/*z*: (rel. intensity): 271 (M^+, 51), 225 (24), 214 (97), 186 (92), 121 (100). Anal. calcd for $C_{12}H_{13}FeN_3O$: C, 53.17; H, 4.83; N, 15.50. Found: C, 53.03; H, 4.78; N, 15.62%.

4.2.2. (*R*,*R*)-1,1′-Bis(2-azido-1-hydroxyethyl)ferrocene, 10. Prepared according to the general procedure, starting from α-azidoacetylferrocene **1** (1.52 g, 5.65 mmol), and using (*S*)-CBS-oxazaborolidine (2.38 mmol, 1 M in toluene, 2.38 mL) in anhydrous CH_2Cl_2 (5 mL), BH_3–THF (1.59 mmol; 1 M in THF, 1.59 mL) and BH_3–SMe_2 (8.75 mmol; 4.37 mL), in the same solvent (6 mL); yield = 92%; $[\alpha]_D = -73$ (*c* 1.78, $CHCl_3$), de = 80%); mp 67–69°C; IR (Nujol) 3341, 2109, 1455, 1278, 1079, 1028, 875, 812 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.24–3.41 (m, 4H), 3.19–4.19 (m, 10H), 4.55–4.68 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 58.40 (2×CH_2), 66.64 (2×CH, Cp), 66.91 (2×CH, Cp), 68.48 (2×CH, Cp), 68.55 (2×CH, Cp), 69.58 (2×CH-OH), 89.40 (2q, Cp); EIMS *m*/*z*: (rel. intensity): 356 (M^+, 75), 299 (72), 242 (98), 186 (75), 121 (100). Anal. calcd for $C_{14}H_{16}FeN_6O_2$: C, 47.21; H, 4.53; N, 23.60. Found: C, 47.00; H, 4.38; N, 23.75%.

4.3. General procedure for the preparation of β-amino alcohols, 4 and 11

A suspension of Pd/C (10%) in acetic acid was treated by dropwise addition of a solution of the appropriate β-azido alcohol (**3** or **10**) in dry ethanol, and the reaction mixture was stirred at room temperature for 3 h, while a stream of H_2 was bubbled over the solution. The solution was filtered over a zelite pad, which was washed with ethanol (3×15 mL) and chloroform (3×15 mL). The combined filtrates were evaporated to dryness under reduced pressure and the residue was triturated in Et_2O to give a solid, which was crystallized from CH_2Cl_2/Et_2O.

4.3.1. (*R*)-2-Amino-1-ferrocenylethanol, 4. Prepared according to the general procedure, starting from (*R*)-2-azido-1-ferrocenylethanol **3** (0.2 g, 0.74 mmol), in dry ethanol (25 mL), and a suspension of Pd/C (10%) (0.05 g) in acetic acid (5 mL) to give **4** in 83% yield; $[\alpha]_D = -27$ (*c* 1.22, $CHCl_3$); mp 131–133°C; IR (Nujol) 3345, 3273, 1609, 1455, 1309, 1135, 1105, 1093, 999, 840, 815 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.87 (bs, 2H), 2.75–2.98 (m, 2H), 4.11–4.33 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 48.66 (CH_2), 65.79 (CH, Cp), 66.86 (CH, Cp), 67.99 (2×CH, Cp), 68.48 (5×CH, Cp), 70.98 (CH-OH), 91.07 (q, Cp); EIMS *m*/*z*: (rel. intensity): 245 (M^+, 76), 227 (100), 215 (43), 187 (56), 186 (86), 162 (57), 161 (52), 121 (89). Anal. calcd for $C_{12}H_{15}FeNO$: C, 58.80; H, 6.17; N, 5.71. Found: C, 58.99; H, 6.01; N, 5.55%.

4.3.2. (*R*,*R*)-1,1′-Bis(2-amino-1-hydroxyethyl)ferrocene, 11. Prepared according to the general procedure, starting from 1,1′-bis(2-azido-1-hydroxyethyl)ferrocene **10** (1 g, 2.8 mmol), in dry ethanol (25 mL), and a suspension of Pd/C (10%) (0.25 g) in acetic acid (5 mL) to give **11** in 82% yield; $[\alpha]_D = -12$ (*c* 1.52, MeOH); mp 116–118°C; IR (Nujol) 3344, 3285, 1606, 1302, 1104, 1080, 1021 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.50–2.56 (m, 2H), 2.67–2.71 (m, 2H), 4.10–4.13 (m, 8H), 4.24 (bs, 2H); ^{13}C NMR (DMSO-d_6) δ 49.20 (2×CH_2), 66.13 (2×CH, Cp), 66.87 (2×CH, Cp), 67.40 (2×CH, Cp), 67.51 (2×CH, Cp), 70.42 (2×CH-OH), 91.49 (2q, Cp); EIMS *m*/*z*: (rel. intensity): 304 (M^+, 92), 256 (74), 179 (57), 162 (100), 121 (49). Anal. calcd for $C_{14}H_{20}FeN_2O_2$: C, 55.28; H, 6.63; N, 9.21. Found: C, 55.56; H, 6.80; N, 9.43%.

4.3.3. Ethyl-(*R*)-(2-azido-1-ferrocenyl)benzoate, 6. To a solution of (*R*)-2-azido-1-ferrocenylethanol **3** (0.35 g, 1.3 mmol) in anhydrous THF cooled at −78°C and under nitrogen, a solution of *n*-BuLi (1 M in hexane) (0.0013 mol, 0.81 mL) was added dropwise and the solution was stirred for 1 h. Then, a solution of benzoyl chloride (0.2 g, 1.43 mmol) in the same solvent was added slowly. After stirring for 2 h at −78°C, the mixture was evaporated and the residue chromatographed on a silica gel column with CH_2Cl_2/EtOAc (20:1) as eluent to give **6**, which was used without further purification. Yield: 80%; IR (Nujol) 2101, 1720, 1455, 1112, 1079, 1027, 712 cm^{-1}; ^1H NMR

($CDCl_3$) δ 3.62–3.74 (m, 2H), 4.12 (s, 5H), 4.20 (s, 2H), 4.27 (m, 1H), 4.39 (m, 1H), 6.16 (dd, 1H, $J=7.2$ Hz, $J=4.2$ Hz), 7.42–7.60 (m, 3H), 8.12 (d, 2H, $J=8.4$ Hz). ^{13}C NMR ($CDCl_3$) δ 54.85 (CH_2), 66.91 (CH, Cp), 68.45 (CH, Cp), 68.61 (CH, Cp), 69.01 (5×CH, Cp), 71.57 (CH), 84.48 (q, Cp), 128.40 (2×CH), 129.70 (2×CH), 133.18 (CH), 165.79 (C=O).

4.4. General procedure for the preparation of β-hydroxyamides, 5

To a suspension of (*R*)-2-amino-1-ferrocenylethanol **4** (0.25 g, 1.02 mmol) in dry CH_2Cl_2 (10 mL), dry triethylamine (0.21 mL, 1.5 mmol) was added and the mixture was stirred at room temperature and under nitrogen for 5 min. Then, a solution of an equimolar amount of the corresponding acyl chloride, in the same solvent, was added dropwise and the reaction mixture was stirred at room temperature for 12 h. Afterwards, the solution was concentrated under vacuum and the residue was chromatographed on a silica gel column with CH_2Cl_2/MeOH (9:1), as eluent. The pure compounds were crystallized from CH_2Cl_2/Et_2O (1:3).

4.4.1. (*R*)-*N*-(2-Ferrocenyl-2-hydroxyethyl)benzamide, 5a. **Method A**: Prepared according to the general procedure, described above; yield = 95%; $[\alpha]_D=-2.1$ (*c* 1.74, $CHCl_3$); mp 105–107°C; IR (Nujol) 3332, 1648, 1539, 1456, 1315, 1108, 1075, 815, 716 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.27 (ddd, 1H, $J=13.2$ Hz, $J=9.0$ Hz, $J=5.1$ Hz), 3.78 (ddd, 1H, $J=13.2$ Hz, $J=6.0$ Hz, $J=3.6$ Hz), 4.11 (t, 2H, $J=1.8$ Hz), 4.20–4.25 (m, 7H), 4.56 (ddd, 1H, $J=9.0$ Hz, $J=5.4$ Hz, $J=3.6$ Hz), 5.04 (d, 1H, $J=5.4$ Hz), 7.44–7.55 (m, 3H), 7.91 (m, 2H), 8.53 (bt, 1H); ^{13}C NMR (DMSO-d_6) δ 46.36 (CH_2), 65.62 (CH, Cp), 66.97 (CH, Cp), 67.05 (2×CH, Cp), 67.29 (CH-OH), 68.34 (5×CH, Cp), 90.49 (q, Cp), 127.17 (2×CH, Ph), 128.15 (2×CH, Ph), 130.98 (CH, Ph), 134.59 (q, Ph), 166.30 (C=O); EIMS *m*/*z*: (rel. intensity): 349 (M$^+$, 19), 332 (50), 331(100), 266 (51), 226 (41), 186 (12), 105 (59), 77 (69). Anal. calcd for $C_{19}H_{19}FeNO_2$: C, 65.35; H, 5.48; N, 4.01. Found: C, 65.56; H, 5.28; N, 4.14%.

Method B: To a solution of the azido ester **6** (0.098 g, 0. 26 mmol) in dry THF (20 mL) and under nitrogen, *n*-Bu_3P (0.3 mmol, 0.067 mL) was slowly added and the reaction mixture was stirred at room temperature for 48 h and the product was isolated (40%) and purified as above.

4.4.2. (*R*)-*N*-(2-Ferrocenyl-2-hydroxyethyl)ferrocenecarboxamide, 5b. Yield = 70%; $[\alpha]_D=+6.0$ (*c* 2.28, $CHCl_3$); mp 114–116°C; IR (Nujol) 3423, 3306, 1628, 1532, 1455, 1298, 1106, 1072, 1001, 815 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.18 (ddd, 1H, $J=13.4$ Hz, $J=8.7$ Hz, $J=5.2$ Hz), 3.73 (ddd, 1H, $J=13.4$ Hz, $J=6.2$ Hz, $J=3.4$ Hz), 4.15 (t, 2H, $J=1.8$ Hz), 4.20 (s, 5H), 4.21–4.25 (m, 7H), 4.34 (t, 2H,. $J=1.8$ Hz), 4.52 (ddd, 1H, $J=8.7$ Hz, $J=5.2$ Hz, $J=3.4$ Hz), 4.80–4.85 (m, 2H), 5.00 (d, 1H, $J=5.2$ Hz), 7.86 (bt, 1H); ^{13}C NMR (DMSO-d_6) δ 45.83 (CH_2), 65.63 (CH, Cp), 67.06 (CH, Cp), 67.14 (2×CH, Cp), 67.63 (CH-OH), 68.12 (CH, Cp). 68.24 (CH, Cp), 68.42 (5×CH, Cp), 69.38 (5×CH, Cp), 69.80 (2×CH, Cp), 76.80 (q, Cp), 90.66 (q, Cp), 169.25 (C=O); EIMS *m*/*z*: (rel. intensity): 457 (M$^+$, 55), 440 (48), 439 (100), 374 (12), 254 (13), 253 (12), 228 (63), 213 (71), 186 (43), 121 (53). Anal. calcd for $C_{23}H_{23}Fe_2NO_2$: C, 60.43; H, 5.07; N, 3.06. Found: C, 60.21; H, 4.83; N, 3.19%.

4.4.3. (*R*,*R*)-2,2-Dimethyl-*N*,*N*′-bis(2-ferrocenyl-2-hydroxyethyl)propanediamide, 5c. Prepared according to the general procedure, starting from (*R*)-2-amino-1-ferrocenylethanol **4** (0.25 g, 1.02 mmol) and dimethylmalonyl chloride (0.51 mmol). Yield = 87%; $[\alpha]_D=-4.5$ (*c* 2.92, $CHCl_3$); mp 68–70°C; IR (Nujol) 3375, 1652, 1527, 1456, 1307, 1231, 1192, 1108, 1070, 822 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 6H), 2.75 (bs, 2H), 3.18–3.22 (m, 2H), 3.67–3.69 (m, 2H), 4.14–4.24 (m, 18H), 4.43–4.48 (m, 2H), 6.90 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 23.94 (2×CH_3), 46.38 (2×CH_2), 49.77 (q), 66.22 (2×CH, Cp), 66.90 (2×CH, Cp), 68.51 (4×CH, Cp), 68.90 (10×CH, Cp), 90.23 (2×q, Cp), 174.22 (2×C=O); EIMS *m*/*z*: (rel. intensity): 586 (M$^+$, 9), 568 (7), 550 (100), 485 (24), 297 (38), 253 (51), 227 (35), 214 (15), 199 (11), 186 (23), 121 (47), 69 (57). Anal. calcd for $C_{29}H_{34}Fe_2N_2O_4$: C, 59.41; H, 5.85; N, 4.78. Found: C, 59.61; H, 5.66; N, 4.60%.

4.4.4. (*R*,*R*)-*N*,*N*′-Bis(2-ferrocenyl-2-hydroxyethyl)-1,1′-ferrocenedicarboxamide, 5d. Prepared according to the general procedure, starting from (*R*)-2-amino-1-ferrocenylethanol **4** (0.25 g, 1.02 mmol) and 1,1′-ferrocenedicarbonyl dichloride (0.51 mmol). Yield = 71%; $[\alpha]_D=-29.2$ (*c* 0.6, MeOH); mp 152–154°C; IR (Nujol) 3336, 1611, 1552, 1457, 1298, 1067, 1032, 826 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.14–3.32 (m, 2H), 3.72–3.83 (m, 2H), 4.13 (bs, 4H), 4.20–4.28 (m, 14H), 4.38 (bs, 2H), 4.43 (bs, 2H), 4.55–4.68 (m, 2H), 4.77 (bs, 2H), 4.80 (bs, 2H), 5.20 (d, 2H, $J=5.20$ Hz), 8.02 (bt, 2H); ^{13}C NMR (DMSO-d_6) δ 45.78 (2×CH_2), 65.60 (2×CH, Cp), 67.18 (2×CH, Cp), 67.28 (2×CH, Cp), 67.38 (2×CH, Cp), 68.39 (2×CH, CH-OH), 68.46 (10×CH, Cp), 69.52 (2×CH, Cp), 70.15 (2×CH, Cp), 71.30 (2×CH, Cp), 71.49 (2×CH, Cp), 77.72 (2×q, Cp), 90.16 (2×q, Cp), 168.70 (2×C=O); EIMS *m*/*z*: (rel. intensity): 692 (M$^+$–2H_2O, 100), 627 (79), 319 (40), 255 (23), 212 (45), 199 (40), 186 (36), 121 (75). Anal. calcd for $C_{36}H_{36}Fe_3N_2O_4$: C, 59.38; H, 4.98; N, 3.85. Found: C, 59.59; H, 5.12; N, 3.65%.

4.4.5. (*R*,*R*)-1,1′-Bis(2-phenylcarbonylamino-1-hydroxyethyl)ferrocene, 5e. Prepared according to the general procedure, starting from (*R*,*R*)-1,1′-bis(2-amino-1-hydroxyethyl)ferrocene **11** (0.25 g, 0.82 mmol) and benzoyl chloride (1.64 mmol). Yield = 57%; $[\alpha]_D=-2.6$ (*c* 0.75, MeOH); mp 148–150°C; IR (CH_2Cl_2): 3334, 1642, 1539, 1464, 1122, 1075, 710 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.29 (ddd, 2H, $J=13.0$ Hz, $J=8.4$ Hz, $J=5.1$ Hz), 3.64 (dd, 2H, $J=13.0$ Hz, $J=5.8$ Hz, $J=4.4$ Hz), 4.18 (m, 4H), 4.21 (bs, 2H), 4.25 (bs, 2H), 4.58 (ddd, 2H, $J=8.4$ Hz, $J=4.5$ Hz, $J=4.4$ Hz), 5.26 (d, 2H, $J=4.5$ Hz), 7.41–7.54 (m, 3H), 7.88 (dd, 2H, $J=7.95$ Hz, $J=1.35$ Hz), 8.49 (bs, 2H); ^{13}C NMR (DMSO-d_6) δ 46.76 (2×CH_2), 66.23 (2×CH, Cp), 67.26 (2×CH, Cp), 67.36 (2×CH, Cp), 67.87 (2×CH, Cp; 2×CH-OH), 90.94 (2×q, Cp), 127.17 (4×CH, Ph),

128.15 (4×CH, Ph), 130.98 (2×CH, Ph), 134.59 (2×q, Ph), 166.31 (2×C=O); EIMS m/z: (rel. intensity): 494 (M^+-H_2O, 96), 477 (42), 476 (M^+-2H_2O, 86), 373 (35), 266 (67), 248 (35), 105 (100), 77 (79). Anal. calcd for $C_{28}H_{28}FeN_2O_4$: C, 65.64; H, 5.51; N, 5.47. Found: C, 65.44; H, 5.74; N, 5.31%.

4.4.6. (*R*,*R*)-1,1′-Bis(2-ferrocenylcarbonylamino-1-hydroxyethyl)ferrocene, 5f. Prepared according to the general procedure, starting from (*R*,*R*)-1,1′-bis(2-amino-1-hydroxyethyl)ferrocene **11** (0.25 g, 0.82 mmol) and 1,1′-ferrocenedicarbonyl dichloride (1.64 mmol). Yield = 87%; $[\alpha]_D = -12$ (*c* 1.28, $CHCl_3$); mp 74–76°C; IR (CH_2Cl_2): 3338, 1635, 1538, 1470, 1382, 1290, 1109, 1029, 828 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.29 (ddd, 2H, $J = 14.0$ Hz, $J = 7.3$ Hz, $J = 5.5$ Hz), 3.69 (ddd, 2H, $J = 14.0$ Hz, $J = 6.2$ Hz, $J = 2.8$ Hz), 4.16–4.22 (m, 18H), 4.28 (bs, 2H), 4.33 (t, 4H, $J = 1.8$ Hz), 4.68 (bs, 4H), 4.74 (dd, 2H, $J = 7.3$ Hz, $J = 2.8$ Hz), 6.45 (bt, 2H); ^{13}C NMR ($CDCl_3$) δ 47.88 (2×CH_2), 66.17 (2×CH, Cp), 67.17 (2×CH, Cp), 68.00 (2×Ch, Cp), 68.21 (2×CH, Cp), 68.30 (4×CH, Cp), 69.81 (10×CH, Cp), 70.00 (2×CH-OH), 70.50 (4×CH, Cp), 75.52 (2×q, Cp), 90.64 (2×q, Cp), 171.95 (2×C=O); EIMS m/z: (rel. intensity): 710 (M^+-H_2O, 49), 693 (45), 692 (M^+-2H_2O, 100), 463 (53), 213 (70), 185 (40), 121 (47). Anal. calcd for $C_{36}H_{36}Fe_3N_2O_4$: C, 59.38; H, 4.98; N, 3.85. Found: C, 59.12; H, 4.76; N, 3.99%.

4.5. General procedure for the preparation of 2,5-disubstituted thiazolines, 7

To a suspension of the appropriate β-hydroxyamide (1 equiv.) in dry THF (20 mL) Lawesson's reagent (2 equiv.) was added and the mixture was heated at reflux temperature and under nitrogen, for 3 h. Then, the solvent was removed under reduced pressure and the residue was directly chromatographed on a silica gel column using CH_2Cl_2–EtOAc (20:1) and then using CH_2Cl_2–MeOH (15:1) to give the corresponding thiazoline.

4.5.1. (*R*)-2-Phenyl-5-ferrocenylthiazoline, 7a. Yield = 65%; $[\alpha]_D = -11.0$ (*c* 1.73, $CHCl_3$); mp 96–98°C; IR (CH_2Cl_2) 1595, 1576, 1490, 1449, 1312, 1267, 1236, 1106, 1002, 826, 708 cm^{-1}; ^1H NMR (CDCl3) δ 4.12–4.28 (m, 9H), 4.61 (m, 2H), 4.94 (t, 1H, $J = 7.2$ Hz), 7.36–7.45 (m, 3H), 7.80–7.85 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 51.55 (CH, thiaz.), 66.96 (CH, Cp), 67.29 (CH, Cp), 68.42 (2×CH, Cp), 68.93 (5×CH, Cp), 72.00 (CH_2, thiaz.), 89.26 (q, Cp), 128.34 (2×CH, Ph), 128.54 (2×CH, Ph), 131.16 (CH, Ph), 133.52 (q, Ph), 167.41 (q, thiaz.); EIMS m/z: (rel. intensity): 347 (M^+, 100), 244 (69), 186 (33), 178 (45), 91 (51). Anal. calcd for $C_{19}H_{17}FeNS$: C, 65.72; H, 4.93; N, 4.03; found: C, 65.92; H, 4.80; N, 3.87%.

4.5.2. (*R*)-2,5-Diferrocenylthiazoline, 7b. Yield = 84%; $[\alpha]_D = 64.0$ (*c* 2.27, $CHCl_3$); mp 114–116°C; IR (CH_2Cl_2) 1607, 1457, 1414, 1377, 1308, 1289, 1109, 1057, 1003, 742 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.14 (t, 2H, $J = 1.8$ Hz), 4.16–4.25 (m, 12H), 4.35 (t, 2H, $J = 1.8$ Hz), 4.28 (dd, 1H, $J = 15.45$ Hz, $J = 7.80$ Hz), 4.45 (dd, 1H, $J = 15.45$ Hz, $J = 5.40$ Hz), 4.67 (m, 1H), 4.72 (m, 1H), 4.85 (dd, 1H, $J = 7.80$ Hz, $J = 5.40$ Hz); ^{13}C NMR ($CDCl_3$) δ 51.01 (CH, thiaz.), 66.70 (CH, Cp), 67.32 (CH, Cp), 68.33 (2×CH, Cp), 68.86 (5×CH, Cp), 69.20 (CH, Cp), 69.27 (CH,Cp), 69.96 (5×CH, Cp), 70.38 (2×CH, Cp), 71.34 (CH_2, thiaz.), 77.28 (q, Cp), 89.59 (q, Cp), 167.64 (q, thiaz.); EIMS m/z: (rel. intensity): 455 (M^+, 100), 244 (85), 211 (41), 178 (19), 121 (44). Anal. calcd for $C_{23}H_{21}Fe_2NS$: C, 60.69; H, 4.65; N, 3.08; found: C, 60.58; H, 4.79; N, 3.21%.

4.5.3. (*R*,*R*)-2,2-Bis(5-ferrocenylthiazolin-2-yl)propane, 8. Yield 30%; yellow oil; IR (CH_2Cl_2) 1613, 1463, 1289, 1106, 1028, 1001, 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55 (s, 6H), 4.10–4.17 (m, 18H), 4.38–4.45 (m, 4H), 4.78–4.84 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 26.64 (2×CH_3), 47.61 (q), 51.66 (2×CH, thiaz.), 67.00 (2×CH, Cp), 67.37 (2×CH, Cp), 68.28 (4×CH, Cp), 68.86 (10×CH, Cp), 71.51 (2×CH_2, thiaz.), 89.38 (2×q, Cp), 174.57 (2×q, thiaz.); EIMS m/z: (rel. intensity): 582 (M^+, 100), 566 (24), 518 (6), 517 (19), 515 (10), 395 (20), 313 (48), 253 (37), 212 (36), 121 (27). Anal. calcd for $C_{29}H_{30}Fe_2N_2S_2$: C, 59.81; H, 5.19; N, 4.81; found: C, 59.97; H, 5.00; N, 4.69%.

4.5.4. (*R*,*R*)-1,1′-Bis(5-ferrocenylthiazolin-2-yl)ferrocene, 9. Yield: 40%; $[\alpha]_D = +43.2$ (*c* 2.27, $CHCl_3$); mp 195–197°C; IR (CH_2Cl_2) 1612, 1458, 1104, 1059, 1004, 819 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.14–4.23 (m, 18H), 4.36–4.43 (m, 8H), 4.67–4.76 (m, 4H), 4.84–4.91 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 51.47 (2×CH, thiaz.), 66.87 (2×CH, Cp), 67.46 (2×CH, Cp), 68.48 (2×CH, Cp), 68.51 (2×CH, Cp), 68.99 (10×CH, Cp), 70.79 (2×CH, Cp), 70.96 (2×CH, Cp), 71.51 (2×CH_2, thiaz.), 72.76 (4×CH, Cp), 78.77 (2×q, Cp-), 79.51 (2×q, Cp), 167.62 (2×q, thiaz.); EIMS m/z: (rel. intensity): 724 (M^+, 100), 659 (14), 481 (33), 480 (24), 335 (55), 244 (64), 212 (70), 186 (26), 121 (31). Anal. calcd for $C_{36}H_{32}Fe_3N_2S_2$: C, 59.70; H, 4.45; N, 3.87; found: C, 59.82; H, 4.38; N, 3.71%.

4.5.5. (*R*,*R*)-1,1′-Bis(2-ferrocenylthiazolin-5-yl)ferrocene, 12. Yield = 60%; $[\alpha]_D = +23.7$ (*c* 0.72, $CHCl_3$); mp 131–133°C; IR (CH_2Cl_2) 1600. 1504, 1459, 1308, 1294, 1110, 1029, 1003, 831 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.17–4.20 (m, 18H), 4.37 (bs, 8H), 4.69–4.74 (m, 4H), 4.85–4.90 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 50.77 (2×CH, thiaz.), 67.58 (2×CH, Cp), 68.27 (2×CH, Cp), 69.43 (4×CH, Cp), 69.53 (4×CH, Cp), 70.10 (10×CH, Cp), 70.73 (4×CH, Cp), 71.07 (2×CH_2, thiaz.), 90.09 (2×q, Cp), 168.39 (2×q, thiaz.); EIMS m/z: (rel. intensity): 724 (M^+, 100), 481 (13), 479 (23), 391 (31), 389 (15), 211 (64). Anal. calcd for $C_{36}H_{32}Fe_3N_2S_2$: C, 59.70; H, 4.45; N, 3.87; found: C, 59.88; H, 4.32; N, 3.66%.

4.5.6. (*R*,*R*)-1,1′-Bis(2-phenylthiazolin-5-yl)ferrocene, 13. Yield = 45%; $[\alpha]_D = +13.2$ (*c* 1.21, $CHCl_3$); mp 76–78°C; IR (CH_2Cl_2) 1598, 1579, 1492, 1447, 1312, 1288, 1178, 1046, 1027, 1009, 945, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.16 (s, 4H), 4.21 (s, 2H), 4.25 (2H), 4.51 (dd, 2H, $J = 16$ Hz, $J = 6$ Hz), 4.61 (dd, 2H, $J = 16$ Hz, $J = 8.1$ Hz), 4.49 (dd, 2H, $J = 8.1$ Hz, $J = 6.0$ Hz), 7.37–7.47 (m, 6H), 7.81–7.84 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 51.29 (2×CH, thiaz.), 67.87 (2×CH, Cp), 68.10 (2×CH, Cp),

69.41 (2×CH, Cp), 69.49 (2×CH, Cp), 72.12 (2×CH_2, thiaz.), 89.90 (2×q, Cp), 128.35 (4×CH, Ph), 128.55 (4×CH, Ph), 131.22 (2×CH, Ph), 133.40 (2×q, Ph), 167.32 (2×q, thiaz.); EIMS *m/z*: (rel. intensity): 508 (M^+, 100), 284 (32), 283 (62), 121 (27), 91 (73), 77 (19). Anal. calcd for $C_{28}H_{24}FeN_2S_2$: C, 66.14; H, 4.76; N, 5.51; found: C, 66.33; H, 4.89; N, 5.61%.

4.6. X-Ray crystallographic analysis for compound, 7b

Crystal data: $C_{23}H_{21}Fe_2NS$, Mr = 455.17, orthorhombic, *P*2(1)2(1)2(1), $a = 5.8393(4)$, $b = 11.5854(10)$, $c = 27.4509(15)$ Å, $V = 1857.1(2)$ Å^3, $Z = 4$, λ(Mo Kα) = 0.71073 Å, $T = -100$°C. *Data collection*: colorless block 0.60×0.40×0.14 mm, Siemens P4 diffractometer, 3463 intensities (3241 unique), $2\theta_{max}$ 50°. *Structure solution and refinement*: Patterson method, refined on F^2 (program SHELXL-93, Sheldrick, G. M., University of Göttingen), $\mu = 1.682$ mm^{-1}, absorption correction = Psi-scans, H atoms with riding model, $R_1{}^{21a} = 0.0265$, $wR_2{}^{21b} = 0.0797$, 244 parameters, $S = 1.098$, Absolute structure parameter $X^{16} = -0.01(2)$, max. $\delta\rho = 0.257$ e Å^{-3}. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. 186514 **7b**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

We thank the Dirección General de Investigación (MCYT, Spain) project BQU2001-0014, for financial support.

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21. (a) $R_1 = \Sigma\big||F_o|-|F_c|\big|/\Sigma|F_o|$ for reflections with $I > 2\sigma(I)$; (b) $wR_2 = [\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[w(F_o^2)^2]^{0.5}$ for all reflections; $w^{-1} = \sigma^2(F^2)+(aP)^2+bP$, where $P = (2F_c^2+F_o^2)/3$ and *a* and *b* are constants set by the program).