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Synthesis of new central and planar chiral enantiomerically pure 5-ferrocenyl-oxazolines and a 5-ferrocenyl-thiazoline

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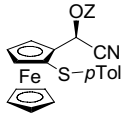
Abstract—Enantiomerically pure central and planar chiral ferrocenyl cyanohydrins have been used for the synthesis of previously unreported 5-ferrocenyl-oxazolines and a 5-ferrocenyl-thiazoline where the central chirality lies on the carbon bearing the oxygen or the sulfur atom. The epimerization at C_5 of the oxazoline ring has also been investigated.

1. Introduction

Enantiomerically pure cyanohydrins are versatile synthetic intermediates with two functional groups that can easily be manipulated into a wide range of other homochiral products, such as α-hydroxy acids, α-hydroxy aldehydes, α-hydroxy ketones, β-amino alcohols, N-substituted β-amino alcohols and α-amino acid derivatives.[1–3] The usual synthetic route to cyanohydrins involves the addition of a cyanide source to an aldehyde or ketone. This methodology is extremely versatile and usually gives very good yields. In order to obtain enantiomerically pure cyanohydrins, a number of asymmetric syntheses have been developed utilizing different catalysts including enzymes, polymeric reagents, organometallic species and peptides;[1,2,4] some examples of diastereoselective cyanation of chiral carbonyl compounds have also been reported.[2]

Chiral ferrocene derivatives[5] have found applications ranging from ligands for asymmetric catalysis to bioelectrochemistry[6] and the development of new pharmaceuticals against malaria.[7] Among the plethora of chiral ferrocene derivatives that have been synthesized,[5c,d] only a few examples have been reported concerning the synthesis of central chiral ferrocenyl cyanohydrins.[8] Recently we reported the synthesis of the first ferrocene cyanohydrins **1a** and **1b** containing both central and planar chirality[9] (Fig. 1); herein we report the reactivity of these derivatives that allows the preparation of different chiral heterocycles.



1a Z = H
1b Z = $SiMe_3$

Figure 1.

2. Results and discussion

Ferrocenyl cyanohydrins **1a** can be obtained by the reaction of (*S*)-(2-*p*-tolylthio)ferrocencarboxyaldehyde[9,10] with diethylaluminium cyanide (Et_2AlCN) at −78 °C in THF whereas the silyl derivative **1b** can be synthesized by reacting the same aldehyde with trimethylsilylcyanide at −50 °C in CH_2Cl_2 in the presence of a catalytic amount of ZnI_2. Both derivatives **1a** and **1b** have been obtained as a single diastereoisomer, in enantiomerically pure forms and quantitative yields in very short reaction times (i.e., a few minutes) (Scheme 1).[9]

The absolute configuration at the newly formed stereocentres of **1a** and **1b** was assigned as (*S*) by analogy with

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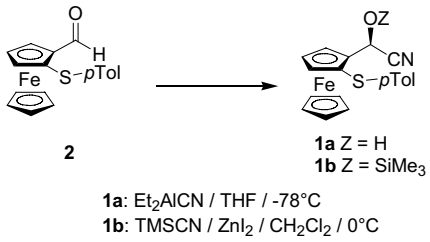


Scheme 1.

previously obtained results on (1*S*)-1-[(S_{Fc})-2-(*p*-tolylsulfanyl)-ferrocenyl](phenyl)methanol **3** (Fig. 2) that furnished a suitable crystal for X-ray analysis[9] (considering that the *ipso*-C-atom in ferrocene has a higher CIP priority than the cyano group[8c]).

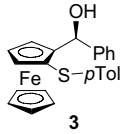
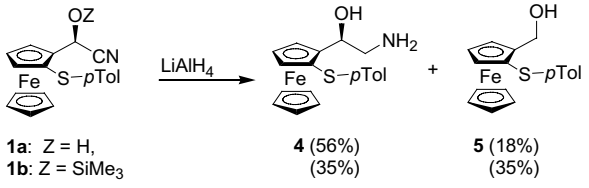


Figure 2.

The ferrocenyl cyanohydrins **1a** and **1b** were then easily reduced to the corresponding β-amino alcohol **4** using $LiAlH_4$ (Scheme 2) in THF/Et_2O. The reaction proceeded very quickly at reflux and furnished **4** in moderate to good yields (particularly when cyanohydrin **1a** was used) and as a single diastereoisomer as detected from the ^1H and ^{13}C NMR spectra of the crude mixture. A by-product of this reaction was the primary alcohol **5**, derived from the in situ reduction of aldehyde (*S*)-**2**, formed from the ferrocenyl cyanohydrins via HCN or TMSCN elimination.



Scheme 2.

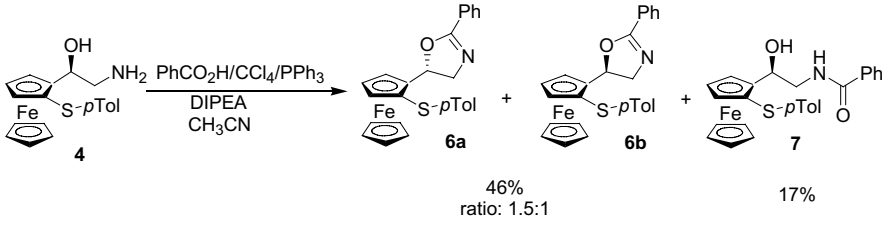
Chiral nonracemic oxazolines have found widespread application as ligands in a multitude of metal-catalyzed asymmetric reactions.[11] Among these ligands the ferrocenyl-oxazolines constitute a special group as they can present both central and planar chirality. These oxazolines have been described independently by several groups with various types of effective planar chiral ferrocene ligands being developed.[12] Recently, we reported[13] the synthesis of ferrocenyl oxazolines via ring expansion of *N*-ferrocenoyl-aziridine-2-carboxylic esters.

Among the available procedures described in the literature for the synthesis of oxazolines starting from β-amino alcohols, the most common are (i) single step methodologies[14] or (ii) cyclic dehydration reactions of a β-hydroxy amide (by converting the hydroxyl group into a good leaving group using numerous different reagents).[15] In particular, 5-substituted oxazolines have been obtained, using chiral secondary amino alcohols, either with complete inversion of configuration at the carbinol carbon,[15a,b,j,16] or with complete retention of configuration[16b,17] with only partial racemization being observed in a few cases.[18] To our knowledge, no examples of 5-ferrocenyl-oxazolines have been reported so far.

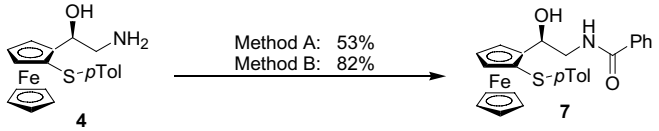
In light of the importance of these derivatives, we used the β-amino alcohol **4** as a precursor for this type of unknown ferrocenyl oxazolines. The β-amino alcohol **4** was reacted with PPh_3/CCl_4/DIPEA/CH_3CN and benzoic acid in a single step procedure affording the oxazolines **6** in 46% yield as a mixture of two diastereoisomers in a 1.5:1 ratio beside 17% of the β-hydroxyamide **7** (Scheme 3).

The β-hydroxy amide **7** was successfully prepared in 53% yield by acylation of **4** with benzoyl chloride in CH_2Cl_2 in the presence of Et_3N at room temperature, or in a higher yield (82%) by condensation with benzoic acid in THF in the presence of 1,3-dicyclohexylcarbodiimide (DCC) (Scheme 4). The β-hydroxy amide **7** was obtained as a single diastereoisomer since only one set of signals could be detected by ^1H and ^{13}C NMR spectra of the crude reaction mixture.

Amide **7** was then cyclodehydrated using different reagents as reported in Table 1. The use of Burgess's reagent {[(methoxycarbonyl)sulfamoyl]triethylammonium hydroxide},[19] according to Corey's conditions,[20] gave the diastereomeric oxazolines **6a** and **6b** in 55% total yield in a 1.5:1 ratio. Reaction with $SOCl_2$ at −20 °C afforded **6a** and **6b** in 81% yield in a 3:1 ratio.

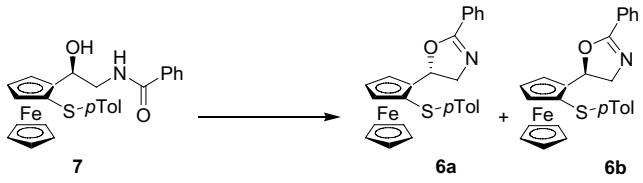


Scheme 3.



Scheme 4. Reagents and conditions: method A: $PhCOCl/Et_3N/CH_2Cl_2$, method B: $PhCO_2H/DCC$.

Table 1.



Entry	Reaction conditions	Total yield of **6** (%)	**6a**/**6b**
1	Burgess reagent/THF/rt	55	1.5:1
2	$DAST/CH_2Cl_2/-78\,°C$	70	2.5:1
3	$SOCl_2/CH_2Cl_2/-20\,°C$	81	3:1
4	$TsCl/Et_3N/DMAP/CH_2Cl_2/rt$	—	—

Treatment of β-hydroxy amide **7** with a slight excess (1.1 equiv) of DAST at −78 °C, yielded **6a** and **6b** in 70% yield in a 2.5:1 ratio. The use of $TsCl/DMPA/Et_3N$ left the starting β-hydroxyamide **7** unreacted. In all the reactions examined the major diastereoisomer **6a** was the same as obtained with the direct methodology (Scheme 3).

The two diastereomeric oxazolines **6** were separated by chromatography on deactivated neutral alumina with the absolute configuration of the major diastereoisomer **6a** being assigned as (*R*) by X-ray analysis (Fig. 3).[21]

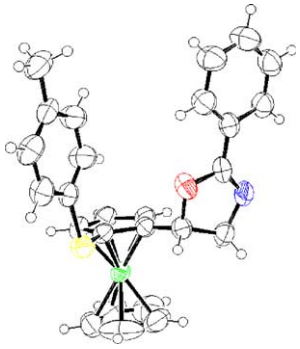
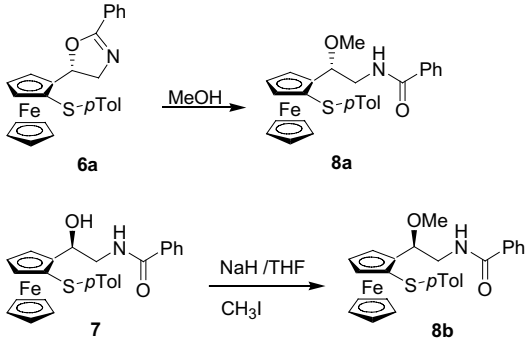


Figure 3. X-ray crystal structure of (R,S_{Fc})-**6a**.

During the ^1H NMR study of the two diastereomeric oxazolines, we observed an interconversion between (*R*)-**6a** and (*S*)-**6b**. The extent of interconversion was highly dependent on the solvent used. The pure major diastereoisomer (*R*)-**6a** was kept in $CDCl_3$ solution for 5 days and afforded a 1.7:1 mixture of **6a** and **6b**.[22] The minor diastereoisomer (*S*)-**6b** in $CDCl_3$ equilibrated in 5 days to a mixture of **6a** and **6b** in a 1.5:1 ratio.[23] (*R*)-**6a** was found to be very stable in C_6D_6, and was in fact recovered unchanged after 5 days. Conversely **6b** afforded, after 5 days, a 1:5 mixture of **6a**/**6b**. Apparently the more acidic $CDCl_3$ favoured the interconversion between **6a** and **6b**. Moreover, chromatography on silica gel resulted in extensive decomposition. Treatment of the major diastereoisomer (*R*)-**6a** with methanol afforded amide **8a**, arising from a ring opening reaction, as a single diastereoisomer in a quantitative yield. We assumed that the configuration of **8a** was (*R*), on the basis of the fact that we obtained the other diastereoisomer **8b**, with an (*S*)-configuration for the carbon bearing the methoxy group, starting from (*S*)-**7** via a methylation procedure[24] (NaH, CH_3I) (Scheme 5).



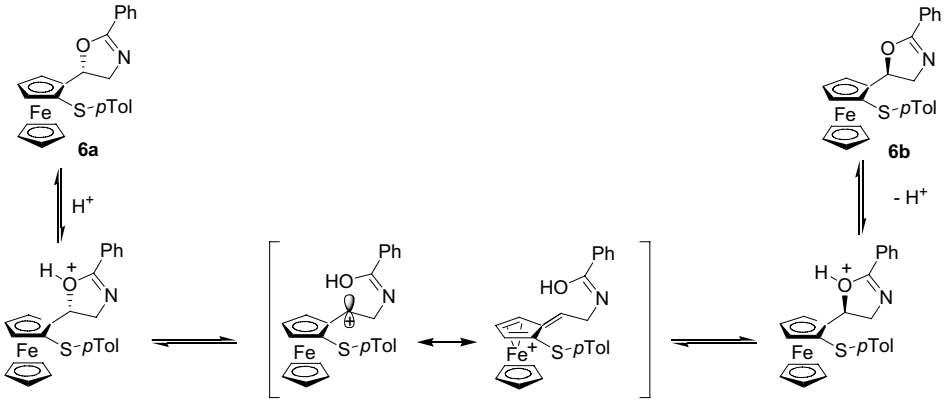
Scheme 5.

It is known that nucleophilic displacement on α-heterosubstituted ferrocenes usually takes place with full retention of configuration (retentive substitution of the S_N1 type) due to the pronounced stabilization of ferrocenylalkyl cations[25] by assuming metal participation or iron hyperconjugation. However, in our case the major isomer (*R*)-**6a** was the product formed with inversion of configuration. This could be explained by the first formed oxazoline, (*S*)-**6b**, partially epimerizing to the more stable **6a** due to the acidity of the reaction conditions.

The instability of oxazolines **6**, especially in the presence of trace amounts of acids, can be attributed to the outstanding ability of the ferrocenyl groups to stabilize an adjacent positive charge,[25,26] strengthened, in our case, by the electron donating ability of the thiotolyl group present in the *ortho*-position of the ferrocene.

These properties render the oxazolines prone to a variety of ring opening processes such as the interconversion between **6a** and **6b** (Scheme 6) in $CDCl_3$ solution, the instability on silica gel and the nucleophilic ring opening in MeOH. The much reduced degree of epimerization of **6** in C_6D_6 is probably due to the lower acidity of this solvent.

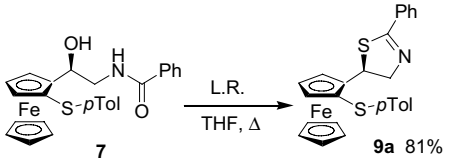
The thiazoline ring system is a common feature in a variety of biologically active natural products,



Scheme 6.

particularly of marine origin.[27] As far as the asymmetric catalysis is concerned, chiral thiazolines have received poor attention despite the fact that the electronic and steric effects resulting from the replacement of the oxygen with sulfur could change the behaviour of the chelating heterocycle towards metals; there have been only few reports on the preparation of chiral thiazoline analogues of known oxazoline ligands.[28] Moreover only one example of a central chiral ferrocenyl thiazoline has been very recently reported.[29]

The β-hydroxy amide **7** was submitted to a reaction with an excess amount of Lawesson's reagent[30] (L.R., 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide) in THF at reflux and yielded the corresponding ferrocenyl-thiazoline **9a** combining the thionation and the cyclodehydration reactions in a one step procedure (Scheme 7). The ^{1}H and ^{13}C NMR spectra of the crude reaction mixture showed the presence of a single diastereoisomer. Chromatography on deactivated neutral alumina gave the thiazoline **9a** in 81% yield. Epimerization at C_5 of the thiazoline ring was observed during chromatography on silica gel that furnished the two diastereoisomers **9a** and **9b** in a 8:1 ratio.



Scheme 7.

We assume that the cyclodehydration takes place with full retention of configuration in accordance with previously reported data[29] affording the thiazoline with an (*S*)-configuration at C_5. Moreover the ^{1}H NMR spectrum of this compound is very similar to the spectrum of the minor diastereoisomer (*S*)-**6b** of the corresponding oxazoline. The thiazoline **9a** was found configurationally more stable with respect to oxazoline **6**. A solution of **9a** in $CDCl_3$ was indeed found unchanged after several days.

3. Conclusions

In conclusion, starting from enantiomerically pure planar and central chiral ferrocenyl cyanohydrins, we have obtained the previously unreported 5-ferrocenyl-oxazolines **6** and thiazolines **9** with central and planar chirality where the stereogenic centre lies on the carbon bearing the oxygen or sulfur atom. The possibility of using these compounds as ligands for asymmetric catalysis will be investigated in the future.

4. Experimental

4.1. General

Melting points (uncorrected) were determined with a Büchi melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Varian Gemini 300 at 300 and 75.46 MHz, respectively, or with a Varian Mercury Plus 400 at 400 and 100.57 MHz, respectively, using $CDCl_3$ or C_6D_6 solutions of the samples. Chemical shifts (δ) are reported in ppm relative to $CHCl_3$ ($\delta = 7.26$ for ^{1}H and $\delta = 77.0$ for ^{13}C). J Values are given in Hz. ^{13}C NMR spectral assignments were made by DEPT experiments. IR spectra were recorded on a Perkin–Elmer model 257 grating spectrometer. Mass spectra were obtained using a VG 7070-E spectrometer at an ionizing voltage of 70 eV or with an electrospray ionization source (ESIMS). All the ESIMS spectra were performed using MeOH as the solvent. $[\alpha]_D$ values were measured with Perkin–Elmer Polarimeter 341 and are given in 10^{-1} deg cm^2 g^{-1}. The originality of all compounds was checked by a CAS-on-line structure search. Reactions were conducted in oven-dried (120 °C) glassware under a positive Ar atmosphere. Transfer of anhydrous solvents or mixtures was accomplished with oven-dried syringes/septum techniques. THF was distilled from sodium/benzophenone prior to use and stored under Ar. CH_2Cl_2 was passed through basic alumina and distilled from CaH_2 prior to use. Other solvents were purified by standard procedures. Light petroleum ether refers to the fraction with a bp 40–60 °C. The reactions were monitored by TLC, using silica gel plates (Baker-

flex IB2-F). Column chromatography was performed with Merck silica gel 60 (70–230 mesh). Preparative thick layer chromatography was carried out on glass plates using a 1 mm layer of Merck silica gel 60 Pf 254. All chemicals were used as obtained or purified by distillation as needed. Ferrocenyl cyanohydrins **1a** and **1b** were prepared as previously described.[9]

4.2. (S,S_{Fc})-2-Amino-1-[2-(*p*-tolylsulfanyl)ferrocenyl]-1-ethanol 4 (reduction of 1a)

To a solution of $LiAlH_4$ 1 M in THF (2.8 mL, 2.8 mmol) cooled at 0 °C, a solution of **1a** (200 mg, 0.54 mmol) in dry Et_2O (160 mL) was slowly added. The reaction was monitored by TLC and after 1 h at reflux was quenched with cold water, filtered and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The ^1H and ^{13}C NMR spectra of the crude reaction mixture showed the presence of amino alcohol **4** as a single diastereoisomer beside the primary alcohol **5**. Column chromatography (*n*-hexane/EtOAc 1:1 and then EtOAc/MeOH from 10:1 to 3:1) afforded alcohol **5** as the first R_f product in 18% yield as a yellow solid; mp 120–122 °C; $[\alpha]_D^{20} = +62.3$ (c 0.74, $CHCl_3$); (found; C, 64.00; H, 5.39. $C_{18}H_{18}FeOS$ required C, 63.92; H, 5.36); ν_{max} (CCl_4)/cm^{-1} 3589 (OH); δ_H (300 MHz, $CDCl_3$) 2.04 (1H, br s, OH), 2.13 (3H, s, CH_3), 4.12 (5H, s, FcH), 4.2 (1H, m, FcH), 4.23 (H, d, J 12, H_a–CH_2), 4.35 (2H, m, FcH), 4.44 (1H, d, J 12, H_b–CH_2), 6.90 (4H, s, ArH); δ_C (75 MHz, $CDCl_3$) 21.0 (q), 59.5 (t), 69.0, 70.1, 70.5, 75.6 (d), 90.9, 10.1 (s), 126.5, 129.8 (d), 135.3, 136.6 (s); m/z (ESI) 338 (M^+) and the amino alcohol **4** as the second R_f product in 56% yield as a yellow solid; mp 96–98 °C; $[\alpha]_D^{20} = -191$ (c 0.5, CH_2Cl_2); (found; C, 62.19; H, 5.70. $C_{19}H_{21}FeNOS$ required C, 62.13; H, 5.76); ν_{max} (CCl_4)/cm^{-1} 3415 (br OH); δ_H ($CDCl_3$, 300 MHz) 1.89 (1H, br s, OH), 2.24 (3H, s, CH_3) 2.24 (1H, dd, J 13 and 7, H_a–CH_2), 2.58 (1H, dd, J 13 and 3.3, H_b–CH_2), 4.29 (5H, s, FcH), 4.34 (1H, t, J 2.5, FcH), 4.46 (2H, d, J 2.5, FcH), 4.57 (1H, dd, J 7 and 3.3, CH), 6.90 (2H, d, J 8.4, ArH), 6.98 (2H, d, J 8.4, ArH); δ_C ($CDCl_3$, 75 MHz) 21.0 (q), 48.4 (t), 67.4, 68.85, 69.4, 70.3 76.0 (d) 75.2, 94.2 (s), 129.6, 129.7, (d), 135.1, 135.7 (s); m/z (ESI) 368 (M^++1).

4.3. (S,S_{Fc})-2-Amino-1-[2-(*p*-tolylsulfanyl)ferrocenyl]-1-ethanol 4 (reduction of 1b)

To a solution of $LiAlH_4$ 1 M in THF (1 mL, 1 mmol) cooled at 0 °C, a solution of **1b** (88 mg, 0.2 mmol) in Et_2O (15 mL) was slowly added. The reaction was monitored by TLC and after 15 min at reflux was quenched with cold water, filtered and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The ^1H and ^{13}C NMR spectra of the crude reaction mixture showed the presence of amino alcohol **4** as a single diastereoisomer beside the primary alcohol **5**. Column chromatography (*n*-hexane/EtOAc, 1:1 and then EtOAc/MeOH from 10:1 to 3:1) afforded alcohol **5** as the first R_f product in 35% yield as a yellow solid and amino alcohol **4** as the second R_f product in 56% yield as a yellow solid.

4.4. *N*-((2*S*)-2-Hydroxy-2-[(S_{Fc})-2-(*p*-tolylsulfanyl)ferrocenyl]ethyl)benzenecarboxamide 7

To a solution of **4** (165 mg, 0.45 mmol) and Et_3N (0.63 mmol, 0.1 mL) in CH_2Cl_2 (20 mL) cooled at 0 °C, under argon, benzoyl chloride (69 mg, 0.47 mmol) was added. The reaction was left overnight and quenched with 1 M NaOH. The organic layer was extracted with CH_2Cl_2 washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The ^1H and ^{13}C NMR spectra of the crude reaction mixture showed the presence of a single diastereoisomer. The crude was purified by chromatography on silica gel (light petroleum/Et_2O, 3:1) affording the title compound as a yellow solid in 53% yield; mp 60–62 °C (dec); $[\alpha]_D^{20} = +3.7$ (c 0.505, $CHCl_3$); (found; C, 66.29; H, 5.29. $C_{26}H_{25}FeNO_2S$ required C, 66.25; H, 5.35); ν_{max} (CCl_4)/cm^{-1} 1656 (CO); δ_H (300 MHz, $CDCl_3$) 2.25 (3H, s, CH_3), 3.32 (1H, m, H_a–CH_2), 3.57 (1H, 2m, H_b–CH_2), 4.29 (5H, s, FcH), 4.33 (1H, m, FcH), 4.46 (1H, m, FcH), 4.51 (1H, m, FcH), 4.84 (1H, dd, J 7 and 9, CH), 6.38 (1H, br t, NH), 6.94–7.03 (4H, m, ArH), 7.35–7.52 (3H, m, ArH), 7.67 (2H, d, J 8, ArH); δ_C (75 MHz, $CDCl_3$) 21.0 (q), 46.7 (t), 68.2, 68.7, 68.9 70.4, 75.9 (d), 74.9, 93.3 (s), 126.3, 126.9, 128.5, 129.6, 131.5 (d), 134.1, 135.3, 136.1 (s), 168.5 (s, CON); m/z (ESI) 471 (M^+), 494 (M^++Na).

4.5. *N*-((2*S*)-2-Hydroxy-2-[(S_{Fc})-2-(*p*-tolylsulfanyl)ferrocenyl]ethyl)benzenecarboxamide 7

N,*N*-Dicyclohexycarbodiimide (DCC) (202 mg, 0.98 mmol) was added to a stirred and cooled (0 °C) solution of benzoic acid (120 mg, 0.98 mmol) in CH_2Cl_2 (3 mL) and the obtained solution left for 30 min. Amino alcohol **4** (300 mg, 0.82 mmol) was then added in one portion and the reaction mixture was stirred at room temperature for 2 h. The mixture was then filtered on Celite and successively washed with sodium carbonate solution 10% (10 mL) and brine (10 mL) then dried and concentrated. The ^1H and ^{13}C NMR spectra of the crude reaction mixture showed the presence of a single diastereoisomer. The crude was purified by chromatography on silica (light petroleum/Et_2O, 3:1) affording the title compound in 81% yield as a yellow solid.

4.6. (5*R*)-5-[(S_{Fc})-2-(*p*-Tolylsulfanyl)ferrocenyl]-2-phenyl-1,3-oxazoline 6a and (5*S*)-5-[(S_{Fc})-2-(*p*-tolylsulfanyl)-ferrocenyl]-2-phenyl-1,3-oxazoline 6b (direct methodology)

To a solution of **4** (100 mg, 0.27 mmol), benzoic acid (33 mg, 0.27 mmol), triphenylphosphine (0.21 g, 0.8 mmol) and DIPEA (0.17 mL, 0.81 mmol) in CH_2Cl_2 (5 mL) cooled at 0 °C, under argon atmosphere, CCl_4 (0.16 mL, 1.35 mmol) was added in 1 h. The mixture was left overnight at room temperature and then concentrated under vacuum. The ^1H and ^{13}C NMR spectra of the crude reaction mixture showed the presence of **6a** and **6b** in a 1.5:1 ratio, and amide **7** with the absence of the starting amino alcohol **4**. Chromatography of the crude on deactivated neutral alumina (light petroleum/EtOAc, 10:1) afforded as the first R_f fraction the minor

diastereoisomer (5*S*)-**6b** (22 mg, 18%), as the second R_f fraction the major diastereoisomer (5*R*)-**6a** (34 mg, 28%) and as the third R_f fraction the amide **7** (22 mg, 17%).

4.6.1. (5*R*)-6a. Mp 138–139 °C; $[\alpha]_D^{20} = +103.2$ (*c* 0.578, C_6H_6); (found; C, 68.58; H, 5.22. $C_{26}H_{23}FeNOS$ required C, 68.88; H, 5.11); ν_{max} (CCl_4)/cm^{-1} 1648(CON); δ_H (400 MHz, $CDCl_3$) 2.31 (3H, s, CH_3), 4.25 (5H, s, FcH), 4.28 (1H, dd, *J* 14.7 and 7.7, H_a–CH_2), 4.39 (1H, m, FcH), 4.41 (1H, dd, *J* 14.7 and 4.6 H_b–CH_2), 4.46 (1H, br t, FcH), 4.54 (1H, dd, *J* 2.5 and 1.4, FcH), 5.82 (1H, dd, *J* 10.1 and 7.7, CH), 7.05 (1H, m, ArH), 7.10 (1H, m, ArH), 7.34 (2H, m, ArH), 7.43 (1H, m, ArH), 7.74 (2H, m, ArH); δ_C (100 MHz, $CDCl_3$) 20.9 (q), 60.2 (t), 68.3, 69.8, 70.2, 76.26 (d, FcCH), 76.29 (d), 77.7, 88.7 (s, FcC), 127.0 (d), 127.9 (s), 128.12, 128.17, 129.3, 131.1 (d), 135.1, 136.3 (s), 163.6 (s, CNO); *m*/*z* (ESI) 453 (M^+), 454 (M^++1), 476 (M^++Na).

4.6.2. (5*S*)-6b. Mp 112–113 °C; $[\alpha]_D^{20} = +270.8$ (*c* 0.446, C_6H_6); (found; C, 68.58; H, 5.22. $C_{26}H_{23}FeNOS$ required C, 68.88; H, 5.11); ν_{max} (CCl_4)/cm^{-1} 1634 (CON); δ_H (400 MHz, $CDCl_3$) 2.23 (3H, s, CH_3), 3.52 (1H, dd, *J* 14.8 and 7.9, H_b–CH_2), 3.86 (1H, dd, *J* 14.7 and 10, H_a–CH_2), 4.33 (1H, br s, FcH), 4.336 (1H, br s, FcH), 4.344 (5H, s, FcH), 4.46 (1H, br t, FcH), 5.65 (1H, dd, *J* 10 and 7.9, CH), 6.93 (4H, m, ArH), 7.46 (3H, m, ArH), 7.96 (2H, m, ArH); δ_C (100 MHz, $CDCl_3$) 20.8 (q), 62.5 (t), 66.85, 68.8, 70.45, 75.38, (d, FcCH), 77.28 (d), 88.7, 91.6 (s, FcC), 126.45 (d), 127.8 (s), 128.1, 128.4, 129.45, 131.2 (d), 135.1, 136.2 (s), 163.5 (s, CNO); *m*/*z* (ESI) 453 (M^+), 454 (M^++1), 476 (M^++Na), 494 (M^++K).

4.7. (5*R*)-5-[(S_{Fc})-2-(*p*-Tolylsulfanyl)ferrocenyl]-2-phenyl-1,3-oxazoline 6a and (5*S*)-5-[(S_{Fc})-2-(*p*-tolylsulfanyl)-ferrocenyl]-2-phenyl-1,3-oxazoline 6b (Burgess reagent)

A solution of **7** (110 mg, 0.23 mmol) and Burgess's reagent (107 mg, 0.43 mmol) in 5 mL of THF was reacted overnight at room temperature. The crude was concentrated under vacuum. The ^{1}H and ^{13}C NMR spectra of the crude reaction mixture showed the presence of **6a** and **6b** in a 1.5:1 ratio. Chromatography of the crude on deactivated neutral alumina (light petroleum/EtOAc, 10:1) afforded as the first R_f fraction the minor diastereoisomer **6b** (23 mg, 22%) and as the second R_f fraction the major diastereoisomer **6a** (35 mg, 33%).

4.8. (5*R*)-5-[(S_{Fc})-2-(*p*-Tolylsulfanyl)ferrocenyl]-2-phenyl-1,3-oxazoline 6a and (5*S*)-5-[(S_{Fc})-2-(*p*-tolylsulfanyl)-ferrocenyl]-2-phenyl-1,3-oxazoline 6b ($SOCl_2$)

Thionyl chloride (59 mg, 0.5 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise to a cold (−20 °C) solution of amide **7** (120 mg, 0.25 mmol) in dry CH_2Cl_2 (8 mL). After stirring at −20 °C for 1 h and at 0 °C for 1 h, cold 20% aqueous K_2CO_3 (25 mL) was added and the solution stirred at room temperature for 30 min and then extracted with CH_2Cl_2 (10 mL × 3). The extract was dried over $MgSO_4$ and concentrated in vacuo. The ^{1}H and ^{13}C NMR spectra of the crude reaction mixture showed the presence of **6a** and **6b** in a 3:1 ratio. Purification of the crude by column chromatography on deactivated neutral alumina (light petroleum/EtOAc, 10:1) afforded as the first R_f fraction the minor diastereoisomer **6b** (23 mg, 20%) and as the second R_f fraction the major diastereoisomer **6a** (69 mg, 61%).

4.9. (5*R*)-5-[(S_{Fc})-2-(*p*-Tolylsulfanyl)ferrocenyl]-2-phenyl-1,3- oxazoline 6a and (5*S*)-5-[(S_{Fc})-2-(*p*-tolylsulfanyl)-ferrocenyl]-2-phenyl-1,3-oxazoline 6b (DAST)

Diethylaminosulfur trifluoride (44 mg, 0.275 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a cold (−78 °C) solution of **7** (120 mg, 0.25 mmol) in CH_2Cl_2 (5 mL). After stirring for 1 h at −78 °C, anhydrous K_2CO_3 (52 mg, 0.375 mmol) was added in one portion and the mixture then allowed to warm to ambient temperature. The reaction was poured into saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ filtered and concentrated in vacuo. The ^{1}H and ^{13}C NMR spectra of the crude reaction mixture showed the presence of **6a** and **6b** in a 2.5:1 ratio. Purification of the crude by column chromatography on deactivated neutral alumina (light petroleum/EtOAc, 10:1) afforded as the first R_f fraction the minor diastereoisomer **6b** (22 mg, 20%) and as the second R_f fraction the major diastereoisomer **6a** (57 mg, 50%).

4.10. (5*R*)-5-[(S_{Fc})-2-(*p*-Tolylsulfanyl)ferrocenyl]-2-phenyl-1,3-oxazoline 6a and (5*S*)-5-[(S_{Fc})-2-(*p*-tolylsulfanyl)ferrocenyl]-2-phenyl-1,3-oxazoline 6b (TsCl/Et_3N)

p-Tosyl chloride (71 mg, 0.375 mmol) and 4-dimethylaminopyridine (DMAP) (3 mg, 0.025 mmol) were added to a solution of **7** (120 mg, 0.25 mmol) in CH_2Cl_2 (5 mL). After 15 min triethylamine (0.1 mL, 0.75 mmol) was added dropwise and the reaction stirred for 24 h at ambient temperature. The reaction was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The starting amide **7** was quantitatively recovered.

4.11. *N*-((2*S*)-2-Methoxy-2-[(S_{Fc})-2-(*p*-tolylsulfanyl)ferrocenyl]ethyl)benzenecarboxamide 8a

Compound **6a** (50 mg, 0.11 mmol) was dissolved in hot methanol and left overnight. The solution was then concentrated in vacuo affording, in a quantitative yield, product **8a**. Mp 57–60 °C; $[\alpha]_D^{20} = -56.3$ (*c* 0.75, $CHCl_3$); ν_{max} (CCl_4)/cm^{-1} 1669; (found; C, 66.88; H, 5.52. $C_{27}H_{27}FeNO_2S$ required C, 66.81; H, 5.61); δ_H (400 MHz, $CDCl_3$) 2.24 (3H, s, CH_3), 2.92 (3H, s, CH_3), 3.68 (1H, ddd, *J* 13.0, 8.7 and 4.0, H_a–CH_2), 4.33 (5H, s, FcH), 4.42 (2H, m, FcH), 4.46 (1H, m), 4.57 (1H, dd, *J* 8.7 and 4.0), 4.60 (1H, dd, *J* 2.4 and 1.4, FcH), 6.71 (1H,

br t, NH), 7.00 (4H, m, ArH), 7.49 (3H, m, ArH), 7.83 (2H, m, ArH); δ_C (100 MHz, $CDCl_3$) 21.1 (q), 44.0 (t), 56.4 (q) 68.6, 69.6, 70.9, 75.45, 76.2 (d), 88.6 (s), 126.5, 127.2, 128.8, 129.5, 131.7 (d) 134.8, 135.0, 136.6 (s), 167.6 (s, CON); m/z (ESI) 485 (M^+), 508 (M^++Na).

4.12. *N*-((2*R*)-2-Methoxy-2-[(S_{Fc})-2-(*p*-tolylsulfanyl)ferrocenyl]ethyl)benzenecarboxamide 8b

A solution of 35 mg (0.88 mmol 60% in mineral oil) of NaH in THF (3 mL) was cooled in a ice bath and to this mixture added methyl iodide (125 mg, 0.88 mmol) and 50 mg (0.11 mmol) of **7** in THF (2 mL). The solution was left overnight, quenched with saturated $NaHCO_3$ and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Chromatography on preparative TLC afforded the **8b** in 90% yield. δ_H (300 MHz, $CDCl_3$) 2.21 (3H, s, CH_3), 3.40 (1H, 2t, CH), 3.49 (3H, s, OCH_3), 4.05 (1H, 2m, CH), 4.30 (5H, s, FcH), 4.38 (2H, m, FcH+CH), 4.42 (1H, m, FcH), 4.45 (1H, m, FcH), 6.25 (1H, br t, NH), 6.96 (5H, m, ArH), 7.40 (2H, m, ArH), 7.67 (2H, m, ArH); m/z (ESI) 508 (M^++Na).

4.13. (5*S*)-5-[(S_{Fc})-2-(*p*-Tolylsulfanyl)ferrocenyl]-2-phenyl-1,3-thiazoline 9a

Freshly prepared Lawesson's reagent[30] (170 mg, 0.42 mmol) was added to a solution of **7** (100 mg, 0.21 mmol) in THF (8 mL), under an argon atmosphere. The obtained mixture was refluxed for 3 h and then concentrated under vacuum. The ^1H and ^{13}C NMR spectra of the crude reaction mixture showed the presence of the desired thiazoline as a single diastereoisomer. The crude was purified by chromatography on deactivated neutral alumina (eluent light petroleum/EtOAc, 10:1) affording (5*S*)-**9a** in 81% yield (0.17 mmol, 80 mg). The purification of the crude reaction mixture on silica gel column afforded as the first R_f fraction, (5*S*)-**9a** (40 mg, 0.084 mmol, 40%) and as the second R_f fraction the epimerized product (5*R*)-**9b** (5 mg, 0.010 mmol, 5%).

4.13.1. (5*S*)-9a. Mp 103–104 °C; $[\alpha]_D^{20}$ = +421.5 (*c* 0.64, $CHCl_3$); ν_{max} (CCl_4)/cm^{-1} 1492, 1606; (found; C, 66.59; H, 4.88. $C_{26}H_{23}FeNS_2$ required C, 66.52; H, 4.94); δ_H (400 MHz, $CDCl_3$) 2.26 (3H, s, CH_3), 3.69 (1H, dd, *J* 16.0 and 7.2, H_a–CH_2), 4.09 (1H, dd, *J* 16.0 and 8.9, H_b–CH_2), 4.26 (5H, s, FcH), 4.35 (1H, t, *J* 2.6, FcH), 4.46 (1H, dd, *J* 2.6 and 1.4, FcH), 4.56 (1H, dd, *J* 2.6 and 1.4, FcH), 5.34 (1H, dd, *J* 8.9 and 7.2, CH), 6.98 (4H, m, ArH), 7.44 (3H, m, ArH), 7.83 (2H, m, ArH); δ_C (100 MHz, $CDCl_3$) 21.1 (q), 51.0, 68.5, 69.2, 70.9 (d), 72.85 (t), 75.6 (d) 77.2, 92.1 (s), 126.7, 128.4, 128.7, 129.8, 131.4 (d) 133.5, 135.5, 136.5 (s), 167.4 (s, CNS); m/z (ESI) 470 (M^++1), 492 (M^++Na).

4.13.2. (5*R*)-9b. δ_H (400 MHz, $CDCl_3$) 2.295 (3H, s, CH_3), 4.26 (5H, s, FcH), 4.32 (2H, m, FcH), 4.50 (1H, dd, *J* 2.4 and 1.5, FcH), 4.70 (1H, dd, *J* 16.0 and 8.8, H_a–CH_2), 5.00 (1H, dd, *J* 16.0 and 3.8, H_b–CH_2), 5.13 (1H, dd, *J* 8.8 and 3.8, CH), 7.01 (4H, m, ArH), 7.38 (3H, m, ArH), 7.72 (2H, m, ArH); m/z (ESI) 470 (M^++1), 492 (M^++Na).

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22. ^{1}H NMR spectra of a solution of pure (*R*)-**6a** in $CDCl_3$ were recorded. After 12 h a 7.8:1 mixture of **6a**/**6b** was detected, after 24 h a 4.0:1 mixture, after 36 h a 2.3:1 mixture, after 48 h a 1.9:1 mixture, after 72 h a 1.7:1 mixture, after 5 days a 1.7:1 mixture and after 12 days a 1.7:1 mixture.
23. ^{1}H NMR spectra of a solution of pure (*S*)-**6b** in $CDCl_3$ were recorded. After 12 h a 1:2.55 mixture of **6a**/**6b** was detected, after 24 h a 1:1.9 mixture, after 48 h a 1.1:1 mixture, after 5 days a 1.5:1 mixture and after 12 days a 1.5:1 mixture.
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