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Chemoenzymatic approach to novel chiral difunctionalised ferrocenes

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Abstract

The optimisation of the kinetic resolution of 1,2-dihydroxy-3-ferrocenylpropane, (±)-**1**, by lipase-catalysed transesterification reactions is discussed. Enantiomerically pure forms of **1** gave access to the corresponding epoxide **8** that had been used as a homochiral starting material for the preparation of several difunctionalised ferrocenes bearing a stereocentre at the β-position of the ferrocene backbone.

1. Introduction

The development of new synthetic methods for the preparation of non-racemic chiral ferrocenes is an important goal[1] in view of the use of these compounds as ligands in asymmetric synthesis, due to their ability to form complexes with different metals that induce an efficient transfer of chirality in several cases.[2] Difunctionalised ferrocenes possessing 1,2- or 1,1′-substitution patterns can be obtained in high enantiomeric excess using well-known reaction protocols.[3,4] Nucleophilic substitution with retention of configuration[5] on chiral 1-acetoxy-alkylferrocenes with diamines or aminoalcohols gives the access to ferrocenyl derivatives possessing different functional groups on the same side chain and a stereogenic carbon α to the cyclopentadienyl ring. Other routes starting from ferrocene carboxaldehyde[6] or ferrocenyl cyanohydrin are also reported.[7]

Ferrocenyl derivatives bearing a stereocentre in the β-position of the side chain have received much less attention[8] due to the lack of suitable homochiral starting material. We have recently developed a biocatalytic procedure for the kinetic resolution of 1,2-dihydroxy-3-ferrocenyl propane, (±)-**1**,[9] and envisaged that the corresponding β-ferrocenyl epoxide **8** could be a useful synthon for the preparation of novel difunctionalised ferrocenes.

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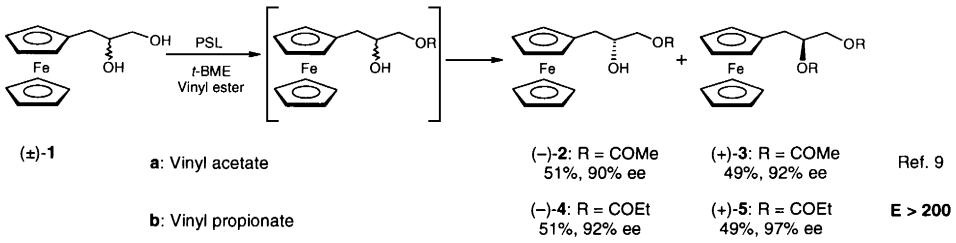
Herein, we reported the optimisation of the lipase-catalysed resolution of (±)-**1** and the use of its enantiopure forms in the preparation of several aminoalcohols with potential catalytic activity.

2. Results and discussion

2.1. Lipase-catalysed transesterification reactions

In a previous communication we have described the resolution of (±)-**1** by sequential esterification with vinyl acetate in *tert*-butyl methyl ether (*t*-BME) in the presence of *Pseudomonas cepacia* lipase (PSL) that afforded diacetate (+)-**3** and monoacetate (−)-**2** with satisfactory chemical yield and enantiomeric excess.[9]

Since enantiodifferentiation occurred on the primary monoester, formed in situ in quasi racemic form, the use of a different acyl ester could be a means of generating a structural modification in the substrate suitable for the optimisation of the lipase recognition. Using vinyl propionate under the same reaction conditions we observed a marked improvement of the enantioselectivity of the esterification that proceeded with the same course and a better reaction rate. So, after 24 h reaction time, dipropionate (+)-**5** with 97% ee and monopropionate (−)-**4** with 92% ee could be recovered from the reaction mixture in approximately a 1:1 ratio, allowing the calculation of a value of $E > 200$[10] (Scheme 1).



Scheme 1.

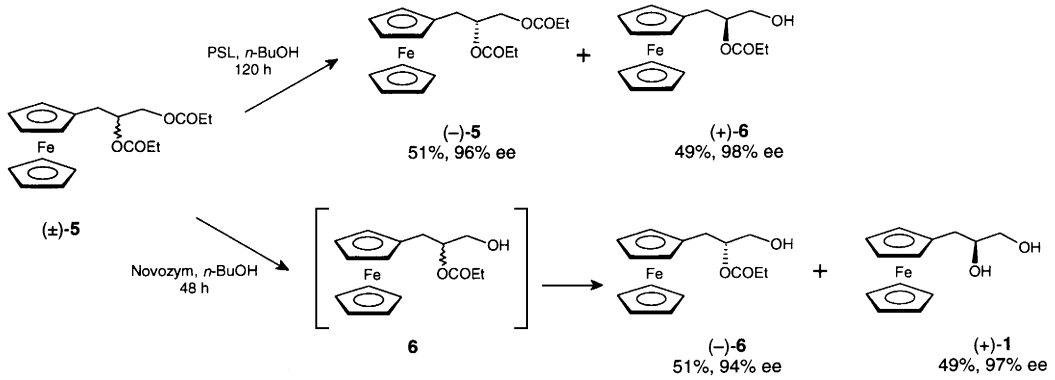
The finding of this positive 'acyl effect' has led us to choose the dipropionate (±)-**5**, rather than the diacetate (±)-**3**, as the substrate for the complementary transesterification reaction of alcoholysis with *n*-butanol.

Parallel experiments were carried out in *t*-BME in the presence of lipases from *P. cepacia*, *Candida antarctica* (immobilised, Novozym® 435) and *Mucor miehei* (immobilised, Lipozyme® IM) that had shown a good activity in the lipase-screening for the esterification of (±)-**1**. All the lipases employed showed high enantioselectivity values but catalysed the alcoholysis of (±)-**5** with different reaction courses.

The PSL promoted alcoholysis of (±)-**5** required about 120 h to afford the unreacted (−)-**5** and the secondary monoester (+)-**6** as the only products in 1:1 ratio, both in enantiopure form. Prolonging the reaction time the formation of diol **1** was not observed, so that kinetic resolution of (±)-**5** occurred in a single step with high regio- and enantioselectivity.[11] Chemical hydrolysis of (+)-**6** afforded diol (+)-**1**, confirming the *S*-stereopreference of the lipase.

When Novozym® 435 was used as the catalyst, the alcoholysis of (±)-**5** proceeded with a higher reaction rate in a sequential two-step fashion. In the early stage of the alcoholysis the monopropionate (±)-**6** was formed regioselectively and then its *S*-enantiomer was enantioselectively converted into diol (+)-**1**. After 48 h reaction time, diol (+)-**1** with 97% ee and unreacted (−)-**6** with 94% ee could be recovered from the reaction mixture. The same reaction course was observed in the presence of

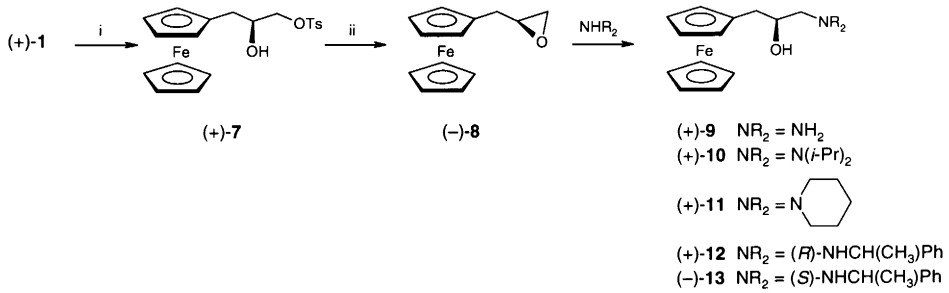
Lipozyme® IM which displayed a slightly lower enantioselectivity in the second step of alcoholysis (E=130). Although the three lipases investigated all exhibited an S-stereopreference, by utilising their different behaviour evidenced in the alcoholysis of (±)-**5**, both enantiomers of selectively protected ester **6** could be prepared (Scheme 2).



Scheme 2.

2.2. Synthesis of chiral difunctionalised ferrocenes

Enantiopure esters from the biocatalysed transesterification reactions have been hydrolysed to the corresponding diol (+)-**1** and (−)-**1** and used for the preparation of both enantiomers of β-ferrocenyl epoxide **8** via monotosylate **7** (Scheme 3). Treatment of (+)-**1** with TsCl/Py at 0°C for 12 h afforded (+)-**7** that was almost quantitatively converted into (−)-**8** by intramolecular nucleophilic displacement of the tosylate in the presence of sodium methoxide.

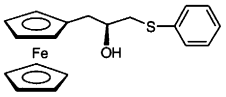


Scheme 3. Reagents: (i) TsCl/Py in CH_2Cl_2, 4°C, 8 h; (ii) NaOMe in toluene

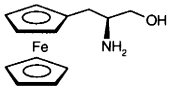
Nucleophilic cleavage of the oxirane ring of (−)-**8** appears as a general strategy for the preparation of difunctionalised ferrocenes. We focused our attention on the reaction of this epoxide with amines because it is known that metal complexation with chiral aminoalcohols or their related derivatives plays an important role in some asymmetric reactions.[12]

Epoxide (−)-**8** reacted smoothly under mild reaction conditions with an aqueous solution of NH_4OH, diisopropylamine or piperidine to afford the corresponding derivatives (+)-**9**, (+)-**10** and (+)-**11** in good yield as single isomers. Moreover, the two diastereoisomeric aminoalcohols (+)-**12** and (−)-**13** were prepared by reaction of (−)-**8** with both enantiomers of α-methylbenzylamine. The amino groups introduced in compounds **10**–**13** have been chosen because of their reported positive effects on asymmetric induction in the addition of diethylzinc to aldehydes.[13]

Benzene thiolate was also considered as an alternative nucleophile to amines and the reaction of its sodium salt with (−)-**8** in a dioxane/water mixture afforded the hydroxysulfide (−)-**14** in high yield. In contrast, for the substitution of the hydroxyl group on the stereogenic carbon we employed a different approach starting from the selectively protected ester (−)-**4** which was reacted with phthalimide under Mitsunobu conditions.[14] Aminolysis of the intermediate phthalimido derivative with $NH(CH_3)_2$ afforded compound (+)-**15** with the same configuration as the isomeric (+)-**9**.



(−)-**14**



(+)-**15**

3. Conclusion

In conclusion, we have shown that ferrocenyl epoxide **8**, easily available in both enantiomeric forms from ferrocenyl diol **1**, is a versatile starting material for the preparation of new difunctionalised ferrocenes bearing a stereocentre in the β-position of the side chain. By means of lipase-catalysed transesterification reactions it is possible to achieve the kinetic resolution of (±)-**1** with high enantioselectivity and prepare selectively protected esters of **1** that can be used as substrates for subsequent transformations. All the new ferrocenyl derivatives synthesised are potentially useful as bidentate ligands in asymmetric synthesis. The investigation of their catalytic properties is ongoing and the results will be published elsewhere.

4. Experimental

4.1. General procedures

^1H and ^{13}C NMR spectra were recorded at 250.13 and 62.9 MHz, respectively. Chemical shifts (δ) are reported in ppm relative to TMS in the solvent specified and all coupling constants (J) are in hertz. Optical rotations were measured on a DIP 135 JASCO instrument. Chiral HPLC analyses were performed on a Ciclobond I 2000 column on a Varian instrument equipped with an UV detector as previously reported.[9]

Lipase from *Pseudomonas cepacia* was from Amano International Enzyme Co. Lipozyme® IM (immobilised lipase from *Mucor miehei*) and Novozym® 435 (immobilised lipase from *Candida antarctica*) are registered marks from Novo Nordisk. Racemic (±)-**1** was available from previous work.[9] Column chromatography was performed on silica gel using specified eluants.

4.2. Kinetic resolution of (±)-*1* by lipase-catalysed esterification

Diol (±)-**1** (500 mg, 1.92 mmol) was dissolved in *t*-BME (50 ml) and to this solution PSL (1 g) and vinyl propionate (1 ml, 2.4 equiv.) were added. The suspension was maintained at 300 rpm and 45°C for 24 h and then the enzyme removed by filtration.The solution was taken to dryness and the residue purified on silica gel column (hexane:ethyl acetate, 7:3) to give (−)-**4** (300 mg, 49% yield, 92% ee) and (+)-**5** (336 mg, 47% yield, 97% ee). Compound (−)-**4** was dissolved in MeOH (10 ml) and treated with K_2CO_3 for 30 min at room temperature. After addition of water the solution was extracted with *t*-BME

and the organic phase dried over Na_2SO_4 and taken to dryness to afford quantitatively diol (−)-**1**. Using the same procedure diol (+)-**1** was obtained starting from diester (+)-**5**.

4.3. (R)-1-Propionyloxy-2-hydroxy-3-ferrocenylpropane (−)-4

Data for (−)-**4**: $[\alpha]_D$ −7.2 (*c* 0.77, C_6H_6); ^{1}H NMR ($CDCl_3$) δ 1.16 (3H, t, *J*=7.5), 2.39 (2H, q, *J*=7.5), 2.57 (2H, d, *J*=6.5), 3.87 (1H, ddd, *J*=6.7, 6.5 and 3.5), 3.98 (1H, m), 4. 13 (10H, bs); ^{13}C NMR ($CDCl_3$) δ 9.1, 27.5, 34.1, 67.7, 67.9, 68.0, 68.7, 68.9, 69.0, 70.7, 83.3, 174.6. Anal. calcd for $C_{16}H_{20}FeO_3$: C, 60.78; H, 6.37; Fe, 17.66. Found: C, 61.02; H, 6.33; Fe, 17.53.

4.4. (S)-1,2-Dipropionyloxy-3-ferrocenylpropane (+)-5

Data for (+)-**5**: $[\alpha]_D$ +44.0 (*c* 0.38, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.13 (3H, t, *J*=7.5), 1.14 (3H, t, *J*=7.5), 2.33 (4H, m), 2.66 and 2.72 (AB system, each 1H, dd, *J*=14.5 and 6.5), 3.99 (1H, dd, *J*=11.8 and 6.5), 4.07 (4H, m), 4.11 (5H, s), 4.21 (1H, dd, *J*=11.8 and 3.5), 5.07 (1H, dddd, *J*=6.5, 6.5, 6.5 and 3.5); ^{13}C NMR ($CDCl_3$) δ 9.1, 27.5, 27.7, 31.5, 64.3, 67.9, 68.7, 69.1, 72.0, 82.5, 173.7, 174.1. Anal. calcd for $C_{19}H_{24}FeO_4$: C, 61.31; H, 6.50; Fe, 15.00. Found: C, 61.49; H, 6.55; Fe, 15.12.

4.5. Alcoholysis of (±)-5 with PSL

Conventional acylation of (±)-**1** with $(EtCO)_2O$/Py gave (±)-**5** in 95% yield. To a solution of (±)-**5** (300 mg) in *t*-BME (30 ml) lipase (600 mg) and *n*-BuOH (0.5 ml, 2.5 equiv.) were added and the mixture was shaken at 45°C. The reaction course was monitored by TLC and after 120 h the reaction was stopped by filtering off the enzyme. After evaporation of the solvent, the residue was purified on silica gel column (hexane:ethyl acetate, 7:3) to give (−)-**5** (150 mg, 50% yield, 96% ee) and (+)-**6** (120 mg, 47% yield, 98% ee).

4.6. (S)-1-Hydroxy-2-propionyloxy-3-ferrocenylpropane (+)-6

Data for (+)-**6**: $[\alpha]_D$ +50.2 (*c* 0.22, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.15 (3H, t, *J*=7.5), 1.80 (1H, bt), 2.36 (2H, q, *J*=7.5), 2.69 (2H, d, *J*=6.7), 3.59 (1H, m), 3.70 (1H, m), 4.08 (2H, bs), 4.11 (7H, bs), 4.88 (1H, ddd, *J*=6.7, 5.8 and 3.5); ^{13}C NMR ($CDCl_3$) δ 9.1, 27.8, 31.2, 63.9, 67.8, 68.7, 69.1, 75.8, 83.0, 174.5. Anal. calcd for $C_{16}H_{20}FeO_3$: C, 60.78; H, 6.37; Fe, 17.66. Found: C, 61.06; H, 6.43; Fe, 17.55.

4.7. Alcoholysis of (±)-5 with Novozym® 435

The alcoholysis of (±)-**5** (300 mg) in the presence of Novozym® 435 was carried out using the same procedure described for the reaction with PSL. At 48 h reaction time the mixture was worked-up as above to give (−)-**6** (125 mg, 49% yield, 94% ee), $[\alpha]_D$ +47.9 (*c* 0.25, $CHCl_3$), and (+)-**1** (96 mg, 46% yield, 97% ee).

4.8. (S)-1-Tosyloxy-2-hydroxy-3-ferrocenylpropane (+)-7

To a solution of diol (+)-**1** (300 mg, 1.15 mmol, 97% ee) in CH_2Cl_2 (15 ml) *p*-toluenesulfonyl chloride (300 mg, 1.57 mmol) and pyridine (1 ml) were added. The solution was maintained at 0°C for 12 h, then diluted with cold water and extracted with ethyl acetate. After washing with dil. HCl the organic

phase was dried over Na_2SO_4 and the solvent evaporated in vacuo. Purification on silica gel (hexane:ethyl acetate) from unreacted diol afforded (+)-**7** (360 mg, 75% yield), $[\alpha]_D$ +6.9 (*c* 0.60, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.19 (1H, d, *J*=4.5), 2.46 (3H, s), 2.55 (2H, d, *J*=6.2), 3.83 (1H, m), 3.91 (1H, m), 4.00 (1H, m), 4.05 (2H, m), 4.07 (2H, m), 4.09 (5H, s), 7.36 (2H, d, *J*=8.5), 7.80 (2H, d, *J*=8.5); ^{13}C NMR ($CDCl_3$) δ 21.7, 33.6, 68.0, 68.7, 68.8, 69.0, 70.2, 72.7, 82.6, 128.0, 130.0, 132.7, 145.1. Anal. calcd for $C_{20}H_{22}FeO_4S$: C, 57.98; H, 5.35; Fe, 13.48; S, 7.74. Found: C, 57.80; H, 5.31; Fe, 13.36; S, 7.80.

*4.9. (S)-1,2-Epoxy-3-ferrocenylpropane (−)-**8***

Tosylate (+)-**7** (300 mg) was dissolved in toluene (10 ml) and 300 μl of a 30% solution of sodium methoxide in MeOH were added dropwise. A white solid was formed immediately which was removed by filtration and washed with toluene. The solution was taken to dryness to give pure (−)-**8** (160 mg, 90% yield, 97% ee), $[\alpha]_D$ –6.8 (*c* 0.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.52 (1H, m), 2.54 (1H, dd, *J*=15.0 and 5.0), 2.63 (1H, dd, *J* =15.0 and 5.5), 2.80 (1H, bt), 3.12 (1H, m), 4.12 (2H, m), 4.14 (7H, bs); ^{13}C NMR ($CDCl_3$) δ 32.7, 46.9, 52.2, 67.6, 67.7, 68.3, 68.6, 83.6. Anal. calcd for $C_{13}H_{14}FeO$: C, 64.49; H, 5.83; Fe, 23.07. Found: C, 64.75; H, 5.86; Fe, 23.25.

*4.10. (S)-1-Amino-2-hydroxy-3-ferrocenylpropane (+)-**9***

To a solution of (−)-**8** (50 mg, 97% ee) in MeOH (5 ml) 30% aq. NH_4OH (0.5 ml) was added and the mixture maintained at 45°C for 24 h. After addition of water the reaction mixture was partitioned with *t*-BME and the organic phase extracted with 10% solution of citric acid. The acidic aqueous phase was then alkalinised with 1N NaOH and extracted with *t*-BME. The final organic solution was dried over Na_2SO_4 and taken to dryness to afford pure (+)-**9** (32 mg, 60% yield), $[\alpha]_D$ +12.6 (*c* 0.31, C_6H_6); ^{1}H NMR (CD_3COCD_3) δ 2.44 (1H, dd, *J*=14.0 and 6.5), 2.56 (1H, dd, *J*=14.0 and 6.0), 2.74 (1H, dd, *J*=12.0 and 6.0), 3.09 (1H, dd, *J*=12.0 and 6.5), 3.87 (1H, m), 4.02 (2H, m), 4.08 (5H, s), 4.13 (2H, m); ^{13}C NMR (CD_3COCD_3) δ 36.5, 51.6, 68.0, 68.1, 69.2, 69.7, 69.9, 78.2, 85.9. Anal. calcd for $C_{13}H_{17}FeNO$: C, 60.26; H, 6.61; N, 5.40; Fe, 21.55. Found: C, 60.62; H, 6.68; N, 5.36; Fe, 21.67.

*4.11. (S)-1-Diisopropylamino-2-hydroxy-3-ferrocenylpropane (+)-**10***

Epoxide (−)-**8** (50 mg, 97% ee) was dissolved in MeOH:H_2O (2:1, 5 ml) and treated with (*i*-Pr)$_2$NH (0.5 ml) at 60°C for 24 h. The reaction mixture was extracted as above to give (+)-**10** in 75% yield (53 mg), $[\alpha]_D$ +21.6 (*c* 0.46, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.97 (6H, d, *J*=6.5), 1.02 (6H, d, *J*=6.7), 2.17 (1H, dd, *J*=13.2 and 10.5), 2.40 (1H, dd, *J*=14.0 and 5.5), 2.52 (1H, dd, *J*=13.2 and 3.5), 2.58 (1H, dd, *J*=14.0 and 6.7), 3.00 (2H, m), 3.50 (1H, m), 4.07 (2H, m), 4.10 (5H, s), 4.17 (2H, m); ^{13}C NMR ($CDCl_3$) δ 19.2, 22.6, 36.0, 48.0, 50.3, 67.4, 67.7, 68.6, 69.0, 69.2, 84.9. Anal. calcd for $C_{19}H_{29}FeNO$: C, 66.48; H, 8.51; N, 4.08; Fe, 16.27. Found: C, 66.81; H, 8.59; N, 4.12; Fe, 16.19.

*4.12. (S)-1-Piperidinyl-2-hydroxy-3-ferrocenylpropane (+)-**11***

To a dioxane:H_2O (1:1) solution of (−)-**8** (50 mg, 97% ee) piperidine (0.65 ml) was added and the reaction mixture maintained at 45°C for 15 h. After work-up as above aminoalcohol (+)-**11** was obtained as single compound (44 mg, 65% yield), $[\alpha]_D$ +31.1 (*c* 0.18, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.41 (2H, m), 1.53 (4H, m), 2.15 (1H, dd, *J*=12.2 and 10.0), 2.27 (3H, m), 2.41 (1H, dd, *J*=14.2 and 5.7), 2.49 (2H, m), 2.59 (1H, dd, *J*=14.2 and 6.5), 3.67 (1H, m), 4.06 (2H, m), 4.10 (5H, s), 4.13 (2H, m); ^{13}C NMR ($CDCl_3$)

δ 24.3, 26.1, 35.7, 54.6, 64.3, 67.2, 67.5, 67.6, 68.6, 69.1, 84.4. Anal. calcd for $C_{18}H_{25}FeNO$: C, 66.06; H, 7.70; N, 4.28; Fe, 17.06. Found: C, 66.32; H, 7.63; N, 4.31; Fe, 17.23.

4.13. 1-N-*[(*R*)-1-Phenylethyl]amino-2-(*S*)-hydroxy-3-ferrocenylpropane (+)-**12***

Compound (−)-**8** (50 mg, 97% ee) was dissolved in 5 ml of a 1:1 MeOH:H_2O solution and treated with (*R*)-α-methylbenzylamine (80 μl) at 80°C for 6 h. The reaction mixture was extracted with *t*-BME and the organic phase dried over Na_2SO_4 and taken to dryness. The residue was purified on silica gel column (ethyl acetate:triethylamine, 96:4) to afford pure (+)-**12** (58 mg, 78%yield), $[\alpha]_D$ +30.3 (*c* 0.32, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.35 (3H, d, *J*=6.5), 2.29 (1H, dd, *J*=12.2 and 9.0), 2.39 (1H, dd, *J*=14.0 and 5.0), 2.50 (1H, dd, *J*=14.0 and 7.2), 2.61 (1H, dd, *J*=12.2 and 3.0), 3.68 (1H, m), 3.75 (1H, q, *J*=6.5), 4.08 (9H, bs), 7.22–7.38 (5H, m); ^{13}C NMR ($CDCl_3$) δ 24.5, 35.6, 52.4, 57.8, 67.7, 68.6, 68.9, 69.0, 70.9, 84.4, 126.5, 127.0, 128.5, 145.2. Anal. calcd for $C_{21}H_{25}FeNO$: C, 69.43; H, 6.94; N, 3.86; Fe, 15.37. Found: C, 69.95; H, 7.00; N, 3.91; Fe, 15.45.

4.14. 1-N-*[(*S*)-1-Phenylethyl]amino-2-(*S*)-hydroxy-3-ferrocenylpropane (−)-**13***

Prepared in 74% yield as above from epoxide (−)-**8** and (*S*)-α-methylbenzylamine, $[\alpha]_D$ –40.0 (*c* 0.32, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.36 (3H, d, *J*=6.5), 2.40 (1H, dd, *J*=12.0 and 8.7), 2.46 (2H, d, *J*=6.3), 2.56 (1H, dd, *J*=12.0 and 3.0), 3.56 (1H, m), 3.73 (1H, q, *J*=6.5), 4.08 (9H, bs), 7.23–7.36 (5H, m); ^{13}C NMR ($CDCl_3$) δ 24.2, 35.6, 53.1, 58.6, 67.6, 67.7, 68.6, 68.9, 69.1, 71.1, 84.3, 126.5, 127.0, 128.5, 145.5. Anal. calcd for $C_{21}H_{25}FeNO$: C, 69.43; H, 6.94; N, 3.86; Fe, 15.37. Found: C, 69.87; H, 7.02; N, 3.89; Fe, 15.42.

*4.15. (*S*)-1-Phenylthio-2-hydroxy-3-ferrocenylpropane (−)-**14***

To a solution of (−)-**8** (50 mg, 97% ee) in dioxane (5 ml) benzene thiolate sodium salt (80 mg) and 1N NaOH (1 ml) were added and the mixture taken under reflux for 2 h. After extraction with *t*-BME and evaporation of the solvent, the residue was chromatographed on silica gel (hexane:ethyl acetate, 8:2) to give (−)-**14** (40 mg, 55% yield), $[\alpha]_D$ –19.3 (*c* 0.18, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.44 (1H, d, *J*=3.5), 2.64 (2H, d, *J*=6.3), 2.88 (1H, dd, *J*=13.5 and 8.0), 3.10 (1H, dd, *J*=13.5 and 4.2), 3.72 (1H, m), 4.10 (9H, bs), 7.20–7.37 (5H, m); ^{13}C NMR ($CDCl_3$) δ 36.5, 40.8, 67.9, 68.7, 69.0, 69.1, 70.4, 83.7, 126.5, 129.1, 129.8, 135.4. Anal. calcd for $C_{19}H_{20}FeOS$: C, 64.78; H, 5.72; Fe, 15.85; S, 9.10. Found: C, 65.04; H, 5.70; Fe, 15.98; S, 9.17.

*4.16. (*S*)-1-Hydroxy-2-amino-3-ferrocenylpropane (+)-**15***

A toluene (3 ml) suspension of PPh_3 (55 mg, 0.21 mmol), diethyl azodicarboxylate (33 μl, 0.21 mmol) and phthalimide (31 mg, 0.21 mmol) was added to a toluene solution of monoester (−)-**4** (55 mg, 0.17 mmol, 92% ee). The reaction mixture was maintained at room temperature under continuous stirring for 3 h when TLC analysis showed the complete conversion of the substrate. After filtration the solvent was evaporated and the residue dissolved in THF. A 40% aqueous solution of methylamine was added and the mixture shaken for 3 h. After partitioning between citric acid solution and ethyl acetate, the aqueous phase was basified and extracted with ethyl acetate. The organic phase was taken to dryness to give (+)-**15** (25 mg, 55% yield), $[\alpha]_D$ +23.7 (*c* 0.40, $CHCl_3$); ^{1}H NMR (CD_3COCD_3) δ 2.53 (1H, dd, *J*=14.2 and 7.0), 2.66 (1H, dd, *J*=14.2 and 6.0), 3.23 (1H, dd, *J*=7.5 and 7.2), 3.42 (1H, m), 3.78 (1H, dd, *J*=7.2 and

6.5), 4.05 (2H, m), 4.10 (5H, s), 4.15 (2H, m); ^{13}C NMR (CD_3COCD_3) δ 34.1, 60.3, 68.0, 68.2, 69.2, 69.4, 69.6, 71.1. Anal. calcd for $C_{13}H_{17}FeNO$: C, 60.26; H, 6.61; N, 5.40; Fe, 21.55. Found: C, 60.44; H, 6.57; N, 5.45; Fe, 21.36.

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References

1. (a) Richards, C. J.; Locke, A. *Tetrahedron: Asymmetry* **1998**, *9*, 2377–2407; (b) Siegel, S.; Schmalz, H.-G. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2456–2458; (c) Iftime, G.; Daran, J.-C.; Manoury, E.; Balavoine, G. G. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1698–1701; (d) Ireland, T.; Almena Perea, J. J.; Knochel, P. *Angew. Chem., Int. Ed. Engl*. **1999**, *38*, 1457–1460.
2. (a) Hayashi, T.; Togni, A., Eds. *Ferrocenes*; VCH: Weinheim, 1995, chapters 2 and 3; (b) Togni, A.; Dorta, R.; Kollner, C.; Pioda, G. *Pure Appl. Chem*. **1998**, *70*, 1477–1485; (c) Almena Perea, J. J.; Lotz, M.; Knochel, P. *Tetrahedron: Asymmetry* **1999**, *10*, 375–384.
3. (a) Marquading, D.; Klusacek, H.; Gokel, G., Hoffmann, P.; Ugi, I. *J. Am. Chem. Soc*. **1970**, *92*, 5389–5393; (b) Riant, O.; Samuel, O.; Flessner, T.; Taudien, S.; Kagan, H. *J. Org. Chem*. **1997**, *62*, 6733–6745; (c) Riant, O.; Argouarch, G.; Guillaneux, D.; Samuel, O.; Kagan, H. B. *J. Org. Chem*. **1998**, *63*, 3511–3514.
4. (a) Watanabe, M. *Tetrahedron Lett.* **1995**, *36*, 8991–8994; (b) Schwink, L.; Knochel, P. *Tetrahedron Lett.* **1996**, *37*, 25–28.
5. Gokel, G. W.; Marquading, D.; Ugi, I. K. *J. Org. Chem*. **1972**, *37*, 3052–3058.
6. Glorian, G.; Maciejewski, L.; Brocard, J.; Agbossou, F. *Tetrahedron: Asymmetry* **1997**, *8*, 355–358.
7. Patti, A.; Nicolosi, G.; Howell, J. A. S.; Humphries, K. *Tetrahedron: Asymmetry* **1998**, *9*, 4381–4394.
8. Enders, D.; Peters, R.; Lochtman, R.; Raabe, G. *Angew. Chem., Int. Ed. Engl*. **1999**, *38*, 2421–2423.
9. Patti, A.; Nicolosi, G. *Tetrahedron: Asymmetry* **1999**, *10*, 2651–2654.
10. Calculated for the second step of the reaction according to: Chen, C. S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc*. **1982**, *104*, 7294–7299.
11. The same reaction course, but with lower enantioselectivity, was observed in the alcoholysis with PSL of the phenyl analogue 1-phenylethane-1,2-diol dipropionate described by: Bosetti, A.; Bianchi, D.; Cesti, P.; Golini, P.; Spezia, S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2395–2398.
12. (a) Tomioka, K. *Synthesis* **1990**, 541–549; (b) Soai, K.; Niwa, S. *Chem. Rev*. **1992**, *92*, 833–856; (c) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev*. **1996**, *96*, 835–875.
13. (a) Watanabe, M.; Araki, S., Butsugan, Y. *J. Org. Chem.* **1991**, *56*, 2218–2224; (b) Iuliano, A., Pini, D., Salvadori, P. *Tetrahedron: Asymmetry* **1995**, *6*, 739–744.
14. Mitsunobu, O. *Synthesis* **1981**, 1–28.