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Chemoenzymatic synthesis of optically active 1,2-disubstituted ferrocenes with planar chirality

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ABSTRACT

A new pathway for the synthesis of 2-substituted ferrocenyl compounds with planar chirality using a chemoenzymatic resolution as the key step is described. The kinetic resolution of racemic 2-hydroxymethyl phenylthioferrocene **4** has been optimised and carried out on a multi-gram scale using CAL-B lipase, giving the resulting acetate and remaining alcohols in ee's >99%. The enantiomerically enriched sulfides have been transformed via a two-step sequence, in a new family of 2-substituted ferrocenyl alcohol by using a sulfoxide–lithium exchange/electrophilic trapping sequence; this gives straightforward access to non-racemic ferrocenyl alcohols with planar chirality.

1. Introduction

Enzymes are very useful synthetic tools which integrate numerous methods of organic transformations in a large variety of catalytic reactions. They offer access to a wide range of transformations and their utility has also been reinforced by the possibility to combine enzymatic and homogeneous catalysis. Furthermore, their use also contributes to the development of greener processes for the production of enantioenriched intermediates for organic synthesis.[1] Among them, hydrolytic enzymes display high efficiencies as well as excellent functional specificity.[2] The lipase catalysed kinetic resolution by hydrolysis or transesterification is one of the most efficient practical methods for the efficient production of enantiomerically enriched building blocks and has found wide application in the field of asymmetric synthesis.[3] We have previously shown that the optimisation of a target kinetic resolution reaction can be highly dependent on some key parameters such as the solvent, the nature of the acylating agent or the additive, and that a careful screening of those conditions can lead to efficient processes for the preparation of enantiomerically enriched building blocks.[4]

Among the potential targets for lipase-catalysed kinetic resolution, 1,2-disubstituted ferrocenyl complexes are particularly attractive as they have been extensively used in various areas of chemistry, with a particular focus in the field of asymmetric catalysis.[5] Some chiral ferrocenyl ligands such as ppfa[6] and Josiphos,[7] have been applied to important enantioselective catalytic applications, leading in some cases to large-scale industrial applications.[8]

Previous work from Nicolosi et al. has shown that enantiomerically enriched 2-hydroxymethyl ferrocenyl sulfides could be obtained by lipase-catalysed kinetic resolution,[9] albeit with moderate selectivity factors. We have ourselves recently shown that the activity of some lipases in such reaction could be highly influenced by the alkaloid additives.[10] We have decided to further optimise the kinetic resolution of a racemic 2-phenylthio ferrocenyl alcohol in order to offer a simple and scalable protocol for the production of both enantiomers of this valuable target, which will be used as the common starting material for the preparation of 2-substituted ferrocenyl alcohols with planar chirality.

2. Results and discussion

The starting racemic alcohol **4** was prepared as previously described starting from commercially available *N,N*-dimethylaminoferrocene[11] (Scheme 1). *ortho*-Lithiation by *tert*-butyllithium in diethyl ether followed by electrophilic trapping with diphenyl disulfide afforded the aminosulfide *rac*-**2** in a 92% yield. Alcohol *rac*-**4** was then generated by the reaction of amine **2** in acetic anhydride followed by methanolysis of the resulting acetate.

The synthesis gave a high yield for each step and allowed a straightforward access to alcohol *rac*-**4** on a 10 g scale. The resolution of the alcohol using various commercially available lipases was then studied according to the various parameters of the reaction. The kinetic resolution of this substrate was previously studied by Nicolosi et al.[9] using Novozym and Lipozyme lipases, albeit with modest selectivities ($E < 40$). We have used our previous experience in similar reactions[12], in which we have shown an efficiency threshold linked to the reaction conditions which proved dependent on the amount of lipase, to optimise the selectivity for this

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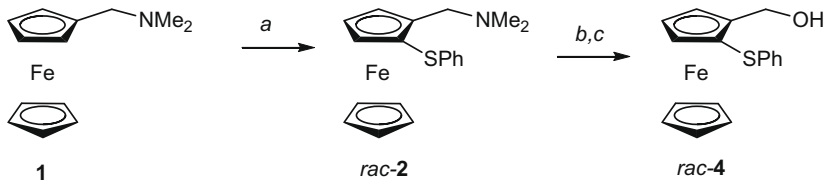
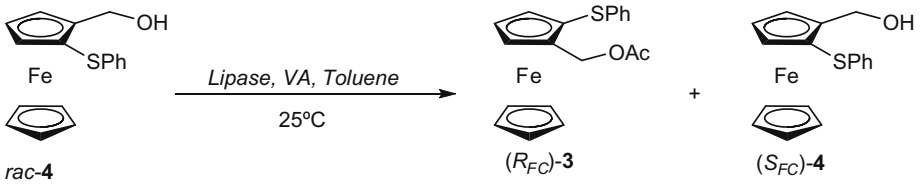


a: *i*: 1.1 equiv. t-BuLi, Et_2O, rt, 15 min, *ii:* 1.5 equiv. PhSSPh,T,12h (92%)
b: Ac_2O, 80°C,12h (95%)
c: K_2CO_3, MeOH,1h (95%)

Scheme 1. Preparation of the starting alcohol *rac*-**4**.



Scheme 2. Enzymatic acylation of *rac*-**4**.

particular substrate. The kinetic resolution experiments on *rac*-**4** were first carried out at room temperature in toluene, using vinyl acetate as the acylating agent (Scheme 2).

Various commercially available lipases were screened and the influence of the amount of the enzyme on both reactivity and selectivity was first tested. The results are summarised in Table 1.

The *Candida cylindracea* lipase (CCL, LA = 3.85 U/mg) which has never been evaluated for this substrate, gave an excellent selectivity of $E = 267$, albeit with a very low reactivity, as only 23% conversion of the starting material was reached after 8 days at room temperature (entry 4). Little or no reactivity was observed when *Pseudomonas cepacia* lipase (PCL, LA > 30,000 U/mg) and *Candida rugosa* lipase (CRL, LA = 1170 U/mg) were used (entries 8–10), but we obtained more promising results when immobilised *Candida antarctica* lipase (CAL-B, LA = 2 U/mg) was used in those experiments (entries 5–7). When a 20 mg of CAL-B lipase per mmol of substrate was used (40 U), only 26% of the substrate was consumed after 8 days with a disappointing selectivity of $E = 17$ (entry 5). However, when the amount of immobilised lipase was doubled in the next experiment (40 mg, 80 U), a 48% conversion of the starting alcohol was reached after 72 h and a selectivity of $E = 152$ could be reached (entry 6). This result shows a significant improvement of previously published results[9] by a careful examination of the reaction parameters. Those experiments also show the influence of the amount of acylating agent (entries 5 and 6) as it is known that a high concentration of the acylating agent is susceptible to induce the reversibility of the enzymatic reaction.[14] The use of a lesser amount of vinyl acetate with an increased amount of the lipase thus brought an increase in both conversion and selectivity for our target reaction.

High selectivities were thus reached for *CCL* and *CAL-B* lipases, but good conversion was obtained only in the case of *CAL-B* lipase.

We have also checked the influence of the solvent on the reactivity of the system by testing the influence of three solvents with different hydrophobicity on the kinetic resolution of *rac*-**4**. We also tested the influence of the acylating agent for this lipase. The choice of the solvent was also guided by the solubility of the substrate and the results are summarised in Table 2.

The experiments with two acylating agents and three solvents show that good to high selectivities were reached in all cases, albeit with some differences in the reactivity of the lipase. When vinyl acetate was used as the acylating agent, high selectivities were reached ($152 < E < 201$) with a reaction time >72 h required to reach a conversion $c = 45\%$. However, when toluene and

Table 1
Initial screening of lipases in the kinetic resolution of *rac*-**4**

Entry	Amount of lipase[a] (Lipase Activity LA)	Time (h)	ee_S[b] (%)	Yield[d] (%)	ee_P[b] (%)	Yield[d] (%)	C[c] (%)	E[c]	Config.
1	CCL (385U)	24	19	ND[f]	99	ND[f]	16	240	(*R*)
2		48	21	ND[f]	99	ND[f]	18	244	
3		72	24	ND[f]	99	ND[f]	20	251	
4		8 days	30	ND[f]	99	ND[f]	23	267	
5	CAL-B (40U)	8 days	30	40	85.5	30	26	17	(*R*)
6	CAL-B (80U)	72	90	45	96	40	49	152	
7[9a]	CAL-B (1296U)	1	58	—	79	—	42	15	(*R*)
8	PCL (>3000U)	13 days	NR[e]	—	NR[e]	—	NR[e]	NR[e]	—
9	PCL (>6000U)	13 days	NR[e]	—	NR[e]	—	NR[e]	NR[e]	—
10[11]	CRL (58500U)	24	25.6	47	94.5	45	21	45	(*R*)

[a] 1 mmol of racemic alcohol **4**, 3 mmol of vinyl acetate in 6 mL of toluene. The indicated amount of lipase was added.
[b] The enantiomeric excesses for both substrate and product are measured by HPLC on a *Chiralpak* AD column.
[c] Conversion[12]: $C = ee_S/ee_P + ee_s$; selectivity[12] $E = \mathrm{Ln}[(1 - C)(1 - ee_{(S)})]/\mathrm{Ln}[(1 - C)(1 + ee_{(S)})]$.[13]
[d] Isolated yield after chromatographic purification.
[e] No reaction.
[f] Not evaluated.

Table 2
Influence of the solvent and acylating agent on the *CAL-B* acylation of *rac*-**4**

Entry	Solvent (log *P*)	Acylating agent	Time (h)	ee_S[c]	Yield[e] (%)	ee_P[c]	Yield[e] (%)	*C*[d] (%)	*E*[d]
1	Toluene (2.5)	IA[a]	72	55	45	99	35	36	345
2		VA[a]	72	90	45	96	40	49	152
3		SA[b]	13 days	5	35	0.5	ND[g]	10	ND[g]
4	TBME (1.35)	IA[a]	24	99	45	94	40	51	168
5		VA[a]	72	99	40	93.5	40	51	155
6		SA[b]	13 days	NR[f]	—	NR[f]	—	NR[f]	NR[f]
7	CH_2Cl_2 (1.01)	VA[a]	72	10.6	45	99	ND[g]	10	201

[a] 1 mmol of racemic alcohol **4**, 3 mmol of enol ester in 6 mL of solvent and 80U of CAL-B.
[b] 1 mmol of racemic alcohol **4**, 1 mmol of succinic anhydride in 6 mL of solvent and 80 U of CAL-B.
[c] The enantiomeric excesses for both substrate and product are measured by HPLC on a *Chiralpak* AD column.
[d] Conversion[12]: $C = ee_S/ee_P + ee_s$; selectivity[12] $E = \mathrm{Ln}[(1 - C)(1 - ee_{(S)})]/\mathrm{Ln}[(1 - C)(1 + ee_{(S)})]$.
[e] Isolated yield after chromatographic purification.
[f] No reaction.
[g] Not evaluated.

dichloromethane were used (entries 1 and 7), the enantiomeric excesses of the remaining substrate remained quite modest. With isopropenyl acetate in TBME (entry 4), the reaction time required to reach an optimised conversion of the substrate was decreased to 24 h with a selectivity of $E = 168$. These optimised conditions were then retained as we wanted to adapt the preparation of the enantiomerically enriched alcohol **4** on a multigram scale. We also wanted to check the possibility of recycling the immobilised lipase in successive acylation reactions. The recycling of the lipase was tested on a reaction, which was carried out on an 8 mmol scale of the *rac*-**4** with isopropenyl acetate (3 equiv) as the acylating agent in *tert*-butyl methyl ether Table 3. The evolution of the acylation reaction was followed by HPLC and the lipase was recovered at the end of the reaction by simple filtration from the reaction medium. After drying the lipase, it was directly reused in another acylation experiment by adapting the amount of substrate to the weight of the recovered lipase (a 0.125 weight ratio of enzyme/substrate was kept for each recycling experiment).

The results show that scaling up the reaction to an 8 mmol amount of the substrate *rac*-**4** gave the same isolated yields in recovered alcohol **4** and acetate **3** with high enantiomeric excesses for both compounds. The reuse of the recovered lipases in three successive experiments always gave high selectivities, albeit with a decrease in reactivity of the lipase. Indeed, a reaction time of 96 h was required to reach a conversion of $C = 51\%$ and the isolated yields of alcohol **4** and acetate **3** were decreased to 29% and 25% (entry 9). This shows that while the selectivity of the lipase was kept when it was recovered from the reaction mixture, its activity was highly decreased and prevents its effective reuse in successive acylation reactions.

We have decided to try out the optimised conditions for the multigram scale synthesis of the enantiomers of alcohol **4** in order to show its potential as a starting material for the asymmetric synthesis of enantiomerically pure 2-substituted ferrocenyl alcohols (see Scheme 3).

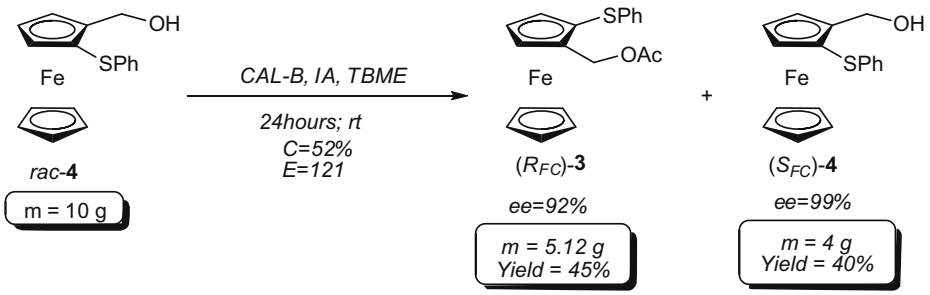
The kinetic resolution was then carried out on a 10 g scale of the starting alcohol *rac*-**4** using the optimised reaction conditions (30.86 mmol of *rac*-**4** in 185 mL of TBME, 3 equiv of isopropenyl acetate and 1.23 g of *CAL-B* lipase at room temperature for 24 h). We were pleased to see that we obtained the same results, regardless of the scale with a $c = 52\%$ and a selectivity of $E = 121$. Acetate (R_{Fc})-**3** was isolated in a 45% yield with an enantioselectivity of 92% and can be easily deprotected to the corresponding enantiomerically enriched alcohol. The enantiomerically pure alcohol (S_{Fc})-**4** (ee = 99%) was also isolated in a 40% yield. Both enantiomers can thus be easily prepared on a large scale and used for further transformations. We have therefore devised a straightforward and high yield preparation of both enantiomers of this alcohol starting from commercially available amine **1** in only four steps.

With both enantiomers of alcohol **4** in hand, we decided to show their potential for the production of enantiomerically pure 2-substituted ferrocenyl alcohols by using a substitution strategy previously described in the literature. The synthesis of enantiomerically enriched ferrocenyl compounds with planar chirality often

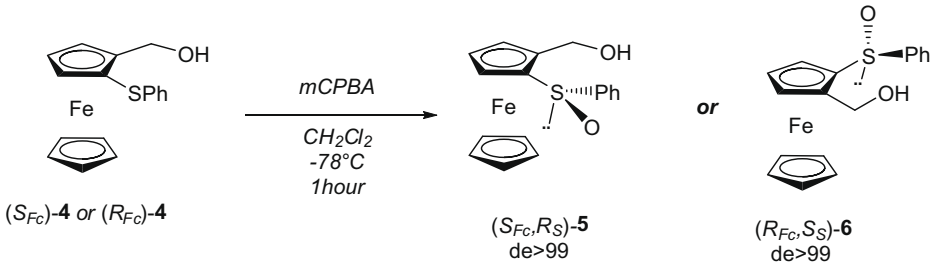
Table 3
Reuse of the *CAL-B* lipase in the acylation of *rac*-**4**

Entry	Recycle N°	Time (h)	ee_S[e]	Yield[g] (%)	ee_P[e]	Yield[g] (%)	*C*[f] (%)	*E*[f]
1	1st use[a]	24	99	45	95.5	40	51	229
2	1st reuse[b]	24	76	ND[h]	98	ND[h]	44	229
3		48	99.9	35	94	30	51.5	243
4	2nd reuse[c]	24	45	ND[h]	98	ND[h]	31.5	154
5		48	99.9	35	92	32	52	180
6	3rd reuse[d]	24	30	ND[h]	99	ND[h]	23	267
7		48	56	ND[h]	97	ND[h]	37	115
8		72	79	ND[h]	96.5	ND[h]	45	136
9		96	98	29	95.5	25	51	200

[a] 8 mmol of racemic alcohol **4**, 24 mmol of isopropenyl acetate in 48 mL of TBME and 640U of CAL-B.
[b] 7.5 mmol of racemic alcohol **4**, 22.5 mmol of isopropenyl acetate in 45 mL of TBME and 600U of CAL-B.
[c] 6.75 mmol of racemic alcohol **4**, 20.25 mmol of isopropenyl acetate in 41 mL of TBME of 540U of CAL-B.
[d] 4.64 mmol of racemic alcohol **4**, 1.53 mmol of isopropenyl acetate in 28 mL of TBME and 372U of CAL-B.
[e] The enantiomeric excesses for both substrate and product are measured by HPLC on a *Chiralpak* AD column.
[f] Conversion[12]: $C = ee_S/ee_P + ee_s$; selectivity[12] $E = \mathrm{Ln}[(1 - C)(1 - ee_{(S)})]/\mathrm{Ln}[(1 - C)(1 + ee_{(S)})]$.
[g] Isolated yield after chromatographic purification.
[h] Not evaluated.



Scheme 3. Application of the kinetic resolution of *rac*-**4** with *CAL-B* on a multigram scale.



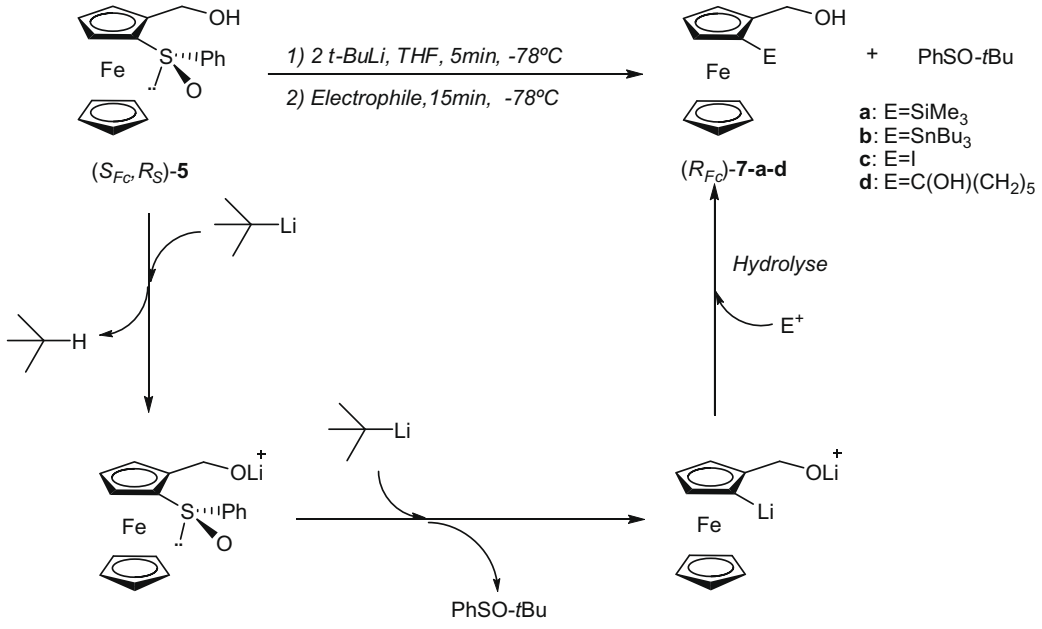
Scheme 4. Oxidation of sulfides **4** by *m*-CPBA.

employs strategies based on the use of chiral orthodirecting group for diastereoselective lithiation-electrophilic capture sequences. It has been shown that aryl sulfoxides were excellent orthodirecting groups for such reaction and that the sulfoxide group could be easily replaced by another functional group by lithium exchange followed by electrophilic capture.[15] We have decided to use this reaction to our substrate in order to devise a new straightforward synthesis of enantiomerically pure ferrocene complexes.

Both enantiomers of sulfide **4** were oxidised to the corresponding sulfoxides **5** by reaction with an equimolecular amount of *m*-CPBA in dichloromethane at −78 °C (Scheme 4).

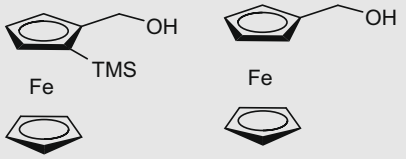
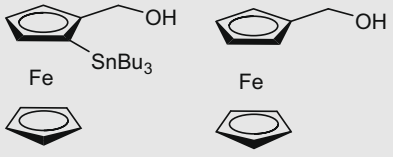
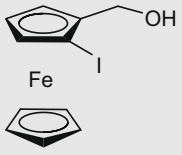
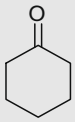
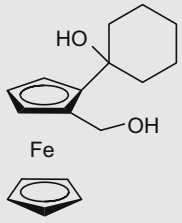
The corresponding sulfoxides were isolated in good yields (75%) along with a small amount of the corresponding sulfones. These sulfoxides had previously been prepared by sodium periodate oxidation of the corresponding sulfides by Nicolosi et al., albeit with very low diastereoselectivity for the oxidation step. In our hand, we found that the use of *m*-CPBA at low temperature gave only the diastereoisomer which was identified by comparison with the reported NMR data.[9a]

Sulfoxides (S_{Fc},R_S)-**5** and (R_{Fc},S_S)-**6** were then used in a transmetallation-electrophilic sequence to prepare the 2-susbtituted ferrocenyl alcohols **7a**–**d** (Scheme 5).



Scheme 5. Transformation of sulfoxide (S_{Fc},R_S)-**5**.

Table 4
Synthesis of 2-substituted ferrocenyl alcohols **7a–d**

Entry	Starting sulfoxide	Electrophile	Products	Yield (%)	$[\alpha]_D$
1	(S_{Fc},R_s)-**5**	TMSCl	 ***(S_{Fc})-7a*** ***8***	70 of **7a**; 20 of **8**	−10.4 (*c* 1, CH_2Cl_2)
2	(S_{Fc},R_s)-**5**	$SnBu_3Cl$	 ***(S_{Fc})-7b*** ***8***	70 of **7b**; 20 of **8**	−1.6 (*c* 1, CH_2Cl_2)
3	(S_{Fc},R_s)-**5**	I_2	 ***(S_{Fc},R)-7c***	80	+21.3 (*c* 1, CH_2Cl_2)
4	(R_{Fc},S_s)-**6**		 ***(R_{Fc})-7d***	90	−5 (*c* 1.5, CH_2Cl_2)

The reaction requires the use of an excess (2.5 equiv) of *tert*-butyl lithium which is added dropwise to a THF solution of sulfoxide **6** in THF at −78 °C. The first equivalent is expected to react with the alcohol to give the lithium alcoholate which then reacts with the second equivalent of *tert*-BuLi by nucleophilic attack on the sulfur atom and elimination of *tert*-butyl phenyl sulfoxide to give the intermediate ferrocenyl lithium dianion. Trapping with various electrophiles and hydrolysis give the *ortho*-substituted alcohols **7a–d** in good yields without the need for prior protection of the alcohol on the starting sulfoxide. The results obtained for the four different electrophiles are summarised in Table 4.

Yield over 70–90% was obtained in all cases after chromatographic purification of alcohols **7a–d**. The only by-product observed in some cases is the ferrocenylmethyl alcohol that is produced by the competitive reaction of the *tert*-butyl lithium on the alcohol and sulfoxide group of substrate **6**. However, the yield of this by-product did not exceed 20% in any case and all the addition adducts were isolated in good overall yields. This method does not require the protection of the alcohol as the reaction of the *tert*-butyl lithium will first deprotonate the alcohol prior to the nucleophilic addition on the sulfur atom. Both reactions are indeed very fast as the conversion of the starting sulfoxide happens during the addition of the *tert*-butyl lithium solution and the electrophile is added as soon as the addition is completed.

3. Conclusion

We have devised a straightforward access to enantiomerically pure 2-substituted ferrocenyl alcohols starting from the inexpensive amine **1**. The optimisation of the resolution step with the CAL-B lipase allowed us to recover both enantiomers of the ferrocenyl alcohol precursors **4** with high enantiomeric purities, which can then be easily transformed into the new alcohols **7**. This methodology is scalable to multi-gram of starting material and thus gives a practical access to non-racemic ferrocenyl compounds that will prove useful for various applications from organic material to asymmetric catalysis.

4. Experimental

4.1. General

NMR spectra were recorded on Brucker spectrometers (300 MHz for ^1H, 75 MHz for ^{13}C). Chemical shifts are reported in δ ppm from tetramethylsilane with the solvent resonance as the internal standard for ^1H NMR and chloroform-*d* (δ 77.0 ppm) for ^{13}C NMR. Coupling constants (*J*) are given in hertz. Following abbreviations classify the multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal. The mass

spectra were obtained from the mass-service at Université catholique de Louvain (FINNIGAN-MAT TSQ 7000 and FINNIGAN-MAT LQC spectrometers). IR spectra were recorded on Shimadzu FTIR-8400S spectrometer. Optical rotations were determined using a Perkin–Elmer 241 Polarimeter at room temperature using a cell of 1 dm length and $\lambda = 589$ nm. The enantiomeric excesses were measured by a chiral stationary phase HPLC on Chiralpak® AD column. Retention times are reported in minutes.

4.2. *N,N*-Dimethylaminomethyl-1-phenylthio-ferrocene *rac*-2

A dry Schlenk tube was loaded under argon with 10 g (41 mmol) of DMAF **1** and diluted with 50 mL of freshly distilled diethyl ether. Next 31.5 mL of a 1.5 M *tert*-butyl lithium solution (1.15 equiv, 47.3 mmol) was added dropwise and the resulting brick-red solution was stirred at room temperature for a further 15 min after the end of the addition. Diphenyl disulfide (13.5 g, 61.5 mmol, 1.5 equiv) in 40 mL of diethyl ether was added dropwise at room temperature and the brown solution was kept at this temperature for a further 1 h before careful quenching with brine. The aqueous phase was extracted with ether and the organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo. The crude brown oil was purified by flash chromatography on silica gel (80/20/1 cyclohexane/ethyl acetate/triethylamine) to give the pure sulfide **2** as a brown solid in 92% yield (13.3 g). $C_{19}H_{21}FeNS$ (351.29). Mp: 70 °C, IR (*film, cm*$^{-1}$): $\nu = 690.4$; 736.7; 817.7; 1026; 1080; 1103.2; 1176.5; 1261.3; 1477.3; 1581.5; 2765.7; 2812; 2939.3. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.02$ (s, 6H, $N(CH_3)_2$); 3.37 and 3.42; 3.43 and 3.47 AB (dd, $J = 13.3$ Hz, 2H, $CH_2N(CH_3)_2$); 4.6 (s, 5H, C_P); 4.32 (s, 1H, C_P), 4.46 and 4.50 (d, 2H, $J = 13.6$ Hz, C_P); 7.01–7.11 (m_a, 5H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 45.13$; 57; 69.14; 70.36; 71.3; 75.62; 76; 88; 124.84; 126.18; 128.49; 140. MS (D-APCI; *m*/*z*): 242.18 ([$FcCH_2NMe_2$]$^+$, 100%); 307 ([$FcSPhCH_2$]$^+$, 49%); 350.08([M−H]$^+$, 35%); 351 ([M]$^+$, 24%); 352.04 ([M+H]$^+$, 6%).

4.3. Acetoxymethyl-1-phenylthioferrocene *rac*-3

At first, 13 g (37 mmol) of sulfide *rac*-**2** is dissolved in (30 mL) of acetic anhydride and the solution was refluxed for 15 h. After filtration on Celite and concentration in vacuo, the crude reaction mixture was purified by flash chromatography on silica gel (80/20 cyclohexane/ethyl acetate). 12.8 g of the pure acetate (95%) is isolated as deep orange crystals. $C_{19}H_{18}FeO_2S$ (366.26). Chiral HPLC analysis (*Chiralpak* AD column) (hexane/EtOH: 99/1; 1 mL/min): $rt_1 = 9.5$ min, $rt_2 = 12.8$ min. Mp: 128 °C. IR (film, cm^{-1}): $\nu = 690.4$; 744.4; 817.7; 952.7; 999; 1022.2; 1238.2; 1369.3; 1577.6; 1728.1 (νC=O). ^{1}H NMR (300 MHz,$CDCl_3$): 1.75 (s, 3H, O=C–CH_3); 4.27 (s, 5H, C_P); 4.41 (s, 1H, C_P), 4.52 and 4.55 (d, 2H, $J = 10.17$ Hz, C_P); 4.90 and 4.94 (d, $J = 11.38$ Hz, 1H) et 5.07–5.11 (d, $J = 12.39$ Hz, 1H) CH_2OH; 7.04–7.2 (m_a, 5H, aromatics). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 20.61$; 61; 69.62; 70.21; 71.83; 76.17; 85; 124.95; 126.17; 128.48; 141.5; 172. MS (EI; *m*/*z*): 43.9 ([Ac]$^+$, 86%); 148.8 ([Fc–H]$^+$, 71%); 185.8 ([Fc]$^+$, 53%); 366 ([M]$^+$, 100%); 367.1 ([M+H]$^+$, 24%).

4.4. Hydroxymethyl-1-phenylthioferrocene *rac*-4

At first, 12 g (32.7 mmol) of racemic acetate **3** was dissolved in 50 mL of dry methanol and stirred overnight with 50 g of potassium carbonate. After filtration on Celite and concentration, the residue is taken up in dichloromethane and washed with water. After standard work up, the pure alcohol *rac*-**4** (10 g, 95%) was isolated as yellow-orange crystals. $C_{17}H_{16}FeOS$ (324.22). Chiral HPLC analysis (*Chiralpak* AD column) (hexane/EtOH: 97/3; 1 mL/min): $rt_1 = 30.6$ min, $rt_2 = 34.1$ min. Mp: 127 °C. IR (film, cm^{-1}): $\nu = 690.4$; 740.6; 817.7; 987.4; 1006.7; 1076.2; 1107; 1249.7; 1481.2; 1581.5; 3244 (ν OH). ^{1}H NMR (300 MHz, $CDCl_3$): 1,510 (sl, OH); 4,270 (s, 5H, C_P); 4,41(s, 1H, C_P); 4,37(m, 2H, C_P), 4,53 (m, 1H, CP + 2H, CH_2OH); 7,06 (m, 3H, Ph); 7,17 (m, 2H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 59$; 96.2; 70.1; 70.6; 75.6; 91; 125.2; 125.8; 128.9; 140. MS (EI; *m*/*z*): 185.8 ([Fc]$^+$, 100%); 323.9([M]$^+$, 100%).

4.5. General procedure for the kinetic resolution experiments by enzymatic acylation of (±)-4

A round-bottomed flask was loaded with the racemic alcohol **4** (1 mmol, 0.324 g) and 3 mmol of enol acetate in 6 mL of the indicated solvent. The lipase was added in one portion and the reaction mixture was stirred at the indicated temperature for a given time. At the end of the reaction, the mixture was filtered over Celite and concentrated in vacuo. The chemical yields were evaluated after separation of the starting alcohols and the acetates by flash chromatography on silica gel (80/20 cyclohexane/ethyl acetate). The enantioselectivities were measured by HPLC on a *Chiralpak* AD column and the absolute configuration was determined by comparison of the rotations with the literature data: (R_{Fc})-2-acetoxymethyl-1-phenylthioferrocene: $[\alpha]_D = +95.7$ (*c* 1.45, CH_2Cl_2) (95% ee); (S_{Fc})-2-hydroxymethyl-1-phenylthioferrocene: $[\alpha]_D = -56.2$ (*c* 1, CH_2Cl_2) (99% ee). (lit.[9a] $[\alpha]_D = -50$ (*c* 1.14, $CHCl_3$); 95% ee).

4.6. General procedure for the preparation of the sulfoxide

Sulfide (S_{FC})-**4** (10 g, 29.41 mmol) was dissolved in 200 mL of freshly distilled dichloromethane and the solution cooled to −78 °C. A solution of 70% *m*-CPBA (1 equiv) in 50 mL of DCM is slowly added to the cooled solution of the sulfide with vigorous stirring (a yellow precipitate appears as soon as the addition of the oxidants starts). The reaction was carefully followed by TLC and stopped after the consumption of the starting sulfide by the addition of a saturated sodium sulfite solution. After standard work-up, the crude brown oil was purified by flash chromatography on silica gel (70/30 cyclohexane/ethyl acetate) to give an orange oil which was further crystallised in diethyl ether. The desired sulfoxide was isolated as brown crystals (75%).

4.7. 2-Hydroxymethyl-1-phenylsulfinyl ferrocene (S_{Fc},R_s)-5

$C_{17}H_{16}FeO_2S$ (340.22). $[\alpha]_D = +381.5$ (*c* 1, CH_2Cl_2) (lit.[9a] $[\alpha]_D = +710$ (*c* 0.1, $CHCl_3$). Mp: 122 °C. IR (film, cm^{-1}): $\nu = 651.9$; 688.5; 748.3; 825.5; 989.4; 1083.9; 1107.06; 1161; 1363.5; 1411.8; 1477.3; 1737.7; 3360 (ν OH). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.40–2.43 (t, $J = 11.36$ Hz, 1H, OH); 4.11 (d, $J = 6{,}23$ Hz, 1H, C_P); 4,32 (s, 1H, C_P); 4,41(s, 5H, C_P); 4,51–4,60(m, 3H, C_P + CH_2OH); 7.43 (d, $J = 5.51$ Hz, 3H, Ph); 7.53–7.62 (m, 1H, Ph); 7.66–7.78 (m, 1H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 57; 58; 65.04; 68.92; 69.89; 70.38; 70.54; 70.96; 72.8; 89; 95; 124.36; 129; 146. MS (D-APCI; *m*/*z*): 338.92 ([Fc–SOPh–C_2H_4]$^+$, 100%); 339.98([M]$^+$, 45%); 340.89 ([M+1]$^+$, 15%).

4.8. 2-Hydroxymethyl-1-phenylsulfinyl ferrocene (R_{Fc},S_s)-6

$C_{17}H_{16}FeO_2S$(340.22). $[\alpha]_D = -288$ (*c* 1, CH_2Cl_2). Mp: 120 °C.

4.9. (S_{Fc})-2-Hydroxymethyl-1-trimethylsilyl ferrocene[16] 7a

A dry Schlenk tube is loaded with 340 mg of sulfoxide (S_{Fc},*R*)-**5** (1 mmol) under argon and dissolved in 30 mL of freshly distilled THF. The solution is cooled to −78 °C and 2.5 equiv of a 1.6 M *tert*-BuLi solution is added dropwise in 3–5 min by a syringe. The

solution turns dark brown during the addition of the alkyl lithium solution followed by 3 equiv of chlorotrimethylsilane. The solution is stirred at this temperature for a further 15 min and the cooling bath is removed. The reaction is quenched with a 2 M NaOH solution and extracted with ether. After standard work-up, the crude alcohol is purified by flash chromatography on silica gel (90/10 cyclohexane/ethyl acetate) and is isolated as orange crystals in a 70% yield. $C_{14}H_{20}FeOSi$ (288.24). $[\alpha]_D = -10.4$ (*c* 1, CH_2Cl_2). Mp: 63 °C. IR (film, cm^{-1}): ν = 651.9; 690.47; 941.2;1375.15; 1440.73; 1737.7; 3253.7 (ν OH). ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.28 (s, 9H, TMS); 4.1 (m, 1H, C_P); 4.15(s, 5H, C_P); 4.30–4.39 (m, 4H, $C_P + CH_2OH$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 0.41; 56.1; 68.44; 70.18; 71.7; 74.8; 89. *MS* (*D-APCI; m/z):* 271.17 ([Fc–TMS–CH_2]$^+$, 100%); 286.98([M]$^+$, 50%); 288.82 ([M+1]$^+$, 35%).

4.10. (S_{FC})-2-Hydroxymethyl-1-*tri*butylstannyl ferrocene 7b

The general procedure was applied with the use of 3 equiv of chlorotributyl stannane as the electrophile. The stannylated alcohol was isolated in 70% yield as orange crystals after flash chromatography on silica gel (90/10 cyclohexane/ethyl acetate). $C_{23}H_{38}FeOSn$ (505.1). $[\alpha]_D = -1.6$ (*c* 1, CH_2Cl_2). Mp: 68 °C. IR (film, cm^{-1}): ν = 688.5; 748.3; 825.5; 989.4; 1083.9; 1107.06; 1161; 1217; 1247.86; 1411.8; 1475.44; 2923.88; 3365.5 (ν OH). ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.91 (t, 9H, 3 × CH_3); 1.06–1.31 (m, 6H, 3 × CH_2); 1.36–1.71(m, 6H, 3 × CH_2); 4.04 (m, 1H, C_P); 4.13 (s, 5H, C_P); 4.24 (d, 1H, C_P); 4.35 (m, 1H, C_P); 4.41 (m, 2H, CH_2OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 10.48; 12.7; 12.75; 13; 15.3; 15.4; 17.54; 19.67; 19.77; 26.43; 26.86; 27.28; 27.45; 27.7; 27.85; 28; 29.28; 61.88; 67; 68; 69; 71; 72; 76.62; 77.04; 77.47. *MS* (*D-APCI; m/z):* 198.97 (25%); 328.98(65%); 329.68 ([Fc–Sn–CH_2O]$^+$, 100%); 330.73 (37%); 442.92 (55%).

4.11. (S_{FC})-2-Hydroxymethyl-1-iodoferrocene[17] 7c

The general procedure was applied with the use of 3 equiv of iodine as the electrophile. The iodo alcohol was isolated in 80% yield as brown crystals after flash chromatography on silica gel (90/10 cyclohexane/ethyl acetate) and crystallisation in hexane. $C_{11}H_{11}FeIO$ (341.95). $[\alpha]_D = +21.3$ (*c* 1, CH_2Cl_2) (lit.[9b] $[\alpha]_D = -24.1$ (*c* 0.5, $CHCl_3$) for ee>98%. Mp: 102 °C. IR (film, cm^{-1}): ν = 702.04; 732.9; 925.77; 952.77; 999.06; 1037.63; 1072.35; 1149.5; 1180.35; 1230.5; 1265.22; 1296; 1365.51; 1411.8; 1681.81; 1758.96; 3444.6 (ν OH). ^1H NMR (300 MHz, C_6D_6): δ (ppm) = 3.78 (t, *J* = 2.28 Hz, 1H, C_P); 4.03 (s, 5H, C_P); 4.082–4.16(m, 3H, C_P + OH); 4.32–4.36 (m, 2H, CH_2OH). ^{13}C NMR (75 MHz, C_6D_6): δ (ppm) = 70.73; 71.18; 71.55; 74.34; 77.64; 70,54; 89. MS (D-APCI; *m/z):* 214.09 ([Fc–CH_2O–1]$^+$, 55%); 275.07 (35%); 324.96 ([Fc–CH_2I–1]$^+$, 40%); 339.09 (([Fc–C_2H_4–I]$^+$, 100%); 345.13 [M+3].

4.12. (R_{FC})-2-Hydroxymethyl-1-ferrocenylcyclohexanol 7d

The general procedure was applied with the use of 3 equiv of cyclohexanone as the electrophile. The diol was isolated in a 90% yield as brown oil after flash chromatography on silica gel (90/10 cyclohexane/ethyl acetate) and is further crystallised from hexane. $C_{17}H_{22}FeO_2$ (314.2). $[\alpha]_D = -5$ (*c* 1.5; CH_2Cl_2). Mp: 85 °C. IR (film, cm^{-1}): ν = 736.76; 921.91; 966.27; 1143.71; 1178.43; 1309.58; 1697.24; 2360.71; 3091.68; 3375.2 (ν OH). ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.23 (m, 1H, Cy); 1.30–1.54 (m, 2H, Cy); 1.46–2.02 (m, 4H, Cy); 2.16 (s, 1H, Cy); 2.32 (t, *J* = 6.63 Hz, 1H, Cy); 2.58 (s, 1H, Cy); 3.63 (sl, 1H, Cy–OH); 4.16 (s, 7H, $C_P + CH_2$–OH), 4.23 (m, 2H, C_P); 4.32 (s, 1H, C_P). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 21; 22; 24.21; 25; 26; 27; 28; 32; 32.29; 33.25; 36; 37; 39; 42; 44; 54; 60; 61; 65.64; 67.96; 68.3; 68.78; 70.45; 87; 96. MS (D-APCI; *m/z):* 314.19 ([M]$^+$, 100%).

4.13. Ferrocenylmethyl alcohol 8

The byproduct was obtained as orange crystals. $C_{11}H_{12}FeO$ (216.064). Mp: 77 °C. IR (film, cm^{-1}): ν = 651.9; 740.61; 806.2; 969.4; 1190; 1253.64; 1350; 1380.94; 1398.3; 1409.87; 1760.7; 2875; 3136 (ν OH). ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.69 (sl, 1H, O*H*); 4.21 (s, 8H, C_P); 4.27 (s, 1H, C_P); 4.33(s, 2H, CH_2OH). ^{13}C NMR (75 MHz, $CDCl_3$):δ (ppm) = 60.74; 67.91; 68; 68.49; 88.6. MS (CI; *m/z):* 216.8 ([M]$^+$, 100%).

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