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Synthesis of new ferrocenyl aminoalcohols and aminonitriles and catalytic properties of the aminoalcohols in the ethylation of benzaldehyde

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Abstract

Chiral ferrocenyl aminoalcohols possessing either OH or NR_2 functionality α to the ferrocenyl ring were prepared and exhibit modest enantioselectivities for the addition of diethylzinc to benzaldehyde. Chiral ferrocenyl aminonitriles exhibit a facile inversion process in protonic solvents.

1. Introduction

Chiral ferrocenes are well known as effective auxiliaries in a number of stereoselective syntheses,[1] and in this context, hydroxyaminoferrocenes were reported as able to catalyse the asymmetric addition of dialkylzinc reagents to aldehydes to yield optically active secondary alcohols.[2] These catalysts can be structurally grouped into three classes. Norephedrine derivatives **1** and **2** (generated in situ from the corresponding α-iodo complex)[3] containing central and central/planar chirality provide a modest enhancement (85–95% e.e.) of the already strong (80–90% e.e.) directing effect of the ephedrine framework in the ethylation of benzaldehyde.[4] Aminoalcohols of structure **3** possessing both planar and central chirality provide effective induction (up to 99% e.e.) for the ethylation of both aromatic and aliphatic aldehydes,[5] while the aminoalcohols **4** and **5** possessing only planar chirality provide more modest degrees of induction (83% and 51%, respectively).[6,7]

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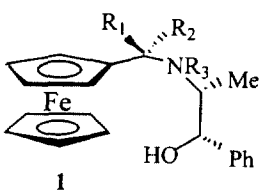

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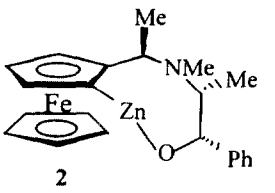

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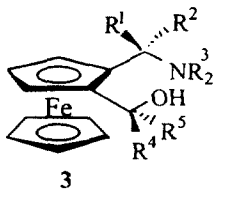

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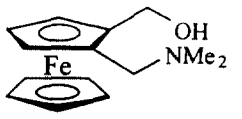

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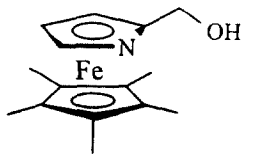

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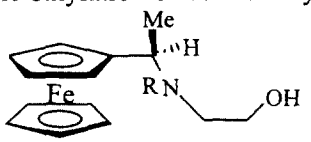
Surprisingly, hydroxyaminoferrocenes containing only single stereogenic centres alpha to the ferrocenyl nucleus have not been investigated. We report here our full results[8] on the synthesis and catalytic properties for asymmetric ethylation of benzaldehyde of aminoalcohols of structures **6** and **7**.



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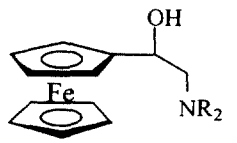

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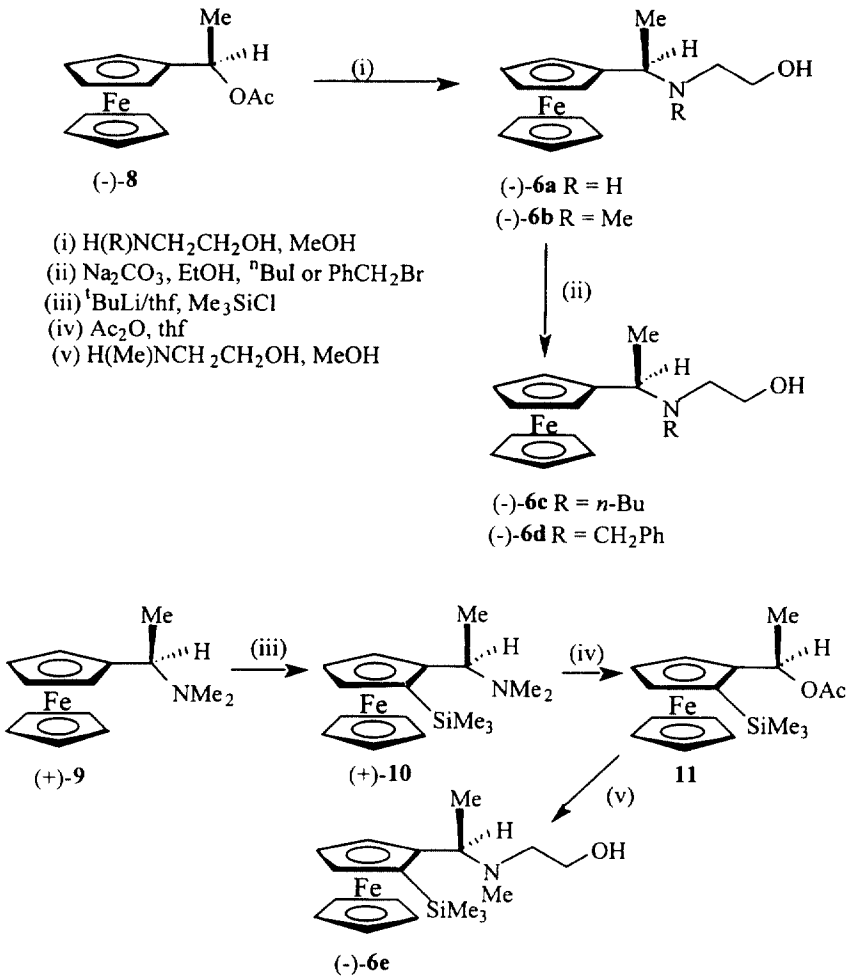
The methods used for the synthesis of aminoalcohols of structure **7** also lend themselves to the potential synthesis of optically active ferrocenyl aminonitriles. These latter compounds have exhibited a facile inversion process in protonic solvents which is described in detail in this paper.

2. Results and discussion

2.1. Synthesis of ferrocenyl aminoalcohols

The new β-aminoalcohols (*R*)-(−)-**6a,b** were obtained by reaction of (*R*)-(−)-1-acetoxyethylferrocene **8** (>95% e.e. from the lipase catalysed kinetic resolution of 1-hydroxyethylferrocene)[9] with ethanolamine or *N*-methylethanolamine under conditions of nucleophilic substitution with retention of configuration.[10] Alkylation of (*R*)-(−)-**6a** with *n*-BuI or benzyl bromide gave (*R*)-(−)-**6c,d**, respectively. (1*R*,*R*)-(−)-**6e** was prepared by diastereoselective lithiation of (*R*)-(+)-*N*,*N*-dimethylaminoethylferrocene **7**[11] to give **10**, followed by stereoselective conversion to the acetate **11** and reaction with *N*-methylethanolamine.

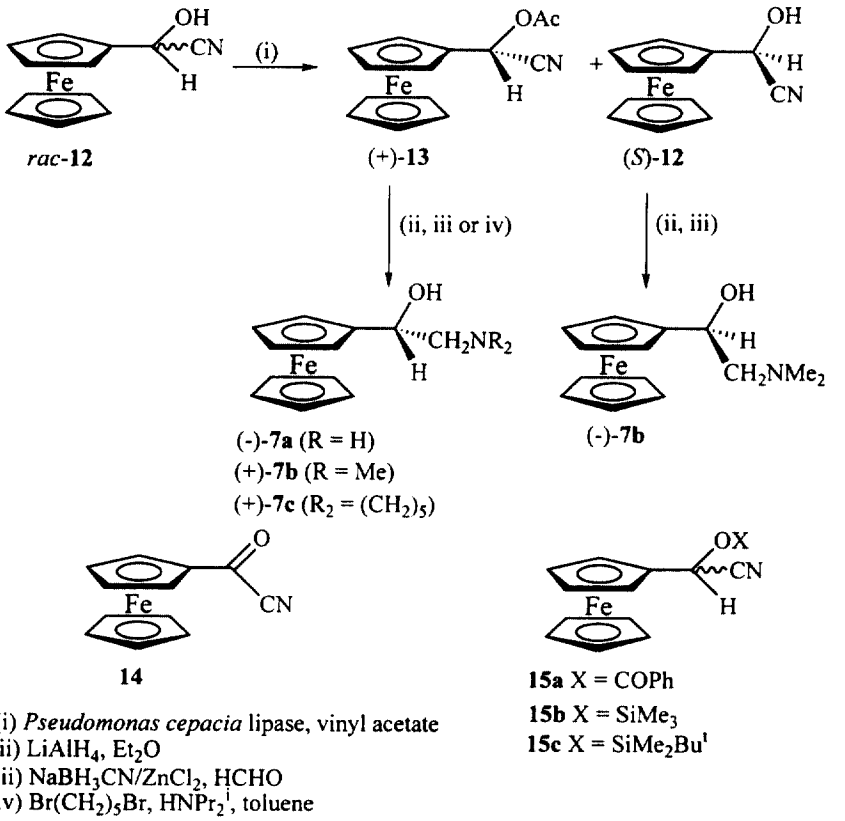
The aminoalcohols (*R*)-(+)-**7b**, (*S*)-(−)-**7b** and (*R*)-(+)-**7c** were obtained via lipase catalysed acylation of ferrocene cyanohydrin **12**[12] followed by reduction and alkylation. Optimal results for the kinetic resolution were obtained using *Pseudomonas cepacia* lipase and neat vinyl acetate as acyl donor and solvent. At 50% conversion to the acetate **13**, NMR analysis also indicated formation of the acyl cyanide **14**[13] as a by-product (10%) resulting from the solution instability of the cyanohydrin **12**. Conversion of **12** to **14** is particularly enhanced in chlorinated solvents in the presence of oxygen, although the mechanism of the formal oxidation has not been investigated. Complexes **12** and **13** are unstable towards chromatography on active silica or alumina, decomposing to a mixture of ferrocene carboxaldehyde and **14**. The acetate **13** may be isolated from the crude products of the lipase catalysed acylation by chromatography on 15% deactivated alumina (during which decomposition of **12** occurs). Use of the



more expensive silica diol as support enables separation and isolation of both **12** and **13** in optical purities of 81% e.e. and 85% e.e., respectively. The enantiomeric excess of the acetate may be increased to >95% e.e. by recrystallisation. Stability towards chromatography is much enhanced in the easily prepared *O*-protected derivatives **15a–c**.

The (*R*)-configuration of the acetate (+)-**13** was confirmed by a single crystal structure determination[8] and is consistent with other results on the lipase catalysed resolution of organic cyanohydrins.[14] Use of other lipases for acylation of **12** (lipase AY from *Candida cylindracea*) or alcoholysis of rac-**13** (lipase PS from *Pseudomonas cepacia*) either proceed too slowly or provide products of lower enantiomeric excess. Use of supported enzymes (lipase PS from *Pseudomonas cepacia*, Chirozyme from *Mucor miehei*) results in more extensive conversion to **14**.

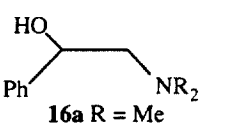
Both **12** and **13** are cleanly reduced[15] to the aminoalcohol **7a** which may be methylated under mild conditions[16] to give **7b** without loss of enantiomeric excess. The vigorous conditions required for alkylation of **7a** to give the piperidino derivative **7c**[17] result in some loss of enantiomeric excess.



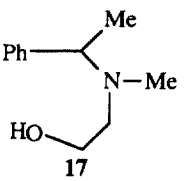
2.2. *Catalytic alkylation of benzaldehyde*

The new ferrocenyl aminoalcohols were examined as catalysts for the asymmetric addition of Et_2Zn to benzaldehyde to give enantiomerically enriched 1-phenyl-1-propanol. The results are summarised in Table 1, together with relevant literature results. The observed product chirality is in agreement with the results obtained using other aromatic and aliphatic β-aminoalcohols containing only a single stereogenic centre.[18] Several points of interest may be noted:

(i) Enantioselectivities in both the **6** and **7** series are modest. In view of the demonstrated influence of the bulkiness of substituents alpha to hydroxy, the slightly better enantioselection in the **6** series is surprising. As observed for complexes of structure **3**,[5a] an increase in the steric bulk of the nitrogen substituent in **6b–d** (entries 2, 8 and 9) results in a decrease in activity and enantioselection. The dramatic decrease in activity and enantioselection of the piperidino derivative **7c** (entries 10 and 11) is, however, surprising in view of the demonstrated efficacy of the piperidino moiety in **3** and in the related phenyl analogue **16b**.[19]



16a R = Me
16b $R_2 = (CH_2)_5$



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(ii) Increasing catalyst concentration (entries 2, 4 and 5) to effect higher conversion results in a substantial loss of enantiomeric excess. This most likely arises from a non-stereoselective ethyl transfer

Table 1
Enantioselective addition of Et_2Zn to benzaldehyde catalysed by ferrocenyl aminoalcohols

Entry	Catalyst	Mol % of catalyst	Time (h)	Conversion (%)	e.e. of (S)-1-phenyl-1-propanol (%)	ref
1	(R)-6a	5	40	57	30	a
2	(R)-6b	5	24	55	41	a
3[b]	(R)-6b	5	6	64	40	a
4	(R)-6b	10	6	82	16	a
5	(R)-6b	20	3	88	7	a
6[c]	(R)-6b	5	24	57	40	a
7	(R)-9	5	3	75	0	a
8	(R)-6c	5	24	53	33	a
9	(R)-6d	5	24	80	11	a
10	(R)-7b	5	24	80	30	a
11	(R)-7c	5	24	46	6	a
12	(1R,R)-6e	5	24	78	63	a
13	3 ($R^1 = R^3 = Me$, $R^2 = H$, $R^4, R^5 = Ph$)	5	2	99	97	5a
14	3 $R^1 = Me$, $R^2 = H$, $R^4, R^5 = Ph$, $R^3{}_2 = (CH_2)_5$	5	1	99	99	5a
15	4	10	3	92	80	6
16	16a	5	24	93	59	19
17	16b	5	24	97	75	19

[a] this work

[b] reaction carried out at 40 °C; the remainder were performed at 25 °C.

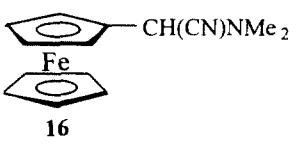
[c] catalyst pretreated with Et_2Zn at 85 °C.

to benzaldehyde, promoted by zinc co-ordination to only the amino group of the catalyst. In the presence of enantiopure (*R*)-(+)-*N*,*N*-dimethylaminoethylferrocene **9**, catalysis affords high conversion to racemic product (entry 7). Pretreatment of the catalyst with one equivalent of Et_2Zn at 85°C[20] provided no alteration in the enantiomeric excess of the product (entry 6). The conversion may be increased by increasing the temperature without loss of enantiomeric excess (entries 2 and 3).

(iii) Given the interest in the ferrocenyl moiety as a three-dimensional phenyl equivalent,[21] the lower enantioselection of **7b** compared to its phenyl equivalent **16a** (entries 10 and 16) is intriguing.

Compound **17**, the phenyl equivalent of **6b** has not been used as a catalyst for alkylation, but provides only a 10% e.e when used as an auxiliary in the $LiAlH_4$ reduction of acetophenone.[22]

(iv) Introduction of planar chirality, though not containing a donor atom, provides a substantial increase in enantioselectivity (entries 2 and 12). Taken together, the results in Table 1 demonstrate decreasing enantioselection as a function of type(s) of chirality in the order (planar+central)>(planar only)>(central only) but with planar chirality providing the dominant influence on enantioselection, particularly when chelation sites are contained in both ferrocenyl substituents.



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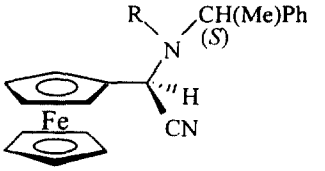
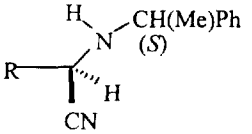
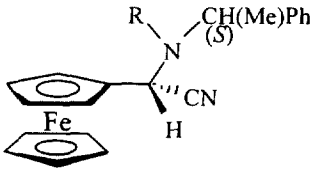


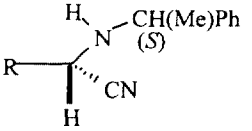
17a R = Me
18a R = H



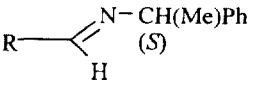
19a R = p-MeOC $_6H_4$
20a R = $(CH_3)_3C$



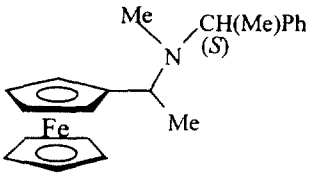
17b R = Me
18b R = H



19b R = p-MeOC $_6H_4$
20b R = $(CH_3)_3C$



21 R = ferrocenyl
22 R = p-MeOC $_6H_4$



23a,b

2.3. *Configurational stability of ferrocenyl aminonitriles*

Aminonitriles constitute valuable precursors to a variety of chiral compounds, including amino acids (via hydrolysis) and diamines (via reduction).[23] We have therefore investigated access to enantiomerically pure ferrocenyl aminonitriles via nucleophilic displacement of acetate from resolved **13**. In view of the well-established stereospecific retention of configuration on reaction of **5** with methanolic Me_2NH at ambient temperature,[10] it was surprising to find that reaction of (+)-**13** under these conditions provides only racemic **16**. No reaction occurs in aprotic solvents such as benzene or dimethylformamide.

Though configurational instability of cyanohydrins has previously been noted,[24] the facility of the

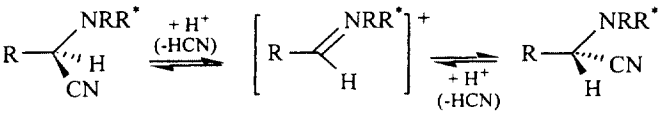
Table 2
Data for epimerisation of aminonitriles **17–20**

Complex	Solvent, Temperature	K_{eq} [b]/[a]	$k_1 + k_{-1}$ (10^6 s^{-1})	k_1 (10^6 s^{-1})	k_{-1} (10^6 s^{-1})
17a,b	MeOH, 30 °C	1.84	1930	1250	680
17a,b	benzene,70 °C	1.82	5.99	3.86	2.13
18a,b	MeOH, 30 °C	2.71	2100	1534	566
19a,b	MeOH, 30 °C	2.74	2360	1729	631
20a,b	MeOH, 30 °C	5.48	830	702	128

presumed racemisation of **16** was unexpected. We have therefore carried out more detailed studies of this inversion process via diastereoisomer interconversion in the ferrocenyl derivatives **17a,b** and **18a,b** and compared the results to the analogous inversion process in the organic aminonitriles **19a,b** and **20a,b** containing electron releasing aromatic and sterically demanding aliphatic substituents, respectively.

Reaction of (+)-**13** with (*S*)-(−)-PhCH(Me)NH(R) (R=Me, H) or a Strecker reaction using ferrocene carboxaldehyde[25] both yield thermodynamic equilibrium mixtures of **17a,b** and **18a,b**. The minor diastereoisomer **17a** may be isolated by crystallisation and shown to have the (*S,S*)-configuration by X-ray crystal structure determination.[26] A pure sample of the major diastereoisomer **18b** was obtained by chromatography. Diastereoisomerically pure and enriched samples of **19b** and **20a** were obtained by modification of literature procedures.[24a,b]

Epimerisation studies were monitored by integration of appropriate ^{1}H NMR resonances; the results are displayed in Table 2. The much reduced rate of epimerisation of **17a** in benzene at elevated temperature and the lack of epimerisation of **19a** at 30°C in the less acidic *t*-amyl alcohol are consistent with a mechanism involving reversible, acid-catalysed dissociation of HCN to generate the iminium cation as intermediate.



Indeed, thermolysis of **18a** or **19a** in benzene at 70°C results in clean loss of HCN without epimerisation, to give the imines **21** and **22**. The similarity of the rates of epimerisation of **18** and **19** indicates a similar ability of the electron releasing ferrocenyl and *p*-anisyl groups to stabilise charge at the α-position. The similarity of the K_{eq} for **18a** and **19a** is consistent with an equal steric demand for the ferrocenyl and *p*-anisyl groups in this system. *N*-Methyl substitution as in **17** has only a minor effect on the diastereoselection and a negligible effect on the rate of epimerisation. A comparison of the rates of epimerisation of **17–19** with **20** indicates that electronic stabilisation of the transition state is more efficient than steric acceleration. The sterically demanding *t*-Bu group is, however, more efficient at promoting higher diastereoselection. Loss of stereochemical integrity is also evident in the reaction of diastereomerically pure **17a** with MeMgI to give **23a,b** as an inseparable 1:1 mixture of diastereoisomers.

3. Experimental

^{1}H and ^{13}C NMR spectra were recorded at 250 or 270 MHz and 62.9 or 68.0 MHz, respectively;

chemical shifts are reported in ppm relative to tetramethylsilane. Optical rotations were measured on Perkin–Elmer 141 polarimeter and JASCO DIP135 instruments.

3.1. Synthesis of (R)-(−)-2-(1-ferrocenylethylamino)ethanol 6a

To a solution of (*R*)-acetoxyethylferrocene (−)-**8** (150 mg, 0.55 mmol) in MeOH was added ethanolamine (830 μl, 13.77 mmol) and the reaction was stirred at room temperature for 3 days. The solution was partitioned between H_2O and diethyl ether and the separated organic layer was extracted with 10% citric acid solution. After basifying with 1 N NaOH, the aqueous layer was extracted with diethyl ether and the organic phase dried over Na_2SO_4. Removal of solvent gave (*R*)-(−)-**6a** as a brown oil (110 mg, 71%). Analysis: calcd for $C_{14}H_{19}FeNO$: C, 61.6; H, 7.01; N, 5.13%; found C, 61.4; H, 7.11; N, 5.04%. ^{1}H NMR ($CDCl_3$): 1.39 (3H, d, J=6.3 Hz, CH_3CH), 2.74 (2H, m, CH_2N), 3.54 (1H, q, CH_3CH), 3.61 (2H, m, CH_2OH), 4.13–4.19 (9H, m, Cp, Cp′). ^{13}C NMR ($CDCl_3$): 21.5 (Me), 48.7, 52.1, 61.0 (CH, CH_2CH_2), 65.7, 67.2, 67.4 (Cp_{2-5}), 68.4 (Cp′), 93.1 (Cp_1). $[\alpha]_D^{25}$ −21.0 (c 1.5, $CHCl_3$).

3.2. 2-[(1-Ferrocenylethyl)methylamino]ethanol 6b

This was prepared in the same way using *N*-methylethanolamine. Analysis: calcd for $C_{15}H_{21}FeNO$: C, 62.7; H, 7.37; N, 4.88%; found C, 62.6; H, 7.50; N, 4.75%. ^{1}H NMR ($CDCl_3$): 1.41 (3H, d, J=6.9 Hz, CH_3CH), 2.06 (3H, s, CH_3N), 2.37, 2.48 (2H, dd, J=12.9 and 5.3 Hz, CH_aH_bN), 3.48 (2H, m, CH_2OH), 3.76 (1H, q, $CHCH_3$), 4.10–4.17 (9H, m, Cp, Cp′). ^{13}C NMR ($CDCl_3$): 15.3 (Me), 36.0 (NMe), 54.2, 57.8, 58.5 (CH, CH_2CH_2), 66.8, 67.2, 68.6, 68.7 (Cp_{2-5}), 67.8 (Cp′), 87.8 (Cp_1). $[\alpha]_D^{25}$ −25.1 (c 1.1, $CHCl_3$).

3.3. Synthesis of (R)-(−)-2-[(1-ferrocenylethyl)butylamino]ethanol 6c

To a solution of (−)-**6a** (180 mg, 0.66 mmol) in EtOH (10 ml) was added *n*-BuI (113 μl, 1.00 mmol) and Na_2CO_3 (105 mg, 1.00 mmol). The mixture was refluxed for 5 h and the solvent was removed. Chromatography on basic alumina (hexane:ethyl acetate) provided (*R*)-(−)-**6c** as a brown oil (109 mg, 50%). Analysis: calcd for $C_{18}H_{27}FeNO$: C, 65.7; H, 8.27; N, 4.25%; found C, 65.5; H, 8.40; N, 4.15%. ^{1}H NMR ($CDCl_3$): 0.88 (3H, t, J=7.3 Hz, CH_3CH_2), 1.27 (4H, m, $CH_3CH_2CH_2$), 1.38 (3H, d, J=6.9 Hz, CH_3CH), 2.30 (2H, m, $CH_3(CH_2)_2CH_2N$), 2.38, 2.50 (2H, dd, J=12.8 and 5.2 Hz, CH_aH_bN), 3.41 (2H, m, CH_2OH), 3.86 (1H, q, $CHCH_3$), 4.08–4.16 (9H, m, Cp, Cp′). ^{13}C NMR ($CDCl_3$): 14.0, 15.2, 20.4, 31.2 (Me, $NCH_2CH_2CH_2CH_3$), 49.7, 50.9, 54.1, 58.2 (CH, NCH_2CH_2OH, $NCH_2CH_2CH_2CH_3$), 66.8, 67.2, 67.9 (Cp), 68.6 (Cp′), (Cp_1). $[\alpha]_D^{25}$ −24.7 (c 1.3, $CHCl_3$).

3.4. Synthesis of (R)-(−)-2-[benzyl(1-ferrocenylethyl)amino]ethanol 6d

To a solution of (−)-**6a** (130 mg, 0.48 mmol) in EtOH (7 ml) were added $PhCH_2Br$ (86 μl, 0.72 mmol) and Na_2CO_3 (76 mg, 0.72 mmol). The mixture was refluxed for 3 h, cooled, and partitioned between aqueous 10% citric acid and diethyl ether. After basifying, the aqueous layer was extracted with diethyl ether. After drying over Na_2SO_4 and removal of solvent, the residue was chromatographed on basic alumina (hexane:acetone) to give (*R*)-(−)-**6d** as a brown oil (98 mg, 56%). Analysis: calcd for $C_{21}H_{25}FeNO$: C, 69.4; H, 6.94; N, 3.86%; found C, 69.3; H, 7.10; N, 3.70%. ^{1}H NMR ($CDCl_3$): 1.48 (3H, d, J=6.8 Hz, $CHCH_3$), 2.48, 2.65 (2H, m, CH_aH_bN), 3.43 (2H, m, CH_2OH), 3.59 (2H, m, CH_2Ph), 3.90 (1H, q, $CHCH_3$), 4.10 (5H, s, Cp′), 4.14–4.20 (4H, m, Cp), 7.33 (5H, m, Ph). ^{13}C NMR ($CDCl_3$):

16.8 (Me), 52.4, 55.8, 56.1, 59.5 (CH_2CH_2OH, NCH_2Ph, CH), 68.9, 69.2, 70.1, 70.2 (Cp_{2-5}), 69.5 (Cp′), 88.4 (Cp_1), 128.7, 129.9, 130.2, 130.4, 140.2 (Ph). $[\alpha]_D^{25}$ −23.2 (c 1.3, $CHCl_3$).

3.5. *Synthesis of (1*R,R*)-(−)-1-trimethylsilyl-2-(*N*-methyl,*N*-hydroxyethyl)aminoethylferrocene* **6e**

To a solution of (+)-*N*,*N*-dimethylaminoethylferrocene (200 mg, 0.78 mmol, Aldrich) in anhydrous tetrahydrofuran (4 ml) cooled to 0°C was added *t*-BuLi (1.17 mmol, 686 μl of a 1.7 M solution in pentane). After 30 min, $(CH_3)_3SiCl$ (198 μl, 1.56 mmol) was added at room temperature. The mixture was stirred for 5 h and refluxed for a further 3 h. After cooling and partitioning between H_2O and diethyl ether, solvent was removed from the organic phase and the residue was purified by chromatography on basic alumina (petroleum ether:diethyl ether) to give (1*R*,*R*)-1-trimethylsilyl-2-*N*,*N*-dimethylaminoethylferrocene (+)-**10** as a brown oil (117 mg, 46%) identified by a comparison of its optical and NMR data with the literature.[11]

(+)-**10** was quantitatively converted into the ester **11** by treatment with acetic anhydride in tetrahydrofuran under reflux for 2 h. After removal of solvent, **11** was dissolved in MeOH and treated with *N*-methylethanolamine (711 μl, 8.85 mmol). After stirring for 4 days at room temperature, the mixture was partitioned between H_2O and diethyl ether. After drying over Na_2SO_4, the organic layer was taken to dryness and the residue purified by chromatography on silica gel (hexane:diethyl ether) to give (1*R*,*R*)-(−)-**6e** as a brown oil (61 mg, 48%). Analysis: calcd for $C_{18}H_{29}FeNOSi$: C, 60.2; H, 8.13; N, 3.90%; found C, 60.0; H, 8.26; N, 3.75%. ^{1}H NMR ($CDCl_3$): 0.32 (9H, s, $(CH_3)_3Si$), 1.33 (3H, d, J=6.8 Hz, CH_3CH), 2.11 (3H, s, CH_3N), 2.45, 2.59 (2H, dd, J=12.6 and 7.0 Hz, CH_aH_bN), 3.49 (2H, m, CH_2OH), 3.88 (1H, q, *CH*CH_3), 4.10 (5H, s, Cp′), 4.33 (3H, m, C_5H_3). $[\alpha]_D^{25}$ −22.8 (c 1.0, $CHCl_3$).

3.6. *Synthesis of* rac-*1-acetoxyferrocenylacetonitrile* ***13***

To *rac*-ferrocene cyanohydrin **12**[12a] [(500 mg, 2.07 mmol); ^{1}H NMR (C_6D_6): 1.68 (1H, d, J=7.9 Hz, OH), 3.97 (5H, s, Cp′), 3.80 (2H, m, Cp), 3.93, 4.14 (each 1H, m, Cp), 4.50 (1H, d, CH)] dissolved in dry diethyl ether (75 ml) was added freshly distilled acetyl chloride (160 mg, 2.07 mmol) and dry pyridine (160 mg, 2.07 mmol). After stirring overnight at room temperature, the solvent was removed and the residue purified by chromatography using 15% deactivated alumina (1:1, petroleum ether:CH_2Cl_2) to give *rac*-**12** as a yellow solid (390 mg, 67%) which was recrystallised from petroleum ether (60–80). Mp: 88–90°C. Analysis: calcd for $C_{14}H_{13}FeNO_2$: C, 59.4; H, 4.59; N, 4.95%; found C, 59.6; H, 4.49; N, 4.67%. ^{1}H NMR (C_6D_6): 1.35 (3H, s, $COCH_3$), 3.97 (5H, s, Cp′), 3.81, 3.86, 4.03, 4.39 (each 1H, m, Cp), 6.17 (1H, s, CH). ^{13}C NMR ($CDCl_3$): 20.5 (Me), 60.6 (CH), 69.6 (Cp′), 67.9, 69.7, 70.0, 70.1 (Cp_{2-5}), 78.0 (Cp_1), 116.0 (CN), 169.1 (CO). The ^{1}H $COCH_3$ resonance is resolved into two on addition of tris[(heptafluoropropylhydroxymethylene)-(+)-camphorato]Eu(III).

3.7. *Synthesis of* rac-*1-benzoyloxyferrocenylacetonitrile* ***15a***

To *rac*-**12** (100 mg, 0.42 mmol) dissolved in dry pyridine (1.5 ml) was added benzoyl chloride (0.07 ml, 0.63 mmol). After stirring for 3 h at room temperature, the solvent was removed and the residue purified by chromatography on 15% deactivated alumina to give **15a** (70 mg, 49%) which was recrystallised from petroleum ether (60–80). Mp: 124–127°C. Analysis: calcd for $C_{19}H_{15}FeNO_2$: C, 66.1; H, 4.35; N, 4.06%; found C, 65.9; H, 4.48; N, 3.96%. ^{1}H NMR (C_6D_6): 3.99 (5H, s, Cp′), 3.82, 3.88, 4.11, 4.46 (each 1H, m, Cp), 6.42 (1H, s, CH), 6.8–7.1, 7.92 (5H, m, Ph).

3.8. Synthesis of rac-ferrocenyltrimethylsiloxyacetonitrile **15b**

Imidazole (450 mg, 6.6 mmol) and $(CH_3)_3SiCl$ (430 mg, 4.0 mmol) were dissolved in dry dimethylformamide (10 ml) and *rac*-**12** (200 mg, 0.83 mmol) was added with stirring. After heating at 40°C for 2 h, the solution was cooled and poured into ice water (50 ml). After extraction with diethyl ether, washing with H_2O and drying over $MgSO_4$, the solvent was removed and the crude product recrystallised from hexane to give *rac*-**15b** as brown crystals (130 mg, 53%). Mp: 80–82°C (lit.[27] 80–82°C). ^{1}H NMR (C_6D_6): 0.05 (9H, s, $(CH_3)_3Si$), 4.07 (5H, s, Cp′), 3.83, 3.87, 3.94, 4.36 (each 1H, m, Cp), 5.03 (1H, s, CH).

Compound *rac*-**15c** was prepared similarly as a brown oil using *t*-$BuMe_2SiCl$ and purified by chromatography on 15% deactivated alumina (1:1, petroleum ether:CH_2Cl_2). Mass spectrum: calcd for $C_{18}H_{25}FeNOSi$ 355.3341; found 355.3325. ^{1}H NMR (C_6D_6): 0.01 (6H, 2s, $Si(CH_3)_2$), 0.88 (9H, s, *t*-Bu), 4.10 (5H, s, Cp′), 3.87 (2H, m, Cp), 4.02, 4.31 (each 1H, m, Cp), 5.01 (1H, s, CH).

3.9. Enzymatic resolution of ferrocenylhydroxyacetonitrile

Compound *rac*-**12** (100 mg, 0.42 mmol) and *Pseudomonas cepacia* lipase (100 mg, Amano lipase PS) were added to distilled vinyl acetate (2.3 ml) under nitrogen and shaken gently at room temperature. The reaction was monitored by NMR until the integrated ratio of the CH resonances due to **12** and **13** had reached 1:1. At this point, resonances assignable to **14** [^{1}H NMR ($CDCl_3$): 4.37 (5H, s, Cp′), 4.86, 4.98 (each 2H, t, Cp)] accounted for 10% of the integrated intensity. The enzyme was removed by filtration, washed with diethyl ether and the residue evaporated to dryness. The reaction may be carried out successfully on a scale of up to 1 g of **12**. Purification was accomplished in two ways:

(i) Careful chromatography on 15% deactivated alumina (1:1, petroleum ether:CH_2Cl_2) eluted first the acetate **13** (40%, 84% e.e.) followed by ferrocene carboxaldehyde. Recrystallisation provided (*R*)-(+)-**13** (>95% e.e., $[\alpha]_D^{25}$ +73.8 (c 0.2, CH_3CN)).

(ii) Chromatography on silica gel under N_2 pressure using 1:4, ethyl acetate:petroleum ether (40–60) eluted first the (*S*)-cyanohydrin **12** (34% yield, 81% e.e. by NMR analysis of the derived acetate), followed by a purplish yellow band which was further purified by chromatography on 15% deactivated alumina (see earlier) to give (*R*)-(−)-acetate **13** (40% yield, 84% e.e. by NMR analysis).

3.10. Synthesis of 2-amino-1-ferrocenylethanol **7a**

A quantity of *rac*-**13** (200 mg, 0.71 mmol) was added to a suspension of $LiAlH_4$ (60 mg, 2.5 mmol) in dry diethyl ether (20 ml) under nitrogen and refluxed for 90 min. After cooling, ice water (20 ml) was added and the yellow precipitate collected and dried over P_2O_5. The crude precipitate was extracted with boiling toluene. After concentration and cooling, the product *rac*-**7a** was collected as golden plates (220 mg, 92%). Mp: 148–150°C. Analysis: calcd for $C_{12}H_{15}FeNO$: C, 58.8; H, 6.12; N, 5.71%; found C, 58.5; H, 6.20; N, 5.48%. ^{1}H NMR ($CDCl_3$): 2.73 (1H, dd, J=7.4, 12.8 Hz, CH_aH_b), 2.92 (1H, dd, J=4.1, 12.8 Hz, CH_aH_b), 4.17 (5H, s, Cp′), 4.14 (3H, m, Cp), 4.22 (1H, m, Cp), 4.29 (1H, dd, CH).

$LiAlH_4$ reduction of *rac*-**12** provides *rac*-**7a** in similar yield. Reduction of (*R*)-(+)-**13** or (*S*)-**12** provides (*R*)-(−)-**7a** ($[\alpha]_D^{25}$ −14.7 (c 0.09, CH_3CN)) or (*S*)-(+)-**7a**, respectively, without loss of optical purity, established using Pirkle's alcohol after conversion to **7b**.

3.11. Synthesis of 2-dimethylamino-1-ferrocenylethanol 7b

To a solution of *rac*-**7a** (500 mg, 2.04 mmol) in MeOH (15 ml) was added HCHO (0.8 ml of 37% solution) followed by a suspension of $ZnCl_2$ (144 mg, 1.02 mmol) and $NaBH_3CN$ (133 mg, 2.04 mmol) in MeOH (15 ml). After stirring for 7 h at room temperature, 1 M NaOH (30 ml) was added and MeOH removed by evaporation under reduced pressure. Extraction with ethyl acetate, drying over $MgSO_4$ and removal of solvent gave a residue which was purified by chromatography on 15% deactivated alumina (1:9, methanol:ethyl acetate) to give *rac*-**7b** as a brown oil (280 mg, 59%) which was crystallised from petroleum ether (60–80). Mp: 56–58°C. Analysis: calcd for $C_{14}H_{19}FeNO$: C, 61.5; H, 6.96; N, 5.13%; found C, 61.6; H, 7.23; N, 5.18%. ^{1}H NMR (C_6D_6): 1.96 (6H, s, NMe_2), 2.13 (1H, dd, J=3.2, 12.0 Hz, CH_aH_b), 2.37 (1H, dd, J=11.1, 12.0 Hz, CH_aH_b), 4.19 (5H, s, Cp′), 4.00 (2H, m, Cp), 4.07, 4.42 (each 1H, m, Cp), 4.47 (1H, dd, CH). ^{13}C NMR ($CDCl_3$): 45.5 (NMe_2), 65.8, 66.1, 66.3, 66.4, 67.7, 67.8 (Cp_{2-5}, CH, CH_2), 68.5 (Cp′), 89.7 (Cp_1). Reaction of (*R*)-(+)-**7a** in the same way provides (*R*)-(+)-**7b** ($[\alpha]_D^{25}$ +42.1 (c 0.3, CH_3CN)). Optical purity may be determined by the resolution of the ^{1}H Cp′ resonance in the presence of (*R*)-(9-anthryl)-2,2,2-trifluoroethanol (Pirkle's alcohol).

3.12. Synthesis of 1-ferrocenyl-2-piperidin-1-ylethanol 7c

To *rac*-**7a** (100 mg, 0.40 mmol) in dry toluene (20 ml) were added *i*-Pr_2NH (0.16 ml, 0.9 mmol) and 1,5-dibromopentane (0.06 ml, 0.40 mmol). The reaction mixture was refluxed gently until TLC indicated disappearance of starting material. After cooling and evaporation of solvent, the residue was purified by chromatotron (1:1, ethyl acetate:petroleum ether) to give **7c** as a brown solid, recrystallised from petroleum ether (60–80) (80 mg, 63%). Mp: 98–99°C. Analysis: calcd for $C_{17}H_{23}FeNO$: C, 65.1; H, 7.35; N, 4.47%; found C, 65.1; H, 7.11; N, 4.41%. ^{1}H NMR (C_6D_6): 1.22 (2H, m, $NCH_cH_dCH_2CH_2$), 1.33 (4H, m, $NCH_cH_dCH_2CH_2$), 2.06 (2H, m, $NCH_cH_dCH_2CH_2$), 2.36 (4H, m, $NCH_cH_dCH_2CH_2$, CH_aH_b), 4.20 (5H, s, Cp′), 4.03 (2H, m, Cp), 4.11, 4.45 (each 1H, m, Cp), 4.52 (1H, dd, J=4.2, 9.6 Hz, CH). ^{13}C NMR ($CDCl_3$): 25.6, 27.5, 55.9 (piperidinyl), 66.3, 67.0, 67.4, 67.8, 68.9, 69.1 (Cp_{2-5}, CH, CH_2), 69.1 (Cp′), 91.0 (Cp_1).

Reaction of (*R*)-(+)-**7a** in the same way provides (*R*)-(+)-**7c**. Optical purity may be determined by resolution of the ^{1}H Cp′ NMR resonance in the presence of Pirkle's alcohol. Some loss of optical purity is evident during reaction. (+)-**7a** of 85% e.e. is converted into crude (+)-**7c** of 60% e.e. which may be enriched to 75% e.e. on recrystallisation. $[\alpha]_D^{25}$ +42.1 (c 0.1, CH_3CN).

3.13. Standard procedure for alkylation of benzaldehyde with $ZnEt_2$

$ZnEt_2$ (1.02 mmol, 927 μl of a 1.1 M solution in toluene) was added under argon at room temperature to a degassed solution of benzaldehyde (0.51 mmol, 52 μl) and catalyst (0.025 mmol) in dry toluene (1.3 ml). Progress of the reaction was monitored by gas chromatography. On completion, the reaction was quenched by addition of saturated NH_4Cl solution, followed by extraction with diethyl ether, drying over Na_2SO_4 and removal of solvent. The enantiomeric excess of the (*S*)-(−)-1-phenyl-1-propanol was determined by acetylation or derivatisation to the methoxy(trifluoromethyl)phenylacetyl ester followed by gas chromatographic analysis on chiral (Chiraldex γ-DA) or achiral (HP-5) columns, respectively.

3.14. Synthesis of ferrocenyl[methyl(1-phenylethyl)amino]acetonitrile **17a,b**

3.14.1. From ferrocene carboxaldehyde

To a stirred solution of $NaHSO_3$ (240 mg, 2.3 mmol) in water (15 ml) was added a solution of ferrocene carboxaldehyde (500 mg, 2.34 mmol) in methanol (12.5 ml). The resulting brown slurry was cooled to 0°C and a solution of (*S*)-(−)-HN(Me)CHMePh[28] (0.49 ml, 3.28 mmol) in methanol (5 ml) was added dropwise, followed by a solution of NaCN (120 mg, 2.34 mmol) in water (10 ml) and diethyl ether (7.5 ml). After separation, the organic layer was extracted with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated to give a brown oil containing diastereoisomers **17a,b** in a 1:4.2 ratio. Crystallisation from petroleum ether (60–80) provided the pure minor diastereoisomer **17a** as yellow needles (130 mg, 16%). Mp: 129–131°C. Analysis: calcd for $C_{21}H_{22}FeN_2$: C, 70.4; H, 6.14; N, 7.82%; found C, 70.6; H, 6.13; N, 7.67%. ^{1}H NMR (C_6D_6): 1.34 (3H, d, J=6.9 Hz, CH*Me*Ph), 2.08 (3H, s, NMe), 3.55 (1H, q, *CH*MePh), 3.88, 4.05, 4.36 (2H, 1H, 1H, m, Cp), 4.01 (5H, s, Cp′), 4.87 (1H, s, *CH*N(Me)CH(Me)Ph), 7.0–7.4 (5H, m, Ph). ^{13}C NMR ($CDCl_3$): 19.3 (CH*Me*), 35.2 (NMe), 53.8 (N*CH*(Me)Ph), 61.8 (*CH*CN), 68.3, 68.8, 69.0, 69.2 (Cp_{2-5}), 69.3 (Cp′), 82.0 (Cp_1), 116.9 (CN), 127.3, 127.4, 127.5, 144.0 (Ph). $[\alpha]_D^{20}$ −85.2 (c 0.2, CH_3CN). The residue was purified to remove traces of aldehyde by chromatography on 15% deactivated alumina (1:4, ethyl acetate:petroleum ether (40–60)) to give a 7.9:1 enriched mixture of the major diastereoisomer **17b** (180 mg, 22%) as a brown oil. ^{1}H NMR ($CDCl_3$): 1.36 (3H, d, J=6.9 Hz, CH*Me*Ph), 2.26 (3H, s, NMe), 4.55 (1H, q, *CH*MePh), 4.07, 4.13, 4.16, 4.37 (each 1H, m, Cp), 4.02 (5H, s, Cp′), 4.50 (1H, s, C*H*N(Me)CH(Me)Ph), 7.2–7.4 (5H, m, Ph). Ferrocenyl(1-phenylethyl)aminoacetonitrile was similarly prepared from ferrocene carboxaldehyde and (*S*)-(−)-1-phenylethylamine as a 1:2.8 mixture of **18a,b** which would not crystallise. Collection of the front-running part of the single yellow band obtained on chromatography (15% deactivated alumina, 1:9, ethyl acetate:petroleum ether (40–60)) gave a pure sample of the major diastereoisomer **18b** as a yellow oil. The configuration of **18b** is assigned as shown by analogy with the determined configuration of **17b**. Mass spectrum: calcd for $C_{19}H_{19}FeN$ (M^+–HCN): 317.2128; found 317.2120. ^{1}H NMR (C_6D_6): 1.05 (3H, d, J=6.3, CH(*Me*)Ph), 3.88, 4.05, 4.32 (2H, 1H, 1H, m, Cp), 3.96 (5H, s, Cp′), 4.06 (1H, s (br), C*H*NHCH(Me)Ph), 4.16, (1H, q, C*H*(Me)Ph), 7.05–7.40 (5H, m, Ph). $[\alpha]_D^{25}$ −9.5 (c 0.2, CH_3CN).

3.14.2. From **13**

To a stirred solution of *rac*-**13** (330 mg, 1.17 mmol) in dry methanol (7 ml) was added (−)-(*S*)-NH(Me)CH(Me)Ph (0.38 ml, 2.56 mmol) at room temperature. After stirring for 24 h, solvent was evaporated and the crude product chromatographed on 15% deactivated alumina (1:4, ethyl acetate:petroleum ether (40–60)) to give a mixture of **17a,b** as a brown oil in a 1:4.1 ratio by NMR (340 mg, 81%). Use of optically pure (+)-**13** provides **17a,b** in the same diastereoisomeric ratio.

Reaction of optically pure (+)-**13** with $HNMe_2$ under the same conditions provides racemic dimethylaminoferrocenylacetonitrile **16** in 81% yield. Mp: 86–88°C (lit.[25] 86–88°C). NMR (C_6D_6): 2.03 (6H, s, NMe_2), 3.85, 3.87, 3.98, 4.32 (each 1H, m, Cp), 4.02 (5H, s, Cp′), 4.27 (1H, s, CH).

3.15. Synthesis of 2-ferrocenyl-2-[methyl(1-phenylethyl)amino]ethane **23a,b**

MgMeI (0.11 ml of a 3 M solution in diethyl ether) was added to a solution of **17a** (20 mg, 0.21 mmol) in diethyl ether (10 ml) at 0°C with stirring. After warming to room temperature and stirring for 1 h, the solution was hydrolysed with saturated NH_4Cl (10 ml) and the aqueous phase extracted with diethyl ether. The combined organic extracts were dried over $MgSO_4$ and evaporated to give an inseparable

mixture of **23a,b** as a yellow oil (20 mg, 27%) in a 1:1 ratio. Mass spectrum: calcd for $C_{21}H_{25}FeN$: 347.2882; found 347.2792. ^{1}H NMR ($CDCl_3$): 1.15–1.24 (6H, m, CH(*Me*)N(Me)CH(*Me*)Ph), 1.89, 1.96 (each 3H, s, NMe), 3.47, 3.54 (each 1H, q, J=6.9 Hz, CH(Me)N(Me)*CH*(Me)Ph), 3.76, 3.83 (each 1H, q, J=6.8 Hz, *CH*(Me)N(Me)CH(Me)Ph), 4.03–4.20 (4H, m, Cp), 3.93, 3.99 (each 5H, s, Cp′), 7.20–7.35 (10H, m, Ph).

*3.16. Synthesis of 4-methoxyphenyl(1-phenylethylamino)acetonitrile **19** and 3,3-dimethyl-2-(1-phenylethylamino)butyronitrile **20***

Reaction of [(*S*)-(−)-NH_3CH(Me)Ph]Cl with *p*-anisaldehyde according to the literature[24b] provided [4-$MeOC_6H_4$CH(CN)NH_2CH(Me)Ph]Cl as a diastereoisomer mixture. A single fractional recrystallisation from CH_2Cl_2:diethyl ether gave the optically pure (*S,S*)-diastereoisomer in 46% yield. ^{1}H NMR ($CDCl_3$): 1.40 (3H, d, J=6.8 Hz, CH(*Me*)Ph), 3.67 (3H, s, MeO), 4.33 (1H, q, *CH*(Me)Ph), 4.36 (1H, s, *CH*CN), 6.8–7.7 (9H, m, Ph). Diastereomerically pure **19b** was generated by neutralisation of the above with $NaHCO_3$ solution, followed by extraction with CH_2Cl_2. ^{1}H NMR ($CDCl_3$): 1.38 (3H, d, J=7.2 Hz, CH(*Me*)Ph), 3.78 (3H, s, MeO), 4.19 (1H, q, *CH*(Me)Ph), 4.30 (1H, s, *CH*CN), 6.85–7.50 (9H, m, Ph). ^{13}C NMR ($CDCl_3$): 24.8 (CH(*Me*)Ph), 51.8, 55.3, 56.7 (MeO, N*CH*(Me)Ph*C*HCN), 119.1 (CN), 114.2, 126.9, 127.3, 127.8, 128.4, 128.8, 143.1, 159.9 (Ph).

A 1:3.8 diastereoisomeric mixture of **20a,b** was prepared according to the literature.[24a] Collection of the front-running part of a broad band from the chromatotron (1:4, ethyl acetate:petroleum ether) provided a 1:1.2 mixture of **20a,b** enriched in the minor (*R,S*)-diastereoisomer which was suitable for epimerisation studies. NMR ($CDCl_3$): **20a** 0.92 (9H, s, *t*-Bu), 1.28 (3H, d, J=6.8 Hz, CH(*Me*)Ph), 3.96 (1H, q, *CH*(Me)Ph), 7.1–7.3 (5H, m, Ph); **20b** 0.97 (9H, s, *t*-Bu), 1.34 (3H, d, J=6.8 Hz, CH(*Me*)Ph), 4.03 (1H, q, *CH*(Me)Ph), 3.97 (1H, s, *CH*CN), 7.1–7.3 (5H, m, Ph).

3.17. Epimerisation studies of aminonitriles

A solution of the aminonitrile in either dry, N_2 degassed MeOH or C_6D_6 was heated in a constant temperature bath (±0.5°C). For studies in MeOH, samples were periodically withdrawn and the solvent removed immediately at 0°C; NMR spectra of the residues were run in $CDCl_3$. Spectra of samples in C_6D_6 were run directly. Values of k_1+k_{-1} were obtained from plots of $\ln(P_\infty - P_t)/(P_t+1)$ versus time, where P is the diastereoisomer ratio obtained by integration using *CH*CN resonances at 4.85, 4.49 ppm for **17a,b**, NCH(*Me*)Ph resonances at 1.31, 1.39 ppm for **18a,b**, *CH*CN resonances at 4.40, 4.29 ppm for **19a,b** and *t*-Bu resonances at 0.92, 0.97 ppm for **20a,b**. All plots gave correlation coefficients of >0.98.

The imines **21**[29] and **22**[30] were identified spectroscopically in situ. **21** (C_6D_6): 1.52 (3H, d, CH*Me*, J=6.8 Hz), 4.25 (1H, q, *CH*Me), 3.92 (5H, s, Cp′), 4.05, 4.59, 4.66 (4H, m, Cp), 7.96 (1H, s, CHN), 7.1–7.5 (5H, m, Ph); **22** (C_6D_6): 1.56 (3H, d, CH*Me*, J=6.9 Hz), 4.33 (1H, q, *CH*Me), 6.7–7.7 (9H, m, Ph), 8.05 (1H, s, CHN).

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