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# Salicylaldehyde Schiff bases derived from 2-ferrocenyl-2-amino alcohols. Part 1: New chiral ligands for the titanium-catalyzed enantioselective cyanation of aldehydes

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We dedicate this paper to the memory of Professor Marcial Moreno-Mañas

**Abstract**—The condensation of a set of diversely substituted (*S*)-2-amino-2-ferrocenyl ethanol derivatives **1a**–**e** with the salicylaldehydes **5A**–**C** resulted in the generation of a small library of new chiral Schiff base-ligands, whose titanium isopropoxide complexes have been tested as catalysts in the asymmetric addition of trimethylsilyl cyanide to aldehydes. The enantioselectivity of the reaction is strongly influenced (a) by the substitution pattern of the 2-amino-2-ferrocenyl ethanol moiety, and (b) by the nature of the $C_{3'}$ substituent in the salicylaldehyde. Computational modelling of the intermediate transition state complexes (based on the Schiff base, benzaldehyde, isopropoxide and cyanide bonded to titanium) show that the experimental results can be accommodated by a careful analysis of the steric interactions between the 2-aminoethanol and salicylaldehyde moieties, and the metal-coordinated aldehyde.


## 1. Introduction

Chiral Schiff bases derived from salicylaldehydes and from 2-amino alcohols constitute a class of 'privileged' ligands[1] whose metal complexes are enantioselective catalysts for important asymmetric processes, such as enantioselective Michael reactions,[2] silylcyanation of aldehydes,[3] addition of diketene[4] and of diethylzinc[5] to aldehydes, oxidation of sulfides,[6] arylation of epoxides,[7] hetero-Diels–Alder and hetero-ene reactions[8] and cyclopropanation of olefins.[9] Although the modular nature of these ligands offers several possibilities for structural modification (Fig. 1), structure/enantioselectivity studies[9d,10] aiming to optimize them have been mainly focused on the substituents of the salicylaldehyde moiety, and a relatively limited set of 2-amino alcohols, most of them derived from α-amino acids, has been used for their preparation (Fig. 2). In particular, as can be seen in Figure 2, the effect of the simultaneous presence of two substituents at $C_2$ does not appear to have been investigated.

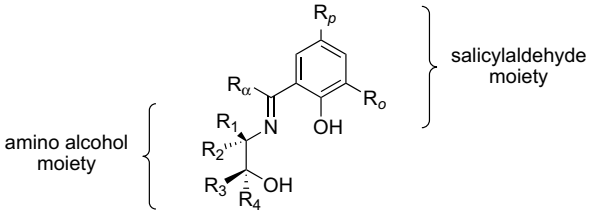


**Figure 1.** General structure of chiral salicylaldehyde Schiff base-ligands.

On the other hand, work from our laboratory resulted in the development of a general, stereoselective and enantiodivergent synthesis of 2-amino-2-ferrocenylalkanols.[11] Chiral auxiliaries and ligands derived from this new type of metallocene amino alcohols have been shown to be useful stereochemical controllers in a variety of carbon–carbon and carbon–heteroatom bond-forming processes.[12,13] Moreover, we have recently demonstrated that the properties of these chiral auxiliaries or ligands can be efficiently modulated by the introduction of substituents in the 2-amino-2-ferrocenylethanol moiety that dictate the conformational preferences of the ferrocenyl group.[13]

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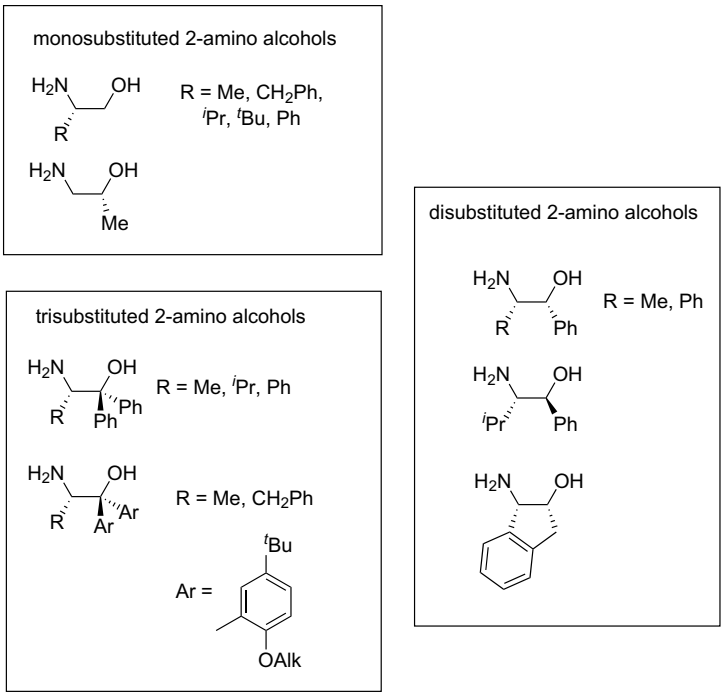



**Figure 2.** Chiral 2-amino alcohols used in the construction of salicylaldehyde Schiff base-ligands.

In light of these precedents, we decided to prepare a collection of salicylaldehyde Schiff base-ligands derived from 2-amino-2-ferrocenylethanols with different degrees of substitution both at the $C_1$ and the $C_2$ positions, in order to investigate the catalytic efficiency of their titanium alkoxide complexes in enantioselective additions to aldehydes. We herein report the first results of this study, showing that these novel chiral complexes are able to catalyze the enantioselective cyanation of aldehydes. The application of these complexes to the asymmetric addition of diketene to aldehydes is discussed in the following paper in this issue.

## 2. Results and discussion

### 2.1. Synthesis of salicylaldehyde Schiff bases derived from 2-amino-2-ferrocenylethanols

At the outset of our studies, we selected the ferrocene derivatives **1a**–**1d**, differing in the number and position of the methyl substituents, and the phenyl-substituted compound **1e**, as the chiral amino alcohols to be incorporated into the salicylaldehyde Schiff base-ligands (Fig. 3).

The preparation of amino alcohols **1a** (99:1 er),[11a] **1c** (96:4 er),[14] and **1d** (97:3 er)[13] has been reported elsewhere, meaning that we shall only describe in some detail our approaches to **1b** and to **1e**. The starting product for the synthesis of **1b** (Scheme 1) is (1*S*,2*R*)-1-ferrocenylpropane-1,2-diol **2**, which can be obtained with a 98:2 er by the Sharpless asymmetric dihydroxylation of (*E*)-1-prop-1-enylferrocene (*E*)-(**3**).[15] Although this compound has been prepared in high diastereomeric purity by means of the Schlosser–Christmann modification of the Wittig reaction,[16] we found that it was much more convenient to use the ca. 4:1 (*E*)/(*Z*) mixture resulting from the addition of ethylmagnesium bromide to ferrocenecarbaldehyde and subsequent alumina-promoted dehydration of the intermediate alcohol. As foreseen,[17] the asymmetric dihydroxylation of this mixture using $(DHQD)_2PYR$ as the chiral ligand afforded, after chromatographic purification, the

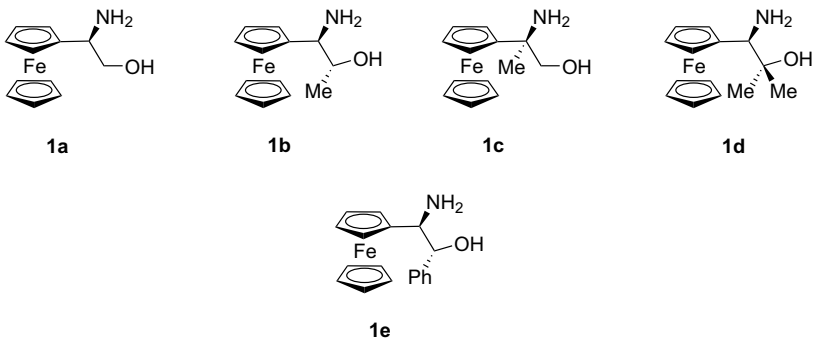
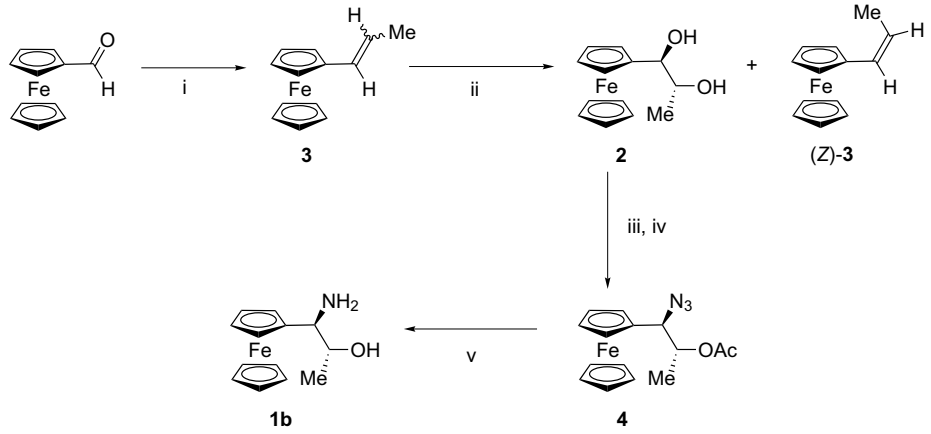


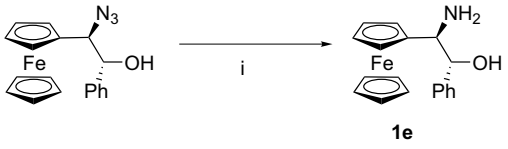

**Figure 3.** Chiral 2-amino-2-ferrocenylethanol derivatives used in this work.




**Scheme 1.** Reagents and conditions: (i) EtMgBr (1.5 equiv), THF, 0 °C to rt, 30 min; $Al_2O_3$, toluene, Dean–Stark, reflux, 5 h, 85% (ca. 4:1 (*E*)/(*Z*) mixture). (ii) $K_3[Fe(CN)_6]$ (3 equiv), $K_2CO_3$ (3 equiv), $(DHQD)_2PYR$ (0.05 equiv), $K_2OsO_2(OH)_4$ (0.05 equiv), 1:1 acetonitrile/water, rt, 30 min, 81% **2** (98:2 er), 19% (*Z*)-**3**. (iii) $Ac_2O$ (25 equiv), pyridine, rt, 12 h, 100%. (iv) $NaN_3$ (10.8 equiv), 1:3 methanol/water, 60 °C, 4.5 h, 70%. (v) $LiAlH_4$ (3.0 equiv), THF, 0 °C to rt, 40 min, 100%.

desired diol **2** in high diastereo- and enantiomeric purity, together with the unreacted (*Z*)-isomer of **3**. After conversion to its diacetate, **2** was treated with sodium azide in aqueous methanol, to give, in 70% yield, the expected (1*S*,2*R*)-azidoacetate **4** with complete regioselectivity and without any loss of stereochemical purity.[18] Finally, reduction of **4** with excess lithium aluminium hydride produced the amino alcohol **1b** in essentially quantitative yield.

On the other hand, enantiopure (99.5:0.5 er) **1e** was readily accessed via the catalytic hydrogenation of (1*R*,2*S*)-2-azido-2-ferrocenyl-1-phenylethanol[11b] (Scheme 2).




**Scheme 2.** Reagents and conditions: (i) $PtO_2$ (cat.), $H_2$ (balloon), EtOH, rt, 12 h, 100%.

The condensation of amino alcohols **1a**–**d** with salicylaldehyde derivatives **5A**–**C** (Fig. 4 and Table 1) in absolute ethanol led to the stable chiral Schiff bases **6aA**–**cC** in good yields. In the case of **1e**, the reaction with **5B** proceeded in a quantitative yield, according to TLC. However, the resulting Schiff base **6eB** was extremely sensitive and decomposed upon attempted isolation. For comparison, Oguni's ligand **7**[3b] was prepared in a similar way from (*R*)-phenylglycinol and 3-*tert*-butyl-2-hydroxybenzaldehyde **5B**.

Since reduced Schiff base-ligands have recently been shown to be active in catalytic asymmetric Strecker reactions[19] and in the enantioselective cyanosilylation of aldehydes,[20] compounds **6dA**, **6aB** and **6bB** were treated with sodium borohydride in the presence of cerium(III) chloride heptahydrate[21] (Luche's reagent)[22] to afford the corresponding *N*-salicyl-β-amino alcohols **8dA**, **8aB** and **8bB** (Scheme 3).

## 2.2. Asymmetric catalytic trimethylsilylcyanation of aldehydes

The enantioselective cyanation of carbonyl and imino groups ranks amongst the most thoroughly studied processes in asymmetric catalysis.[23] Due to the synthetic importance of optically active α-cyanohydrins and α-

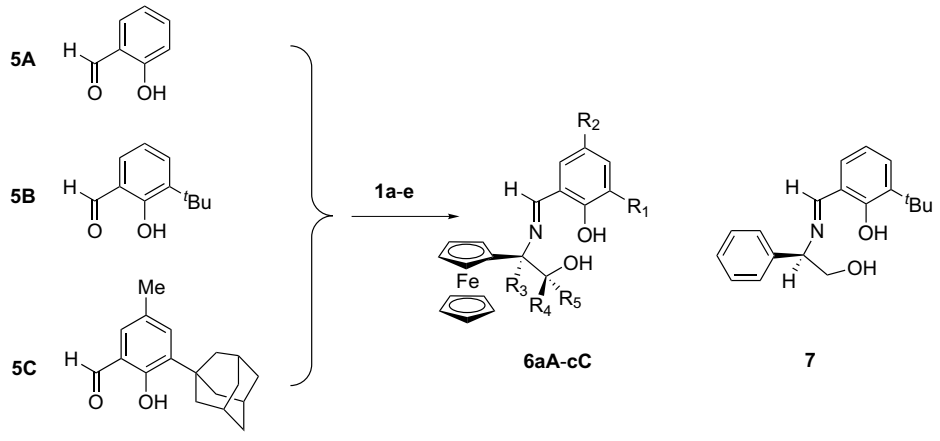
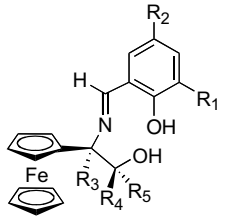



**Figure 4.** Salicylaldehyde Schiff bases prepared in this work.

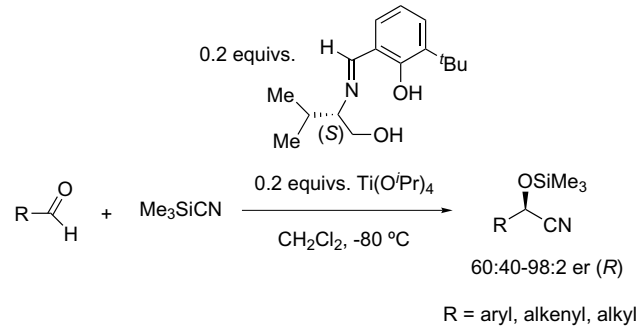
**Table 1.** Synthesis of Schiff base-ligands from ferrocenyl amino alcohols



| $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | Ligand | Yield[a] (%) |
|---|---|---|---|---|---|---|
| H | H | H | H | H | **6aA** | 77 |
| H | H | H | H | Me | **6bA** | 92 |
| H | H | H | Me | Me | **6dA** | 90 |
| $^t$Bu | H | H | H | H | **6aB** | 89 |
| $^t$Bu | H | H | H | Me | **6bB** | 99 |
| $^t$Bu | H | Me | H | H | **6cB** | 75 |
| $^t$Bu | H | H | Me | Me | **6dB** | 93 |
| 1-Adamantyl | Me | H | H | H | **6aC** | 63 |
| 1-Adamantyl | Me | H | H | Me | **6bC** | 88 |
| 1-Adamantyl | Me | Me | H | H | **6cC** | 87 |

[a] Yield of product isolated after chromatographic purification. Reaction conditions: 1.0 mmol amino alcohol **1a–d**, 0.98 mmol salicylaldehyde **5A–C**, 5 ml absolute EtOH, rt (**5A**,**5B**) or 50 °C (**5C**).

aminonitriles, research in this topic continues unabated.[24] One of the earliest non-enzymatic methods for practical enantioselective cyanohydrin synthesis is due to Oguni, who in 1991[3a] reported that chiral Schiff base complexes of titanium alkoxides were effective catalysts for the enantioselective addition of trimethylsilyl cyanide to aldehydes. The screening of a variety of Schiff bases[3b,25] revealed that the best ligand was that derived from 3-*tert*-butyl-2-hydroxybenzaldehyde **5B** and (*S*)-valinol. In the presence of 20 mol % of the titanium di(isopropoxide) complex derived from this ligand, trimethylsilyl cyanide added (at −80 °C in dichloromethane solution) to a variety of aldehydes, affording the (*R*)-cyanohydrins in good yields and, in several instances, with excellent enantiomeric purities (Scheme 4). When the Schiff base derived from 2-hydroxybenzaldehyde **5A** and (*S*)-valinol, lacking the 3-*tert*-butyl substituent, was used as a ligand, the (*S*)-configured cyanohydrin of benzaldehyde was isolated in only 61:39 er, in contrast to the 93:7 er obtained with the ligand derived from **5B**. The stereochemical outcome of the reaction [highly predominant addition to the *si* face of the aldehyde with (*S*)-configured Schiff bases having bulky substituents



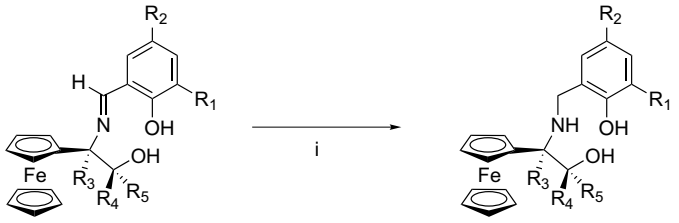

**Scheme 4.** Enantioselective trimethylsilylcyanation of aldehydes catalyzed by a chiral Schiff base–titanium isopropoxide complex, according to Oguni (Refs. 3a,b).

at the 3-position of the salicylaldehyde moiety] was rationalized in terms of a hexacoordinated, aldehyde-bound titanium complex.[3b]

Subsequently, Yaozhong et al.[26] described the use of Schiff bases derived from 2-amino-1,2-diphenylethanol in the same process, and, recently, Feng[20] has found that the amino alcohols obtained by the reduction of these Schiff bases also lead to efficient catalytic systems for enantioselective aldehyde cyanation. On the other hand, Somanathan and Walsh[10] have studied the effect of steric hindrance in the titanium alkoxide complexes of Schiff bases derived from *cis*-1,2-aminoindanol, showing that the presence of bulky substituents at the 3-position of the salicylaldehyde moiety, necessary to achieve good enantioselectivities, inhibits the formation of catalytically inactive $L_2Ti$ species.

We selected the asymmetric addition of trimethylsilylcyanide to benzaldehyde as the benchmark reaction to test the relative catalytic efficiency of our ferrocenyl imino alcohols (Table 2).

Initially, we proceeded to optimize the reaction conditions with the phenylglycinol-derived Schiff base **7** (entry 1 of Table 3). To our satisfaction, we found that by performing the process at −60 °C, the addition was complete after 40 h, affording the benzaldehyde cyanohydrin (*S*)-**9**[27] in 80% yield and in 75:25 er (determined by chiral GC analysis of the corresponding acetate). It is worth noting that with the same ligand but at −80 °C, Oguni[3b,25] had reported a 40% yield (with a 70:30 er) for this compound. Under these

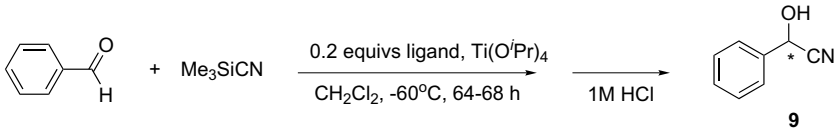



**6dA**, $R_1$,$R_2$,$R_3$=H, $R_4$,$R_5$=Me
**6aB**, $R_1$=$^t$Bu, $R_2$,$R_3$,$R_4$,$R_5$=H
**6bB**, $R_1$=$^t$Bu, $R_2$,$R_3$,$R_4$=H, $R_5$=Me

**8dA**, $R_1$,$R_2$,$R_3$=H, $R_4$,$R_5$=Me
**8aB**, $R_1$=$^t$Bu, $R_2$,$R_3$,$R_4$,$R_5$=H
**8bB**, $R_1$=$^t$Bu, $R_2$,$R_3$,$R_4$=H, $R_5$=Me

**Scheme 3.** Reagents and conditions: (i) $NaBH_4$ (2 equiv), $CeCl_3{\cdot}7H_2O$ (1 equiv), methanol, −78 °C to rt, 75–90 min; 77% (**8dA**), 48% (**8aB**), 73% (**8bB**).

**Table 2.** Asymmetric addition of trimethylsilyl cyanide to benzaldehyde catalyzed by chiral Schiff base–titanium isopropoxide complexes

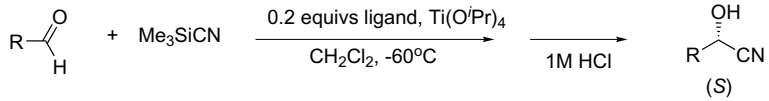



**9**

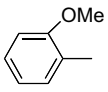
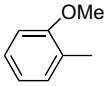
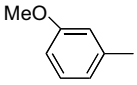
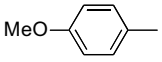
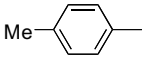
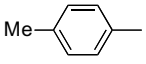
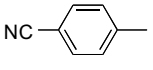
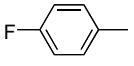
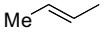
| Entry | Ligand | Yield[a] (%) | Er[b] | Configuration[c] |
|---|---|---|---|---|
| 1 | **7** | 80[d] | 75:25 | (*S*) |
| 2 | **6dA** | 85 | 59:41 | (*S*) |
| 3 | **6aB** | 83 | 85:15 | (*S*) |
| 4 | **6bB** | 72 | 80:20 | (*S*) |
| 5 | **6cB** | 91 | 93:7 | (*S*) |
| 6 | **6dB** | 85[e] | 46:54 | (*R*) |
| 7 | **6eB**[f] | 27 | 62:38 | (*S*) |
| 8 | **6aC** | 32 | 75:25 | (*S*) |
| 9 | **6cC** | 65 | 76:24 | (*S*) |
| 10 | **8aB** | 60 | 58:42 | (*S*) |

[a] Yield of isolated product **10** after chromatographic purification.
[b] By GC (β-DEX 120 column) of the corresponding acetate.
[c] By comparison of the sign of specific rotation values of the acetate with that in the literature.[27]
[d] 40 h of stirring.
[e] 4 days of stirring.
[f] Generated in situ by condensation of **5B** with **1e** before the addition of titanium tetra(isopropoxide).

**Table 3.** Enantioselective addition of trimethylsilyl cyanide to aldehydes catalyzed by Schiff base (**6aB**, **6bB**)–titanium isopropoxide complexes




(*S*)

| Entry | R | Ligand | Time (h) | Yield[a] (%) | Er[b] | Configuration[c] |
|---|---|---|---|---|---|---|
| 1 |  | **6aB** | 70 | 60 | 80:20 | (*S*) |
| 2 |  | **6bB** | 62 | 85 | 77:23 | (*S*) |
| 3 |  | **6aB** | 70 | 85 | 71:29 | (*S*) |
| 4 |  | **6aB** | 63 | 47 | 62:38 | (*S*) |
| 5 |  | **6aB** | 64 | 69 | 82:18 | (*S*) |
| 6 |  | **6bB** | 62 | 55 | 79:21 | (*S*) |
| 7 |  | **6aB** | 64 | 77 | 57:43 | (*S*) |
| 8 |  | **6aB** | 64 | 70 | 73:27 | (*S*) |
| 9 |  | **6aB** | 41 | 76 | 72:28 | (*S*) |
| 10 |  | **6aB** | 41 | 63 | 81:19 | (*S*) |

[a] Yield of isolated product after chromatographic purification.
[b] By $^{19}F$ NMR analysis of their MTPA esters.
[c] By comparison of the sign of optical rotation values with those in the literature.[3b,29,30]

conditions, preformed dichloromethane solutions of the titanium di(isopropoxide) complexes of our ferrocene-derived Schiff bases were stirred at −60 °C with benzaldehyde (5 M equiv) and cyanotrimethylsilane (10 M equiv) for 64–68 h. After acidic hydrolysis, benzaldehyde cyanohydrin **9** was isolated in variable yields and enantiomeric purities. The formation of the titanium complexes was readily evidenced in each case by a colour change of the solution from yellow to red upon addition of titanium tetra(isopropoxide) to the Schiff base solution. Moreover, when a deuterated chloroform solution of **6bA** was treated with equimolar amounts of titanium tetra(isopropoxide) (final concentration 0.1 M), both the $^{1}H$ and the $^{13}C$ NMR spectra of the resulting mixture indicated that a 1:1 ligand–titanium complex was the major species present in solution (together with isopropyl alcohol).[3b,28] As expected,[3,10,25] ligands **6aA**, **6bA** and **6dA**, derived from the unsubstituted salicylaldehyde **5A**, catalyzed the reaction with very low enantioselectivity. The best results were obtained in the case of **6dA** that gave (*S*)-**9** in 85% yield and with a 59:41 er (entry 2). We next turned our attention to the 3-*tert*-butyl-substituted imines **6aB–eB**. The complex derived from **6aB** (entry 3) afforded (*S*)-**9** with an 86:14 er. The enantiomeric purity of the product was not improved by the presence of a methyl substituent at $C_1$ in the amino alcohol moiety (ligand **6bB**, entry 4). When positioned at $C_2$ (ligand **6cB**, entry 5), the methyl group did not change the enantiofacial selectivity of the addition, and a substantial increase in both the yield and in the enantioselectivity of the reaction was observed, since (*S*)-**9** was obtained in excellent yield (91%) and with a 93:7 er (97:3 er when taking into account the enantiomeric purity of **6cB**). The best conditions found by Oguni for benzaldehyde, using the **5B**-(*S*)-valinol Schiff base at −80 °C, afforded (*R*)-**9** in 67% yield and with a 93:7 er.[3] Schiff base **6cB** is, therefore, a very efficient ligand for the titanium-catalyzed asymmetric cyanation of benzaldehyde. The presence of a *gem*-dimethyl moiety (ligand **6dB**, entry 6) or of a phenyl substituent (ligand **6eB**, entry 7) at $C_1$ diminished both the rate and enantioselectivity of the reaction. In the case of **6dB**, the major enantiomer (54:46 er) of the cyanohydrin product **9** had an (*R*)-configuration. In accordance with the findings of Somanathan and Walsh,[10b] replacement of *tert*-butyl by adamantyl in the salicylaldehyde moiety resulted in the generation of less efficient catalysts (ligand **6aC**, entry 8; ligand **6cC**, entry 9), as it was the case with the reduced Schiff base-ligand **8aB** (entry 10). In summary, salicylaldehyde Schiff base-ligands **6** derived from the (*S*)-2-amino-2-ferrocenyl ethanols **1a–e** are active catalysts in the asymmetric trimethylsilylcyanation of benzaldehyde, affording benzaldehyde cyanohydrin (*S*)-**9** with moderate to good enantioselectivity.

We also examined the catalytic performance of the titanium alkoxide complexes derived from Schiff bases **6aB** and **6bB** in the enantioselective addition of trimethylsilyl cyanide to a set of representative aromatic and α,β-unsaturated aldehydes. The results of this study are summarized in Table 3.

As shown in Table 3, most aldehydes were cyanated in good yields (60–85%), and with enantiomeric purities that were strongly dependent upon the structure of the substrate. As for the stereochemistry of the products, the absolute configuration of the cyanohydrins was in all instances (*S*), as determined by the comparison of the sign of the specific rotation values with those reported in the literature (see Experimental). In accordance to the findings of Oguni,[3b,25] the smallest enantioselectivity corresponded to the strongly electron-deficient 4-cyanobenzaldehyde (entry 7), while higher enantiomeric purities were recorded for *p*-tolualdehyde (entries 5 and 6) and for *p*-fluorobenzaldehyde (entry 8). Some interesting trends were observed in the silylcyanation of the *o*-, *m*- and *p*-isomers of anisaldehyde (entries 1–4). Both Oguni[3b,25] and Walsh[10b] had reported that in this case, the enantioselectivity of the reaction markedly decreased in the order $p > m > o$, and only a 60:40 er was obtained for *o*-anisaldehyde with Walsh's *cis*-1,2-aminoindanol-derived ligand.[10b] Remarkably enough, the opposite behaviour was observed with our (*S*)-2-amino-2-ferrocenylethanol-derived ligand **6aB** that afforded (*S*)-2-hydroxy-2-(2-methoxyphenyl)acetonitrile in 80:20 er.[31] On the other hand, and with the same ligand, the trimethylsilylcyanation of *trans*-crotonaldehyde (entry 9) and of methacrolein (entry 10) took place with 73:27 and with 80:20 er, respectively.

### 2.3. Mechanistic considerations. Molecular modelling of intermediate complexes

In 1993, Oguni[3b] proposed that the catalytic asymmetric cyanation of aldehydes was initiated by the coordination of the aldehyde to the initially formed, coordinatively unsaturated Schiff base–titanium di(isopropoxide) complex. The stereochemical outcome of the reaction was then explained by the attack of an external nucleophile (either trimethylsilyl or hydrogen cyanide) to the less hindered face of the aldehyde carbonyl (Fig. 5). In particular, this model successfully explained the crucial role played by

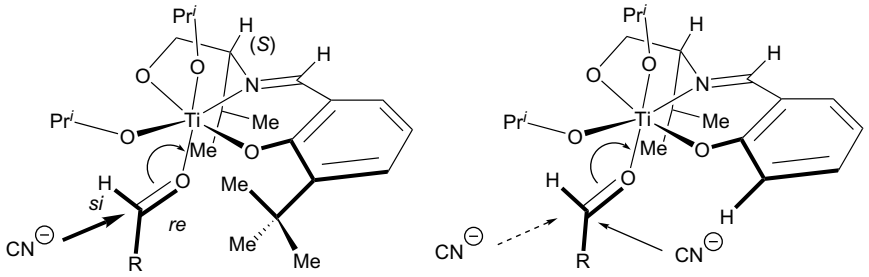



**Figure 5.** Transition states for the enantioselective titanium-catalyzed trimethylsilyl cyanide addition to aldehydes, according to Oguni (Ref. 3b).

the $C_{3'}$ *tert*-butyl substituent in Schiff bases derived from (*S*)-configured 2-amino alcohols and salicylaldehyde **5B** in the blocking of the *re* face of the aldehyde.

In order to see if Oguni's model could rationalize our experimental results, we modelled the Schiff base–titanium di(isopropoxide)–benzaldehyde complexes corresponding to ligands **6aB**, **6bB**, **6cB**, **6dB** and **6eB**, by means of the SYBYL molecular mechanics model[32] as implemented in the SPARTAN package of programs.[33] For each complex, four energetic minima were located, corresponding both to different coordination sites of the aldehyde (*syn* or *anti* to the ferrocenyl group) and to different orientations (IN or OUT)[13] of the latter. However, examination of the resulting models did not allow for the rationalization of experimental results. Thus (see Fig. 6), the minimum energy complexes corresponding to ligands **6cB** (Fig. 6A) and **6dB** (Fig. 6B) predict in every case the preferential attack of the cyanide by the *re* face of benzaldehyde, leading to (*S*)-**9**. The experimental result, however, as we have discussed in the previous section, is at complete variance with this prediction, since although **6cB** affords (*S*)-**9** in 93:7 er, **6dB** produces (*R*)-**9** with low enantioselectivity (compare entries 5 and 6 in Table 2).

We then next turned our attention to a second set of complexes, in which one of the isopropoxy groups was replaced with a cyanide one (Fig. 7). This type of complexes has recently been examined by Somanathan and Cole,[10c] building upon a previous proposal by Shibasaki.[34]

As before, the Schiff base–titanium(isopropoxide)–cyanide–benzaldehyde complexes corresponding to ligands **6aB**, **6bB**, **6cB**, **6dB** and **6eB** were modelled by means of the SYBYL molecular mechanics force field. In this case, eight energetic minima (corresponding to the *fac-mer*,[10c] *syn-anti* and IN–OUT possible arrangements of the ligands around the titanium) were located for each complex. We were pleased to find that these models allowed for a rationalization of the observed trends in enantioselectivity. As shown in Figure 8, the minimum energy complex for ligand **6cB** (Fig. 8A) correctly predicts the predominant formation

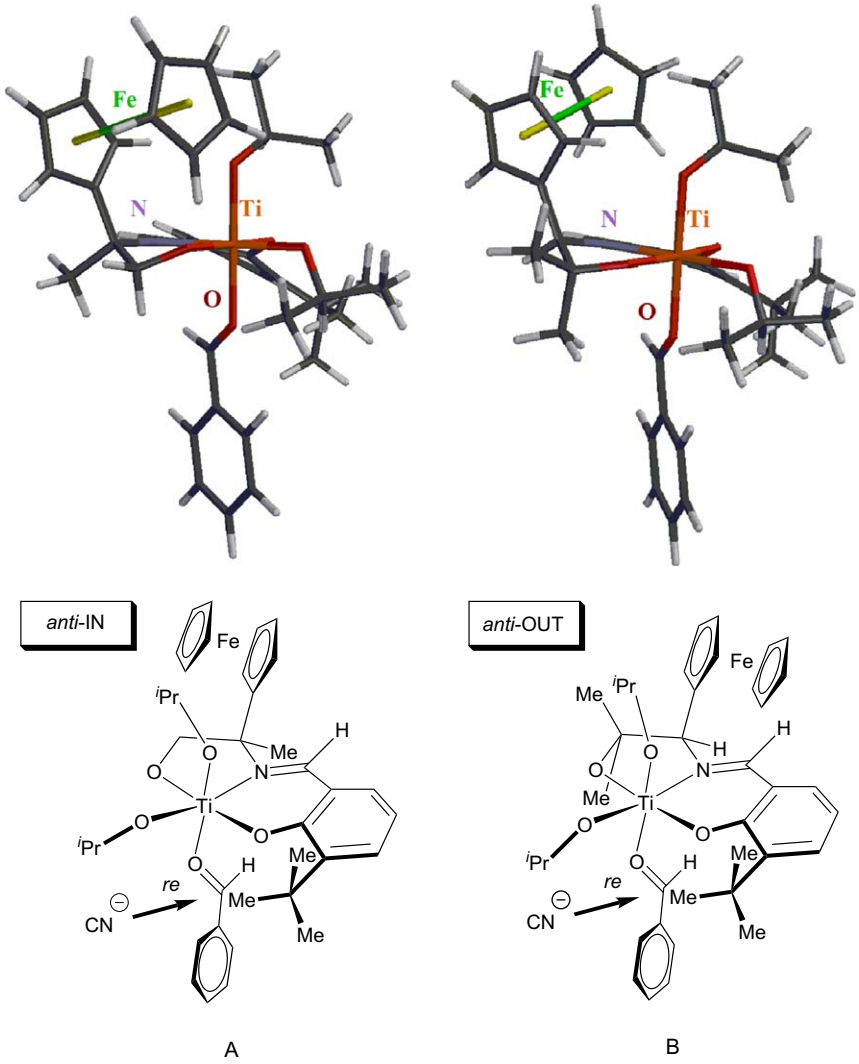



**Figure 6.** (A) Lowest energy transition state complex (SYBYL MM force field) for ligand **6cB**, according to Oguni's model. (B) Lowest energy transition state complex for ligand **6dB**.

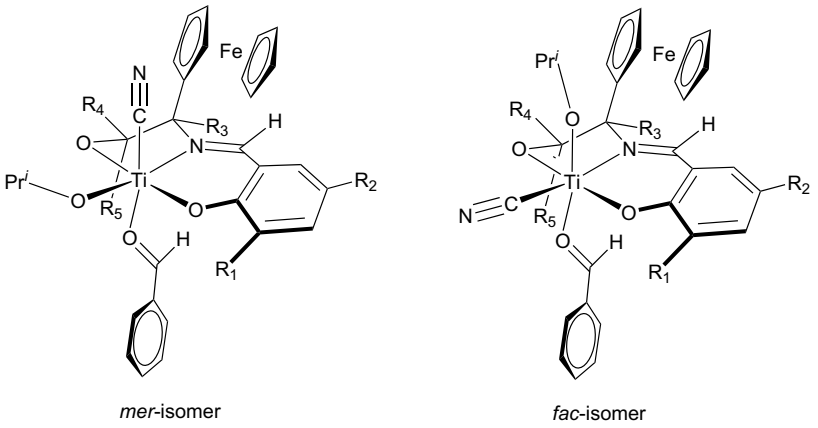



**Figure 7.** Octahedral titanium transition state complex (*mer* and *fac* isomers) in the trimethylsilylcyanation of benzaldehyde, according to Somanathan and Cole's model (Ref. 10c).

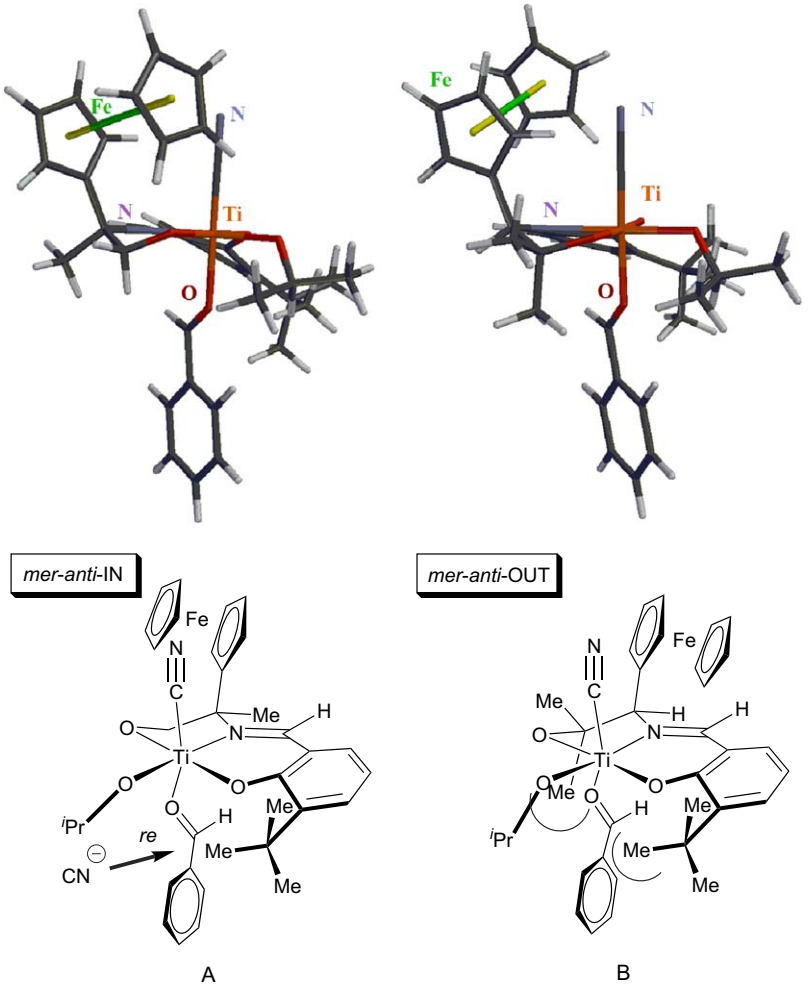



**Figure 8.** (A) Lowest energy transition state complex (SYBYL MM force field) for ligand **6cB**, according to Somanathan and Cole's model. (B) Lowest energy transition state complex for ligand **6dB**.

of cyanohydrin (*S*)-**9**; on the other hand, in the minimum energy complex for **6dB** (Fig. 8B), both the *re* and the *si* faces of the benzaldehyde carbonyl are appreciably blocked by substituents of the Schiff base-ligand (the $C_3$, *tert*-butyl and one of the $C_2$ methyls, respectively), in accordance with the low enantioselectivity obtained with this ligand. We therefore suggest that the cyanide-bound titanium complexes proposed by Somanathan and Cole provide a

better description of the stereochemical course of the asymmetric trimethylsilylcyanation of aldehydes than those forwarded initially by Oguni.

## 3. Conclusions

In conclusion, the incorporation of 2-amino-2-ferrocenylalkanols **1a–e** into salicylaldehyde Schiff bases gives rise to a new class of chiral ligands, whose titanium alkoxide complexes are able to promote the asymmetric addition of cyanotrimethylsilane to aldehydes. Both the enantioselectivity and stereochemical outcome of this process are controlled by the positioning of substituents in the 2-amino-2-ferrocenylethanol moiety. In particular, the titanium complex of Schiff base **6cB**, derived from (*S*)-2-amino-2-ferrocenyl-2-propanol **1c** and 3-*tert*-butyl-2-hydroxybenzaldehyde **5B**, catalyzes the formation of the benzaldehyde cyanohydrin (*S*)-**9** in high yield (91%) and enantioselectivity (93:7 er). On the other hand, ligand **6dB**, in which a *gem*-dimethyl group has been introduced in the (*S*)-2-amino-2-ferrocenylethanol moiety, affords the (*R*) enantiomer of **9** with low enantioselectivity. The dependence of the catalytic properties of these new ligands on the structure of the substrate also appears to be different from that of the previously reported Schiff base–titanium complexes, as seen in the asymmetric silylcyanation of the anisaldehyde regioisomers. On the other hand, molecular mechanics modelling of the intermediate complexes (by means of the SYBYL force field) is in good agreement with the experimental results of our study, and emphasize (a) the crucial role played by the $C_{2'}$ *tert*-butyl substituent in the Schiff base, and (b) the displacement of one of the isopropoxides on the titanium centre by a non-reactive cyanide ion, leading to the formation of a more compact transition state complex.

## 4. Experimental

### 4.1. General materials and methods

Melting points were determined in an open capillary tube and are uncorrected. Optical rotations were measured at room temperature (23 °C); concentrations are given in g 100 ml$^{-1}$. Infrared spectra were recorded in a Fourier transform mode, using NaCl film or KBr pellet techniques. Unless otherwise stated, NMR spectra were recorded in $CDCl_3$ solution. Chemical shifts are given in parts per million and referenced to TMS or $CHCl_3$. Carbon multiplicities were established by DEPT experiments. Mass spectra were performed using chemical ionization (CI) or electrospray ionization (ESI) techniques. Exact mass measurements (HRMS) were performed by the 'Unidad de Espectrometría de Masas de la Universidad de Santiago de Compostela'. Reactions (with the exception of catalytic asymmetric dihydroxylations) were generally run in flame- or oven-dried glassware under a $N_2$ atmosphere. Commercially available reagents were used as received. Diethyl ether and tetrahydrofuran used in the reactions were dried by distillation over metallic sodium and benzophenone (or fluorenone). Dichloromethane, triethylamine and pyridine were distilled from calcium hydride. Amino alcohols **1a**,[11a] **1c**,[14] and **1d**,[13] 3-adamantyl-5-methyl-2-hydroxybenzaldehyde **5C**[8b] and the 'Schiff base **7**[3b] were prepared according to the previously described procedures.

### 4.2. Synthesis of 1-amino-1-ferrocenyl-2-ethanol derivatives

**4.2.1. 1-Ferrocenyl-1-propene 3.** To a cold (0 °C), stirred solution of ferrocenecarbaldehyde (3.0 g, 14 mmol) in anhydrous tetrahydrofuran (40 ml), a 1.0 M solution of ethylmagnesium bromide in tetrahydrofuran (21 ml, 21 mmol) was added dropwise. The resulting mixture was stirred at room temperature for 30 min and cooled again to 0 °C. Saturated aqueous ammonium chloride (60 ml) was added dropwise. After stirring for 5 min at room temperature, the aqueous phase was separated and extracted with ethyl acetate ($3 \times 60$ ml). The combined organic phases were washed with brine (50 ml), dried over sodium sulfate and evaporated under reduced pressure. The crude 1-ferrocenyl-1-propanol (3.4 g, 14 mmol) was not purified further. A solution of this alcohol in dry toluene (80 ml) was heated at reflux in a Dean–Stark apparatus in the presence of neutral alumina (4.0 g, 0.04 mol) for 5 h. After cooling to room temperature, the solvent was eliminated under vacuum and the residue purified by column chromatography (silica gel, hexanes as eluent) to afford 2.70 g (85% yield) of olefins **3** (ca. 4:1 (*E*)/(*Z*) mixture). The $^1$H NMR data for these compounds were identical to those reported in the literature.[16]

**4.2.2. (1*S*,2*R*)-1-Ferrocenylpropane-1,2-diol 2.** To a stirred solution of $K_3Fe(CN)_6$ (6.2 g, 19 mmol) and $K_2CO_3$ (2.6 g, 19 mmol) in 1:1 acetonitrile–water (350 ml), were added $(DHQD)_2PYR$ (0.29 g, 0.30 mmol) and $K_2OsO_2(OH)_4$ (49 mg, 0.30 mmol), and stirring was maintained at room temperature until complete dissolution of the osmate (2 h). At this point, 1-ferrocenylpropene **3** (1.4 g, 6.3 mmol, 4:1 (*E*)/(*Z*) mixture), dissolved in the minimum amount of acetonitrile, was added in one portion. The reaction was monitored by TLC. When no starting alkenylferrocene remained (75 min stirring at room temperature), sodium sulfite (9.9 g, 76 mmol) was added and stirring maintained for 30 min. The reaction mixture was extracted with ethyl acetate ($5 \times 60$ ml), the organic extracts were dried over magnesium sulfate and the solvents removed at reduced pressure. Column chromatography of the crude product (silica gel, hexane–ethyl acetate mixtures as eluent) afforded 1.3 g (81% yield) of (1*S*,2*R*)-1-ferrocenylpropane-1,2-diol (98:2 er, determined by HPLC on a Chiral PAK AD column[15]) as a yellow solid. Mp: 72.4–73.8 °C (lit:[15] 69–71 °C). $[\alpha]_D^{23} = +80.5$ (*c* 0.21, $CH_2Cl_2$) [lit:[15] +73.1 (*c* 0.14, $CH_2Cl_2$)]. $^1$H NMR (200 MHz): $\delta$ 1.07 (d, $J =$ 6.2 Hz, 3H), 2.27 (br s, 1H), 2.54 (br s, 1H), 3.66 (m, 1H), 4.05 (m, 1H), 4.20–4.26 (m, 9H) ppm.

**4.2.3. (1*S*,2*R*)-1-Azido-1-ferrocenyl-2-propyl acetate 4.** To a stirred solution of (1*S*,2*R*)-1-ferrocenyl-2-propane-1,2-diol **2** (3.80 g, 14.5 mmol) in anhydrous pyridine (20 ml), acetic anhydride (30 ml, 0.36 mol) was added and the resulting mixture stirred at room temperature for 12 h. At this point, TLC monitoring revealed that no starting diol remained; excess acetic anhydride and pyridine were removed under vacuum, the addition of toluene

(3 × 15 ml) being necessary to ensure the complete removal of pyridine. In this way, 4.8 g (quantitative yield) of the crude diacetate of **2** was obtained as an orange oil. Without further purification, this product was used directly in the following step. $^1$H NMR (200 MHz): $\delta$ 1.09 (d, $J$ = 6.6 Hz, 3H), 2.01 (s, 3H), 2.19 (s, 3H), 4.16 (m, 9H), 5.02 (m, 1H), 5.80 (d, $J$ = 5.8 Hz, 1H) ppm. $^{13}$C NMR (50 MHz): $\delta$ 16.4 ($CH_3$), 21.0 ($CH_3$), 21.1 ($CH_3$), 66.4 (CH), 67.5 (CH), 67.8 (CH), 68.1 (CH), 68.7 (CH), 68.8 (CH), 72.0 (CH), 84.6 (Cq, Fc), 170.0 (Cq, CO), 170.3 (Cq, CO) ppm.

To a stirred solution of the crude diacetate of **2** (4.8 g, 13.9 mmol) in 3:1 water–methanol (275 ml), sodium azide (10.0 g, 0.15 mol) was added in one portion. The resulting mixture was stirred at 60 °C for 4.5 h (TLC monitoring) and allowed to cool at room temperature. After eliminating most of the methanol at reduced pressure, the mixture was extracted with dichloromethane (4 × 60 ml). The combined organic extracts were washed with brine (2 × 80 ml), dried over magnesium sulfate, stripped of solvents at reduced pressure and purified by column chromatography (silica gel, hexane–ethyl acetate mixtures of increasing polarity) to afford 3.20 g (70% yield) of azido acetate **4** as an orange-coloured oil. $[\alpha]_D^{23} = +91.3$ ($c$ 0.56, $CHCl_3$). IR (NaCl film): $\nu_{max}$ = 3080, 2910, 2100, 1740, 1380, 1250, 1050, 800 cm$^{-1}$. $^1$H NMR (200 MHz): $\delta$ 1.16 (d, $J$ = 6.2 Hz, 3H), 2.08 (s, 3H), 4.11–4.20 (m, 10H), 5.04 (m, 1H) ppm. $^{13}$C NMR (50 MHz): $\delta$ 17.1 ($CH_3$), 21.2 ($CH_3$), 65.2 (CH), 66.7 (CH), 67.9 (CH), 68.0 (CH), 68.2 (CH), 68.9 (CH), 73.2 (CH), 85.2 (Cq, Fc), 170.0 (Cq, CO) ppm. MS (ESI) $m/e$: 327 (M, 100%), 285 (M−42, 94%). HRMS (ESI) $C_{15}H_{17}FeN_3O_2$ (M): calcd 327.0670, found 327.0663.

**4.2.4. (1*S*,2*R*)-1-Amino-1-ferrocenyl-2-propanol 1b.** To a cold (0 °C), stirred suspension of lithium aluminium hydride (366 mg, 9.64 mmol) in anhydrous tetrahydrofuran (36 ml), a solution of azido acetate **4** (1.05 g, 3.21 mmol) in anhydrous tetrahydrofuran (24 ml) was added via a cannula. The mixture was stirred at room temperature for 40 min, cooled again to 0 °C and treated successively with water (1.3 ml), aqueous 15% NaOH (1.6 ml) and again water (1.9 ml). After stirring for 5 min at rt, the mixture filtered through a Celite® pad, the precipitate was washed with ethyl acetate and the solvents were removed under vacuum, to afford 874 mg (100% yield) of the title compound as a yellow solid. Mp: 62.3–65.1 °C. $[\alpha]_D^{23} = +70.1$ ($c$ 0.56, $CHCl_3$). IR (NaCl film): $\nu_{max}$ = 3380, 3300, 3080, 2900, 1570, 1450, 1380, 1080, 1000, 1105, 800 cm$^{-1}$. $^1$H NMR (200 MHz): $\delta$ 1.10 (d, $J$ = 6.2 Hz, 3H), 2.30 (br s, 3H, $NH_2$+OH), 3.36 (d, $J$ = 6.0 Hz, 1H, CH–N), 3.49 (m, 1H, CH–O), 4.16 (m, 9H, Fc) ppm. $^{13}$C NMR (50 MHz): $\delta$ 19.9 ($CH_3$), 56.9 (CH), 64.7 (CH), 67.6 (CH), 67.7 (CH), 68.3 (CH), 71.7 (CH), 91.8 (Cq, Fc) ppm. MS (ESI) $m/e$: 260 (M+1, 23%), 243 (M−16, 100%). HRMS (ESI) $C_{13}H_{18}FeNO$ (M+1): calcd 260.0738, found 260.0733.

**4.2.5. (1*R*,2*S*)-2-Amino-2-ferrocenyl-1-phenylethanol 1e.** To a stirred suspension of $PtO_2$ (18 mg) in absolute ethanol (3 ml), a solution of (1*R*,2*S*)-2-azido-2-ferrocenyl-1-phenylethanol[11b] (182 mg, 0.52 mmol; 99.5:0.5 er) in absolute ethanol (2.2 ml) was added via a cannula. The mixture was stirred at room temperature under a hydrogen atmosphere (balloon) for 12 h, filtered through a Celite® pad and the solvent removed under vacuum, to afford 170 mg (quantitative yield) of the title compound as a yellow solid. Mp: 141.2–142.8 °C. $[\alpha]_D^{23} = -11.5$ ($c$ 0.26, $CH_2Cl_2$). IR (KBr): $\nu_{max}$ = 3373, 3091, 2925, 1455, 1030, 814 cm$^{-1}$. $^1$H NMR (200 MHz): $\delta$ 2.11 (br s, 3H, $NH_2$+OH), 3.84 (m, 2H), 4.06–4.23 (m, 8H), 4.48 (d, $J$ = 4.8 Hz, 1H, C*H*–OH), 7.2–7.4 (m, 5H, Ph) ppm. $^{13}$C NMR (75 MHz): $\delta$ 57.1 (CH–N), 65.3 (CH, Fc), 67.6 (CH, Fc), 68.1 (CH, Fc), 68.3 (CH, Fc), 68.6 (CH, Fc), 77.5 (CH–O), 90.8 (Cq, Fc), 126.5 (CH, Ph), 127.4 (CH, Ph), 128.3 (CH, Ph), 142.2 (Cq, Ph) ppm. MS (CI, $NH_3$) $m/e$: 322 (M+1, 100%), 305 (M−16, 71%). HRMS (CI) $C_{18}H_{19}FeNO$ (M): calcd 321.0816, found 321.0810.

### 4.3. Synthesis of salicylaldehyde Schiff bases

**4.3.1. Typical procedure. Preparation of 2-[((*S*)-1-ferrocenyl-2-hydroxyethylimino)methyl]phenol 6aA.** To a solution of amino alcohol **1a** (300 mg, 1.23 mmol) in absolute ethanol (6.2 ml) was added 0.129 ml (1.23 mmol) of salicylaldehyde **5A**. After stirring for 1 h at room temperature (TLC monitoring), the solvent was distilled off under vacuum and the residue was purified by column chromatography on silica gel (eluting with hexane–ethyl acetate mixtures) to give 328 mg (77% yield) of the Schiff base **6aA** as a yellow solid. Mp: 109.7–111.1 °C. $[\alpha]_D^{23} = +203.0$ ($c$ 0.28, EtOH). IR (KBr): $\nu_{max}$ = 3095, 2925, 1630, 1459, 1279, 1040, 820, 756 cm$^{-1}$. $^1$H NMR (300 MHz): $\delta$ 1.5–1.8 (br s, 1H, O*H*), 3.88 (m, 2H, C$H_2$OH), 4.10–4.23 (m, 10H, Fc+C*H*–N), 6.92 (t, $J$ = 7.5 Hz, 1H, Ar), 7.01 (d, $J$ = 8.1 Hz, 1H, Ar), 7.35 (m, 2H, Ar), 8.51 (s, 1H, C*H*=N), 13.2–13.8 (br s, 1H, O*H* Ar) ppm. $^{13}$C NMR (100 MHz): $\delta$ 66.3 (CH), 66.8 (CH), 67.1 ($CH_2$), 67.7 (CH), 68.1 (CH), 68.6 (CH), 70.4 (CH), 87.0 (Cq, Fc), 117.1 (CH, Ar), 118.4 (Cq, Ar), 118.7 (CH, Ar), 131.6 (CH, Ar), 132.6 (CH, Ar), 161.2 (Cq, Ar, *C*–OH), 165.3 (CH, *C*H=N) ppm. MS (CI, $NH_3$) $m/e$: 348 (M+1, 100%). HRMS (CI) $C_{19}H_{19}FeNO_2$ (M): calcd 347.0820, found 347.0821.

**4.3.2. 2-[((1*S*,2*R*)-1-Ferrocenyl-2-hydroxypropylimino)methyl]phenol 6bA.** In a similar way, salicylaldehyde **5A** (0.120 ml, 1.13 mmol) and amino alcohol **1b** (300 mg, 1.16 mmol) in absolute ethanol (10.2 ml, 100 min at room temperature) afforded 379 mg (92% yield) of the title compound as a yellow solid. Mp: 116.5–118.0 °C. $[\alpha]_D^{23} = +481.0$ ($c$ 0.57, EtOH). IR (KBr): $\nu_{max}$ = 3365, 2971, 1632, 1461, 1279, 1045, 818, 756 cm$^{-1}$. $^1$H NMR (300 MHz): $\delta$ 1.10 (d, $J$ = 6.0 Hz, 3H, $CH_3$), 1.6–1.9 (br s, 1H, O*H*), 3.82 (m, 1H, C*H*–$CH_3$), 3.88 (d, $J$ = 6.6 Hz, 1H, C*H*–N), 4.04 (m, 5H, Fc), 4.16 (m, 1H, Fc), 4.20 (m, 2H, Fc), 4.27 (m, 1H, Fc), 6.90 (td, $J_1$ = 7.3 Hz, $J_2$ = 1.0 Hz, 1H, Ar), 7.03 (d, $J$ = 8.1 Hz, 1H, Ar), 7.34–7.40 (m, 2H, Ar), 8.54 (s, 1H, C*H*=N), 13.4–13.6 (br s, 1H, O*H* Ar) ppm. $^{13}$C NMR (50 MHz): $\delta$ 19.4 ($CH_3$), 66.4 (CH), 66.8 (CH), 67.4 (CH), 67.9 (CH), 68.2 (CH), 68.6 (CH), 71.6 (CH), 75.8 (CH), 87.9 (Cq, Fc), 117.1 (CH, Ar), 118.1 (Cq, Ar), 118.8 (CH, Ar), 132.6 (CH, Ar), 160.5 (Cq, Ar, *C*–OH), 165.0 (CH, *C*H=N) ppm.

MS (CI, $NH_3$) *m*/*e*: 364 (M+1, 100%). HRMS (CI) $C_{20}H_{21}FeNO_2$ (M): calcd 363.0917, found 363.0922.

**4.3.3. 2-[((*S*)-1-Ferrocenyl-2-hydroxy-2-methylpropylimino)-methyl]phenol 6dA.** In a similar way, salicylaldehyde **5A** (38 μl, 0.36 mmol) and amino alcohol **1d** (100 mg, 0.37 mmol) in absolute ethanol (1.8 ml, 70 min at room temperature) afforded 122 mg (90% yield) of the title compound as a yellow solid. Mp: 167.4–168.9 °C. $[\alpha]_D^{23} = +443.0$ (*c* 0.29, EtOH). IR (KBr): $\nu_{max} = 3365$, 3475, 2926, 1630, 1501, 1385, 1281, 1026, 810, 756 $cm^{-1}$. $^1H$ NMR (300 MHz): $\delta$ 1.14 (s, 3H, $CH_3$), 1.15 (s, 3H, $CH_3$), 1.5 (br s, 1H, O*H*), 3.94 (s, 1H, C*H*–N), 4.0 (s, 5H, Fc), 4.18 (m, 2H, Fc), 4.26 (m, 1H, Fc), 4.31 (m, 1H, Fc), 6.94 (t, $J = 7.6$ Hz, 1H, Ar), 7.04 (d, $J = 7.8$ Hz, 1H, Ar), 7.34–7.42 (m, 2H, Ar), 8.58 (s, 1H, C*H*=N), 13.6 (br s, 1H, O*H* Ar) ppm. $^{13}C$ NMR (50 MHz): $\delta = 25.6$ ($CH_3$), 26.2 ($CH_3$), 67.3 (CH), 68.2 (CH), 68.6 (CH), 73.1 (Cq, *C*–OH), 79.4 (CH, *C*H–N), 87.8 (Cq, Fc), 117.1 (CH, Ar), 118.4 (Cq, Ar), 118.8 (CH, Ar), 131.6 (CH, Ar), 132.6 (CH, Ar), 161.1 (Cq, Ar, *C*–OH), 164.9 (CH, *C*H=N) ppm. MS (CI, $NH_3$) *m*/*e*: 377 (M, 100%), 378 (M+1, 27%). HRMS (CI) $C_{21}H_{23}FeNO_2$ (M): calcd 377.1078, found 377.1092.

**4.3.4. 2-*tert*-Butyl-6-[((*S*)-1-ferrocenyl-2-hydroxyethylimino)-methyl]phenol 6aB.** In a similar way, 3-*tert*-butyl-2-hydroxybenzaldehyde **5B** (137 μl, 0.80 mmol) and amino alcohol **1a** (200 mg, 0.82 mmol) in absolute ethanol (4.1 ml, 4.5 h at room temperature) afforded 295 mg (89% yield) of the title compound as a yellow solid. Mp: 67.0–67.8 °C. $[\alpha]_D^{23} = +469.0$ (*c* 0.21, EtOH). IR (NaCl film): $\nu_{max} = 3384$, 2956, 1628, 1559, 1437, 1267, 1040, 818, 752 $cm^{-1}$. $^1H$ NMR (300 MHz): $\delta$ 1.47 (s, 9H, $3 \times CH_3$), 1.7 (br s, 1H, O*H*), 3.89 (m, 2H, C$H_2$OH), 4.13 (s, 5H, Fc), 4.16–4.20 (m, 4H, Fc), 6.86 (t, $J = 7.8$ Hz, 1H, Ar), 7.19 (dd, $J_1 = 7.4$ Hz, $J_2 = 1.6$ Hz, 1H, Ar), 7.36 (dd, $J_1 = 7.8$ Hz, $J_2 = 1.6$ Hz, 1H, Ar), 8.51 (s, 1H, C*H*=N), 13.9 (br s, 1H, O*H* Ar) ppm. $^{13}C$ NMR (50 MHz): $\delta$ 29.4 ($CH_3$), 34.9 (Cq, $^t$Bu), 66.4 (CH), 66.9 (CH), 67.1 ($CH_2$), 67.7 (CH), 68.1 (CH), 68.7 (CH), 70.3 (CH), 87.2 (Cq, Fc), 117.9 (CH, Ar), 118.3 (Cq, Ar), 129.7 (CH, Ar), 129.9 (CH, Ar), 137.5 (Cq, Ar), 160.4 (Cq, Ar, *C*–OH), 166.0 (CH, *C*H=N) ppm. MS (CI, $NH_3$) *m*/*e*: 405 (M, 100%), 406 (M+1, 27%). HRMS (CI) $C_{23}H_{27}FeNO_2$ (M): calcd 405.1391, found 405.1375.

**4.3.5. 2-*tert*-Butyl-6-[((1*S*,2*R*)-1-ferrocenyl-2-hydroxy-propylimino)methyl]phenol 6bB.** In a similar way, 3-*tert*-butyl-2-hydroxybenzaldehyde **5B** (65 μl, 0.37 mmol) and amino alcohol **1b** (100 mg, 0.38 mmol) in absolute ethanol (4.5 ml, 5 h at room temperature) afforded 160 mg (99% yield) of the title compound as a yellow solid. Mp: 52.5–54.6 °C. $[\alpha]_D^{23} = +469.0$ (*c* 0.21, EtOH). IR (NaCl film): $\nu_{max} = 3373$, 2960, 1632, 1437, 1306, 1268, 1044, 818, 752 $cm^{-1}$. $^1H$ NMR (300 MHz): $\delta$ 1.11 (d, $J = 6.0$ Hz, 3H, C$H_3$–OH), 1.49 (s, 9H, $3 \times CH_3$), 1.9 (br s, 1H, O*H*), 3.84 (m, 2H), 4.04 (s, 5H, Fc), 4.15 (m, 1H, Fc), 4.21 (m, 2H, Fc), 4.33 (m, 1H, Fc), 6.87 (t, $J = 7.6$ Hz, 1H, Ar), 7.23 (dd, $J_1 = 7.8$ Hz, $J_2 = 1.4$ Hz, 1H, Ar), 7.38 (dd, $J_1 = 7.8$ Hz, $J_2 = 1.4$ Hz, 1H, Ar), 8.54 (s, 1H, C*H*=N), 14.0 (br s, 1H, O*H* Ar) ppm. $^{13}C$ NMR (50 MHz): $\delta$ 19.4 ($CH_3$), 29.4 ($CH_3$, $^t$Bu), 34.9 (Cq, $^t$Bu), 66.4 (CH), 67.2 (CH), 68.1 (CH), 68.2 (CH), 68.6 (CH), 71.6 (CH), 75.8 (CH), 88.3 (Cq, Fc), 118.0 (CH, Ar), 118.2 (Cq, Ar), 129.7 (CH, Ar), 129.9 (CH, Ar), 137.5 (Cq, Ar), 160.5 (Cq, Ar, *C*–OH), 165.8 (CH, *C*H=N) ppm. MS (CI, $NH_3$) *m*/*e*: 419 (M, 100%), 420 (M+1, 30%). HRMS (CI) $C_{24}H_{29}FeNO_2$ (M): calcd 419.1548, found 419.1538.

**4.3.6. 2-*tert*-Butyl-6-[((*S*)-1-ferrocenyl-2-hydroxy-1-methyl-ethylimino)methyl]phenol 6cB.** In a similar way, 3-*tert*-butyl-2-hydroxybenzaldehyde **5B** (26 μl, 0.21 mmol) and amino alcohol **1c** (55 mg, 0.22 mmol) in absolute ethanol (1.5 ml, 4 h at room temperature) afforded 65 mg (75% yield) of the title compound as a yellow solid. Mp: 67.0–67.8 °C. $[\alpha]_D^{23} = +139.2$ (*c* 1.20, EtOH). IR (NaCl film): $\nu_{max} = 3404$, 3096, 2956, 1626, 1439, 1267, 1108, 1035, 856 $cm^{-1}$. $^1H$ NMR (400 MHz): $\delta$ 1.48 (s, 9H, $3 \times CH_3$), 1.66 (s, 3H, $CH_3$), 2.00 (br s, 1H, O*H*), 3.75–3.86 (m, 2H, C$H_2$OH), 4.19–4.26 (m, 9H, Fc), 6.82 (t, $J = 7.8$ Hz, 1H, Ar), 7.13 (dd, $J_1 = 7.6$ Hz, $J_2 = 1.6$ Hz, 1H, Ar), 7.35 (d, $J = 8.0$ Hz, 1H, Ar), 8.32 (s, 1H, C*H*=N) ppm. The signal corresponding to the phenol hydroxyl proton was not observed. $^{13}C$ NMR (100 MHz): $\delta$ 22.5 ($CH_3$), 29.3 ($CH_3$), 34.8 (Cq, $^t$Bu), 63.2 (Cq, C*H*-Fc), 66.4 (CH, Fc), 67.9 (CH, Fc), 68.2 (CH, Fc), 68.8 (CH, Fc), 71.0 ($CH_2$), 92.5 (Cq, Fc), 117.6 (CH, Ar), 118.5 (Cq, Ar), 129.4 (CH, Ar), 130.1 (CH, Ar), 137.5 (Cq, Ar), 160.8 (Cq, Ar, *C*–OH), 163.3 (CH, *C*H=N) ppm. MS (CI, $NH_3$) *m*/*e*: 420 (M+1, 100%), 243 (M−178, 40%). HRMS (CI) $C_{24}H_{29}FeNO_2$ (M): calcd 419.1548, found 419.1540.

**4.3.7. 2-*tert*-Butyl-6-[((*S*)-1-ferrocenyl-2-hydroxy-2-methyl-propylimino)methyl]phenol 6dB.** In a similar way, 3-*tert*-butyl-2-hydroxybenzaldehyde **5B** (92 μl, 0.54 mmol) and amino alcohol **1d** (150 mg, 0.55 mmol) in absolute ethanol (2.8 ml, 6 h at room temperature) afforded 217 mg (93% yield) of the title compound as a yellow solid. Mp: 91.0–93.5 °C. $[\alpha]_D^{23} = +419.2$ (*c* 0.23, EtOH). IR (NaCl film): $\nu_{max} = 3426$, 2962, 1630, 1437, 1385, 1268, 1146, 1067, 751 $cm^{-1}$. $^1H$ NMR (300 MHz): $\delta$ 1.15 (s, 3H, C$H_3$–COH), 1.17 (s, 3H, C$H_3$–COH), 1.50 (s, 9H, $3 \times CH_3$), 1.56 (br s, 1H, O*H*), 3.91 (s, 1H, C*H*-Fc), 3.99 (s, 5H, Fc), 4.16–4.20 (m, 2H, Fc), 4.38 (m, 1H, Fc), 6.88 (t, $J = 7.2$ Hz, Ar), 7.24 (dd, $J_1 = 7.4$ Hz, $J_2 = 1.8$ Hz, 1H, Ar), 7.39 (dd, $J_1 = 7.4$ Hz, $J_2 = 1.4$ Hz, 1H, Ar), 8.57 (s, 1H, C*H*=N), 14.7 (br s, 1H, O*H* Ar) ppm. $^{13}C$ NMR (50 MHz): $\delta$ 25.6 ($CH_3$), 26.3 ($CH_3$), 29.3 ($CH_3$, $^t$Bu), 34.9 (Cq, $^t$Bu), 67.1 (CH), 67.3 (CH), 68.1 (CH), 68.5 (CH), 73.1 (Cq, *C*–OH), 79.3 (CH), 88.0 (Cq, Fc), 117.9 (CH, Ar), 118.2 (Cq, Ar), 129.7 (CH, Ar), 129.9 (CH, Ar), 137.4 (Cq, ar), 160.4 (Cq, Ar, *C*–OH), 165.7 (CH, *C*H=N) ppm. MS (CI, $NH_3$) *m*/*e*: 434 (M+1, 100%). HRMS (CI) $C_{25}H_{32}FeNO_2$ (M+1): calcd 434.1782, found 434.1761.

**4.3.8. 2-Adamantyl-5-methyl-6-[((*S*)-1-ferrocenyl-2-hydroxy-ethylimino)methyl]phenol 6aC.** In a similar way, 3-adamantyl-5-methyl-2-hydroxybenzaldehyde **5C** (158 mg, 0.58 mmol) and amino alcohol **1a** (150 mg, 0.61 mmol) in absolute ethanol (4 ml, 15 min at 50 °C) afforded 181 mg (63% yield) of the title compound as a yellow solid. Mp: 108.4–109.6 °C. $[\alpha]_D^{23} = +204.2$ (*c* 0.36, EtOH). IR (KBr):

$\nu_{max} = 3398$, 3095, 2904, 2850, 1628, 1596, 1455, 1248, 1040, 816 $cm^{-1}$. $^1H$ NMR (400 MHz): $\delta$ 1.60–1.84 (m, 7H, –O*H*+3 × (C$H_2$) adamantyl), 2.09 (m, 3H, 3 × (C*H*) adamantyl), 2.21 (m, 6H, 3 × (C$H_2$) adamantyl), 2.30 (s, 3H, $CH_3$), 3.81–3.91 (m, 2H, C$H_2$OH), 4.13 (s, 5H, Fc), 4.16–4.19 (m, 4H, Fc), 4.25–4.26 (m, 1H, C*H*-Fc), 6.97 (s, 1H, Ar), 7.11 (s, 1H, Ar), 8.45 (s, 1H, C*H*=N), 13.7 (br s, 1H, O*H* Ar) ppm. $^{13}C$ NMR (100 MHz): $\delta$ 20.7 ($CH_3$), 29.1 (CH adamantyl), 37.0 (Cq, adamantyl), 37.1 ($CH_2$ adamantyl), 40.3 ($CH_2$ adamantyl), 66.5 (CH), 66.9 (CH), 67.1 ($CH_2$), 67.8 (CH), 68.0 (CH), 68.7 (CH), 70.5 (CH), 87.3 (Cq, Fc), 118.1 (Cq, Ar), 126.9 (Cq, Ar), 129.7 (CH, Ar), 130.9 (CH, Ar), 137.5 (Cq, Ar), 158.5 (Cq, Ar, *C*–OH), 166.3 (CH, *C*H=N) ppm. MS (CI, $NH_3$) *m*/*e*: 497 (M, 100%), 498 (M+1, 32%). HRMS (CI) $C_{30}H_{35}FeNO_2$ (M): calcd 497.2018, found 497.2016.

**4.3.9. 2-Adamantyl-5-methyl-6-[((*S*)-1-ferrocenyl-2-hydroxypropylimino)methyl]phenol 6bC.** In a similar way, 3-adamantyl-5-methyl-2-hydroxybenzaldehyde **5C** (160 mg, 0.59 mmol) and amino alcohol **1b** (157 mg, 0.60 mmol) in absolute ethanol (5 ml, 1.5 h at 50 °C) afforded 270 mg (88% yield) of the title compound as a yellow solid. Mp: 89.5–91.1 °C. $[\alpha]_D^{23} = +408.3$ (*c* 0.57, EtOH). IR (KBr): $\nu_{max} = 3407$, 2900, 2845, 1635, 1541, 1456, 1249, 1050 $cm^{-1}$. $^1H$ NMR (400 MHz): $\delta$ 1.02 (d, 3H, $J$ = 6.4 Hz, $CH_3$), 1.84 (m, 6H, 3 × (C$H_2$) adamantyl), 2.10 (m, 3H, 3 × (C*H*) adamantyl), 2.26 (m, 6H, 3 × (C$H_2$) adamantyl), 2.29 (s, 3H, $CH_3$Ar), 3.76 (m, 1H, C*H*–$CH_3$), 3.89 (d, $J$ = 7.2 Hz, 1H, C*H*-Fc), 3.97 (br s, 1H, O*H*), 4.03 (s, 5H, Fc), 4.14 (s, 1H, Fc), 4.21 (s, 1H, Fc), 4.28 (s, 1H, Fc), 4.31 (s, 1H, Fc), 7.12 (s, 1H, Ar), 7.13 (s, 1H, Ar), 8.60 (s, 1H, C*H*=N) ppm. The signal corresponding to the phenol proton was not observed. $^{13}C$ NMR (100 MHz): $\delta$ 20.3 ($CH_3$), 20.6 ($CH_3$, Ar), 29.9 (CH adamantyl), 37.5 (Cq adamantyl), 37.7 ($CH_2$ adamantyl), 40.9 ($CH_2$ adamantyl), 66.9 (CH), 67.5 (CH), 68.5 (CH), 69.2 (CH), 69.3 (CH), 71.7 (CH, C*H*–OH), 76.7 (CH), 90.1 (Cq, Fc), 119.4 (Cq, Ar), 127.2 (Cq, Ar), 130.6 (CH, Ar), 130.8 (CH, Ar), 137.6 (Cq, Ar), 159.3 (Cq, Ar, *C*–OH), 166.4 (CH, *C*H=N) ppm. MS (CI, $NH_3$) *m*/*e*: 512 (M+1, 100%). HRMS (CI) $C_{31}H_{38}FeNO_2$ (M+1): calcd 512.2252, found 512.2235.

**4.3.10. 2-Adamantyl-5-methyl-6-[((*S*)-1-ferrocenyl-2-hydroxy-1-methylethylimino)methyl]phenol 6cC.** In a similar way, 3-adamantyl-5-methyl-2-hydroxybenzaldehyde **5C** (92 mg, 0.34 mmol) and amino alcohol **1c** (90 mg, 0.35 mmol) in absolute ethanol (2.5 ml, 1 h at 50 °C) afforded 151 mg (87% yield) of the title compound as a yellow solid. Mp: 94.7–95.9 °C. $[\alpha]_D^{23} = +137.6$ (*c* 0.50, EtOH). IR (KBr): $\nu_{max} = 3359$, 2903, 2849, 1626, 1453, 1250, 1046, 818 $cm^{-1}$. $^1H$ NMR (400 MHz): $\delta$ 1.72 (s, 3H, C$H_3$-Fc), 1.88 (m, 6H, 3 × (C$H_2$) adamantyl), 2.14 (m, 3H, 3 × (C*H*) adamantyl), 2.30 (m, 6H, 3 × (C$H_2$) adamantyl), 2.33 (s, 3H, $CH_3$), 2.8–2.9 (br s, 1H, O*H*), 3.75 (d, $J$ = 10.4 Hz, 1H, C$H_2$OH), 3.88 (d, $J$ = 10.4 Hz, 1H, C$H_2$OH), 4.24 (m, 6H, Fc), 4.28 (s, 1H, Fc), 4.30–4.32 (m, 2H, Fc), 7.10 (s, 1H, Ar), 7.14 (s, 1H, Ar), 8.55 (s, 1H, C*H*=N) ppm. The signal corresponding to the phenol proton was not observed. $^{13}C$ NMR (100 MHz): $\delta$ 20.8 ($CH_3$), 22.4 ($CH_3$), 29.9 (CH adamantyl), 37.7 (Cq adamantyl), 38.0 ($CH_2$ adamantyl), 41.2 ($CH_2$ adamantyl), 64.0 (Cq, *C*-Fc), 67.1 (CH), 67.5 (CH), 68.3 (CH), 68.7 (CH), 69.6 (CH), 71.1 ($CH_2$), 95.6 (Cq, Fc), 119.7 (Cq, Ar), 127.0 (Cq, Ar), 130.9 (CH, Ar), 131.0 (CH, Ar), 160.1 (Cq, Ar, *C*–OH), 164.2 (CH, *C*H=N) ppm. MS (CI, $NH_3$) *m*/*e*: 511 (M, 10%), 512 (M+1, 100%). HRMS (CI) $C_{31}H_{37}FeNO_2$ (M): calcd 511.2174, found 511.2192.

### 4.4. Reduction of salicylaldehyde Schiff bases derived from 2-ferrocenyl-2-amino alcohols

**4.4.1. Representative experimental procedure. Preparation of 2-[((*S*)-1-ferrocenyl-2-hydroxy-2-methylpropylamino)-methyl]phenol 8dA.** To a cold (−78 °C), stirred solution of 2-[((*S*)-1-ferrocenyl-2-hydroxy-2-methylpropylimino)-methyl]phenol **6dA** (50 mg, 0.13 mmol) and cerium(III) chloride heptahydrate (49 mg, 0.13 mmol) in methanol (2.1 ml), sodium borohydride (10 mg, 0.26 mmol) was added in one portion. The resulting mixture was stirred at room temperature for 75 min (TLC monitoring), and a saturated aqueous solution of ammonium chloride (5 ml) was added dropwise. The reaction mixture was extracted with dichloromethane (3 × 6 ml) and washed with brine (10 ml). After drying over magnesium sulfate, elimination of the solvents followed by chromatographic purification on silica gel using hexane–ethyl acetate mixtures as eluents gave 38 mg (77% yield) of the title compound as a yellow solid. Mp: 93.9–94.6 °C. $[\alpha]_D^{23} = +61.9$ (*c* 1.35, EtOH). IR (KBr): $\nu_{max} = 3300$, 3091, 2973, 2853, 1616, 1589, 1489, 1254, 1001, 754 $cm^{-1}$. $^1H$ NMR (400 MHz): $\delta$ 1.15 (s, 6H, 2 × $CH_3$), 3.22 (s, 1H, C*H*–N), 4.12 (s, 1H, Fc), 4.17–4.20 (m, 8H, Fc), 4.30 (m, 2H, C$H_2$–N), 6.81 (t, $J$ = 7.6 Hz, 1H, Ar), 6.91 (d, $J$ = 8.0 Hz, 1H, Ar), 7.08 (d, $J$ = 7.2 Hz, 1H, Ar), 7.20 (t, $J$ = 7.2 Hz, 1H, Ar) ppm. The signals corresponding to the OH and to the NH protons were not observed. $^{13}C$ NMR (50 MHz): $\delta$ 25.4 ($CH_3$), 26.7 ($CH_3$), 54.7 ($CH_2$), 65.6 (CH), 66.9 (CH), 67.5 (CH), 68.0 (CH), 68.6 (CH), 69.6 (CH), 74.1 (Cq, *C*–OH), 89.3 (Cq, Fc), 116.4 (CH, Ar), 119.3 (CH, Ar), 123.7 (Cq, Ar), 128.1 (CH, Ar), 128.9 (CH, Ar), 157.7 (Cq, Ar, *C*–OH) ppm. MS (CI, $NH_3$) *m*/*e*: 380 (M+1, 100%), 320 (M−59, 36%). HRMS (CI) $C_{21}H_{26}FeNO_2$ (M+1): calcd 380.1313, found 380.1301.

**4.4.2. 2-*tert*-Butyl-6-[((*S*)-1-ferrocenyl-2-hydroxyethylamino)-methyl]phenol 8aB.** In a similar way, 125 mg (0.31 mmol) of **6aB** was treated with sodium borohydride (24 mg, 0.62 mmol) and cerium(III) chloride heptahydrate (116 mg, 0.31 mmol) in methanol (5 ml, 75 min at room temperature) to afford 60 mg (48% yield) of the title compound as a yellow semi-solid. $[\alpha]_D^{23} = +13.4$ (*c* 0.40, EtOH). IR (NaCl film): $\nu_{max} = 3305$, 2921, 2853, 1736, 1651, 1592, 1437, 1239, 1024, 749 $cm^{-1}$. $^1H$ NMR (400 MHz): $\delta$ 1.44 (s, 9H, 3 × $CH_3$), 3.56 (m, 1H, C*H*-Fc), 3.82 (m, 1H, C$H_2$–OH), 3.96 (d, $J$ = 13.6 Hz, 1H, C$H_2$–N), 4.04 (d, $J$ = 13.6 Hz, 1H, C$H_2$–N), 4.05 (m, 1H, C$H_2$–OH), 4.17–4.21 (m, 9H, Fc), 6.74 (t, $J$ = 7.6 Hz, Ar), 6.88 (dd, $J_1$ = 7.6 Hz, $J_2$ = 1.6 Hz, 1H, Ar), 7.21 (dd, $J_1$ = 7.6 Hz, $J_2$ = 1.6 Hz, 1H, Ar) ppm. The signals corresponding to the OH and to the NH protons were not observed. $^{13}C$ NMR (100 MHz): $\delta$ 29.5 ($CH_3$), 34.7 (Cq, $^t$Bu), 50.6 ($CH_2$–N), 57.2 (CH, CH-Fc), 64.7 ($CH_2$–O), 66.1 (CH),

67.5 (CH), 67.7 (CH), 68.3 (CH), 68.7 (CH), 87.1 (Cq, Fc), 118.4 (CH, Ar), 122.9 (Cq, Ar), 126.1 (CH, Ar), 126.6 (CH, Ar), 137.0 (Cq, Ar), 157.0 (Cq, Ar, *C*–OH) ppm. MS (CI, $NH_3$) *m/e*: 408 (M+1, 26%), 229 (M−178, 100%). HRMS (CI) $C_{23}H_{29}FeNO_2$ (M): calcd 407.1548, found 407.1553.

**4.4.3. 2-*tert*-Butyl-6-[((1*S*,2*R*)-1-ferrocenyl-2-hydroxypropylamino)methyl]phenol 8bB.** In a similar way, 70 mg (0.19 mmol) of **6bB** was treated with sodium borohydride (14 mg, 0.37 mmol) and cerium(III) chloride heptahydrate (70 mg, 0.19 mmol) in methanol (2 ml, 90 min at room temperature) to afford 57 mg (73% yield) of the title compound as a yellow solid. Mp: 118.8–119.5 °C. $[\alpha]_D^{23} = +180.8$ (*c* 0.52, EtOH). IR (KBr): $\nu_{max} = 3313$, 3091, 2960, 1654, 1559, 1437, 1239, 1071, 822 $cm^{-1}$. $^1H$ NMR (200 MHz): $\delta$ 1.26 (d, $J = 6.4$ Hz, 3H, C*H*$_3$–CHOH), 1.44 (s, 9H, 3 × C$H_3$), 3.39 (d, $J = 2.8$ Hz, C*H*-Fc), 3.88 (d, $J = 13.6$ Hz, 1H, C$H_2$–OH), 4.10 (d, $J = 13.6$ Hz, 1H, C$H_2$–OH), 4.11 (s, 1H, Fc), 4.17 (s, 5H, Fc), 4.21 (m, 2H, Fc), 4.29 (m, 2H), 6.73 (t, $J = 7.6$ Hz, 1H, Ar), 6.86 (d, $J = 6.0$ Hz, 1H, Ar), 7.21 (dd, $J_1 = 7.8$ Hz, $J_2 = 2.0$ Hz, 1H, Ar) ppm. The signals corresponding to the OH and to the NH protons were not observed. $^{13}C$ NMR (50 MHz): $\delta$ 20.4 (CH$_3$), 29.5 (CH$_3$, $^t$Bu), 34.7 (Cq, $^t$Bu), 51.4 (CH$_2$), 60.6 (CH, CH-Fc), 67.3 (CH), 67.4 (CH), 68.3 (CH), 68.6 (CH), 71.1 (CH), 88.8 (Cq, Fc), 118.3 (CH, Ar), 123.1 (Cq, Ar), 126.0 (CH, Ar), 126.6 (CH, Ar), 136.8 (Cq, Ar), 157.0 (Cq, Ar, *C*–OH) ppm. MS (CI, $NH_3$) *m/e*: 422 (M+1, 10%), 376 (M−45, 30%). HRMS (CI) $C_{24}H_{32}FeNO_2$ (M+1): calcd 422.1782, found 422.1783.

### 4.5. Catalytic asymmetric trimethylsilylcyanation of aldehydes

**4.5.1. General procedure for the enantioselective addition of cyanotrimethylsilane to aldehydes catalyzed by Schiff base–titanium isopropoxide complexes.** To a stirred solution of the chiral Schiff base (0.22 mmol) in anhydrous dichloromethane (2 ml) under an argon atmosphere, titanium tetra(isopropoxide) (60 μl, 0.20 mmol) was added via a syringe. The resulting red-coloured solution was stirred at room temperature for 1 h and cooled to −60 °C. At this point, aldehyde (1.0 mmol) and cyanotrimethylsilane (0.29 ml, 2.2 mmol) were added sequentially via syringe. After stirring at the same temperature for 64–68 h, the solution was poured over a mixture of 1 M aqueous HCl (45 ml) and ethyl acetate (90 ml), and stirred vigorously at room temperature for 20–24 h. The resulting mixture was extracted with ethyl acetate (3 × 25 ml) and the combined extracts were washed with saturated aqueous sodium bicarbonate (2 × 25 ml) and brine (2 × 25 ml), dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent, hexane–ethyl acetate mixtures of increasing polarity).

**4.5.2. Enantioselective cyanotrimethylsilane addition to aldehydes catalyzed by the titanium isopropoxide complex of imine 6aB.**

**4.5.2.1. (*S*)-2-Hydroxy-2-phenylacetonitrile 9.** According to the general procedure described above, freshly distilled benzaldehyde (67 μl, 0.66 mmol) and cyanotrimethylsilane (0.19 ml, 1.45 mmol) were added to a cold (−60 °C), stirred solution of **6aB** (59 mg, 0.14 mmol) and of titanium tetra(isopropoxide) (40 μl, 0.13 mmol) in anhydrous dichloromethane (1.5 ml). After 63 h of stirring, work-up and purification, **9** (73 mg) was isolated in 83% yield and with a 86:14 er.

The enantiomeric purity of this compound was determined in the following way. To a stirred solution of **9** (60 mg, 0.45 mmol) in dry pyridine (0.9 ml, 11 mmol), acetic anhydride (0.6 ml, 0.9 mmol) was added via a syringe. After 15 h of stirring at room temperature (TLC monitoring), the reaction mixture was diluted with ethyl acetate (10 ml), washed with aqueous saturated ammonium chloride (3 × 10 ml) and brine (2 × 10 ml) and dried over magnesium sulfate. Evaporation of the solvents under vacuum afforded the levorotatory {$[\alpha]_D^{23} = -4.2$ (*c* 1.2, $CHCl_3$); {lit.[27] = −7.24 (*c* 2.3, $CHCl_3$)} acetate of **10** that was analyzed by GC using a β-DEX 120 column at 140 °C. $t_{R(R)} = 28.4$ min, $t_{R(S)} = 31.7$ min.

**4.5.2.2. (*S*)-2-Hydroxy-2-(2-methoxyphenyl)acetonitrile.** According to the general procedure described above, freshly distilled 2-methoxybenzaldehyde (82 μl, 0.67 mmol) and cyanotrimethylsilane (0.20 ml, 1.47 mmol) were added to a cold (−60 °C), stirred solution of **6aB** (60 mg, 0.15 mmol) and of titanium tetra(isopropoxide) (40 μl, 0.13 mmol) in anhydrous dichloromethane (1.5 ml). After 70 h of stirring, work-up and purification, the title compound (66 mg) was isolated in 60% yield and with a 80:20 er (determined by $^{19}F$ NMR of the corresponding Mosher ester). $[\alpha]_D^{23} = -23.6$ (*c* 1.40, $CHCl_3$). {lit:[29] $[\alpha]_D$((*S*), 87:23 er) = −23.8 (*c* 3.05, $CHCl_3$)}.

**4.5.2.3. (*S*)-2-Hydroxy-2-(3-methoxyphenyl)acetonitrile.** According to the general procedure described above, freshly distilled 3-methoxybenzaldehyde (80 μl, 0.67 mmol) and cyanotrimethylsilane (0.20 ml, 1.47 mmol) were added to a cold (−60 °C), stirred solution of **6aB** (60 mg, 0.15 mmol) and of titanium tetra(isopropoxide) (40 μl, 0.13 mmol) in anhydrous dichloromethane (1.5 ml). After 70 h of stirring, work-up and purification, the title compound (84 mg) was isolated in 85% yield and with a 70:30 er (determined by $^{19}F$ NMR of the corresponding Mosher ester). $[\alpha]_D^{23} = -14.9$ (*c* 1.40, $CHCl_3$). {lit:[3b] $[\alpha]_D$ ((*R*), 78:22 er) = +22.8 (*c* 1.5, $CHCl_3$)}.

**4.5.2.4. (*S*)-2-Hydroxy-2-(4-methoxyphenyl)acetonitrile.** According to the general procedure described above, freshly distilled 4-methoxybenzaldehyde (0.13 ml, 1.07 mmol) and cyanotrimethylsilane (0.31 ml, 2.35 mmol) were added to a cold (−60 °C), stirred solution of **6aB** (95 mg, 0.23 mmol) and of titanium tetra(isopropoxide) (60 μl, 0.21 mmol) in anhydrous dichloromethane (2.5 ml). After 63 h of stirring, work-up and purification, the title compound (82 mg) was isolated in 47% yield and with a 62:38 er (determined by $^{19}F$ NMR of the corresponding Mosher ester). $[\alpha]_D^{23} = -21.7$ (*c* 1.00, $CHCl_3$). {lit:[29] $[\alpha]_D$ ((*S*), 92:8 er) = −38.3 (*c* 1.86, $CHCl_3$)}.

**4.5.2.5. (*S*)-2-Hydroxy-2-(4-methylphenyl)acetonitrile.** According to the general procedure described above, freshly distilled 4-methylbenzaldehyde (78 μl, 0.66 mmol) and cyanotrimethylsilane (0.19 ml, 2.35 mmol) were added to a cold (−60 °C), stirred solution of **6aB** (59 mg, 0.14 mmol) and of titanium tetra(isopropoxide) (40 μl, 0.13 mmol) in anhydrous dichloromethane (1.5 ml). After 64 h of stirring, work-up and purification, the title compound (67 mg) was isolated in 69% yield and with a 82:18 er (determined by $^{19}$F NMR of the corresponding Mosher ester). $[\alpha]_D^{23} = -35.2$ (*c* 1.70, $CHCl_3$). {lit:[3b] $[\alpha]_D$ ((*R*), 85:15 er) = +36.4 (*c* 1.1, $CHCl_3$)}.

**4.5.2.6. (*S*)-2-Hydroxy-2-(4-cyanophenyl)acetonitrile.** According to the general procedure described above, a solution of 4-cyanobenzaldehyde (96 mg, 0.73 mmol) in anhydrous dichloromethane (0.5 ml) and cyanotrimethylsilane (0.21 ml, 1.61 mmol) was added to a cold (−60 °C), stirred solution of **6aB** (65 mg, 0.16 mmol) and of titanium tetra(isopropoxide) (50 μl, 0.15 mmol) in anhydrous dichloromethane (1.5 ml). After 64 h of stirring, work-up and purification, the title compound (89 mg) was isolated in 77% yield and with a 58:42 er (determined by $^{19}$F NMR of the corresponding Mosher ester). $[\alpha]_D^{23} = -11.2$ (*c* 0.91, $CHCl_3$). {lit:[29] $[\alpha]_D$ ((*S*), 65:35 er) = −11.2 (*c* 1.00, $CHCl_3$)}.

**4.5.2.7. (*S*)-2-Hydroxy-2-(2-fluorophenyl)acetonitrile.** According to the general procedure described above, freshly distilled 2-fluorobenzaldehyde (76 μl, 0.72 mmol) and cyanotrimethylsilane (0.20 ml, 1.58 mmol) were added to a cold (−60 °C), stirred solution of **6aB** (65 mg, 0.16 mmol) and of titanium tetra(isopropoxide) (50 μl, 0.15 mmol) in anhydrous dichloromethane (1.5 ml). After 64 h of stirring, work-up and purification, the title compound (76 mg) was isolated in 70% yield and with a 73:27 er (determined by $^{19}$F NMR of the corresponding Mosher ester). $[\alpha]_D^{23} = -11.6$ (*c* 0.93, $CHCl_3$). {lit:[30] $[\alpha]_D$ ((*R*), 92:8 er) = +21.8 (*c* 3.6, $CHCl_3$)}.

**4.5.2.8. (*S*)-2-Hydroxy-(*E*)-3-pentenenitrile.** According to the general procedure described above, freshly distilled (*E*)-crotonaldehyde (76 μl, 0.86 mmol) and cyanotrimethylsilane (0.25 ml, 1.89 mmol) were added to a cold (−60 °C), stirred solution of **6aB** (74 mg, 0.19 mmol) and of titanium tetra(isopropoxide) (50 μl, 0.15 mmol) in anhydrous dichloromethane (2.0 ml). After 41 h of stirring, work-up and purification, the title compound (63 mg) was isolated in 76% yield and with a 73:27 er (determined by $^{19}$F NMR of the corresponding Mosher ester). $[\alpha]_D^{23} = +11.1$ (*c* 0.21, $CHCl_3$). {lit:[3b] $[\alpha]_D$ ((*R*), 94:6 er) = −35.7 (*c* 0.3, $CHCl_3$)}.

**4.5.2.9. (*S*)-2-Hydroxy-3-methyl-3-butenenitrile.** According to the general procedure described above, freshly distilled methacrolein (69 μl, 0.83 mmol) and cyanotrimethylsilane (0.24 ml, 1.83 mmol) were added to a cold (−60 °C), stirred solution of **6aB** (74 mg, 0.19 mmol) and of titanium tetra(isopropoxide) (50 μl, 0.15 mmol) in anhydrous dichloromethane (2.0 ml). After 41 h of stirring, work-up and purification, the title compound (51 mg) was isolated in 63% yield and with a 81:19 er (determined by $^{19}$F NMR of the corresponding Mosher ester). $[\alpha]_D^{23} = -7.8$ (*c* 0.82, $CHCl_3$). {lit:[3b] $[\alpha]_D$ ((*R*), 92:8 er) = +5.7 (*c* 1.3, $CHCl_3$)}.

### 4.5.3. Enantioselective cyanotrimethylsilane addition to aldehydes catalyzed by the titanium isopropoxide complex of imine 6bB.

**4.5.3.1. (*S*)-2-Hydroxy-2-(2-methoxyphenyl)acetonitrile.** According to the general procedure described above, freshly distilled 2-methoxybenzaldehyde (91 μl, 0.75 mmol) and cyanotrimethylsilane (0.22 ml, 1.65 mmol) were added to a cold (−60 °C), stirred solution of **6bB** (69 mg, 0.15 mmol) and of titanium tetra(isopropoxide) (50 μl, 0.14 mmol) in anhydrous dichloromethane (1.5 ml). After 62 h of stirring, work-up and purification, the title compound (104 mg) was isolated in 85% yield and with a 77:23 er (determined by $^{19}$F NMR of the corresponding Mosher ester).

**4.5.3.2. (*S*)-2-Hydroxy-2-(4-methylphenyl)acetonitrile.** According to the general procedure described above, freshly distilled 4-methylbenzaldehyde (82 μl, 0.69 mmol) and cyanotrimethylsilane (0.20 ml, 1.52 mmol) were added to a cold (−60 °C), stirred solution of **6bB** (64 mg, 0.15 mmol) and of titanium tetra(isopropoxide) (40 μl, 0.13 mmol) in anhydrous dichloromethane (1.5 ml). After 62 h of stirring, work-up and purification, the title compound (56 mg) was isolated in 55% yield and with a 79:21 er (determined by $^{19}$F NMR of the corresponding Mosher ester).

## Note added in proof

Very recently, tridentate Schiff base ligands arising from enantiopure epoxyalcohols have been prepared and evaluated in the titanium-catalyzed trimethylsilyl cyanide addition to aldehydes: Rodríguez, B.; Pastó, M.; Jimeno, C.; Pericàs, M. A. *Tetrahedron: Asymmetry* **2006**, *17*, 151–160.

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