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Influence of the metal and chiral diamine on metal(II)salen catalysed, asymmetric synthesis of α-methyl α-amino acids

Yuri N. Belokon,[b] Jose Fuentes,[a] Michael North[a,*] and Jonathan W. Steed[a]

[a]*Department of Chemistry, King's College London, Strand, London WC2R 2LS, UK*
[b]*A.N. Nesmeyanov Institute of Organo-Element Compounds, Russian Academy of Sciences, Vavilov 28, 117813 Moscow, Russian Federation*

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Abstract—The influence of the metal ion and chiral diamine used to form a metal(salen) complex on the catalytic activity of the complex in the asymmetric benzylation of an alanine enolate was investigated. Only metal ions which could form square-planar complexes gave catalytically active complexes, and best results were obtained with metal ions from the first row of transition metals, particularly copper(II) and cobalt(II). Salen ligands derived from acyclic, chiral 1,2-diamines were found to generate poor catalysts, an effect which seems to correlate with the ability of the substituents within the diamine to adopt a conformation in which they are *anti* to one another. Complexes derived from a variety of 5- and 6-membered cyclic 1,2-diamines did form active catalysts, but the enantioselectivity was always far lower than that of the parent cyclohexane-1,2-diamine derived complex.

1. Introduction

There is currently considerable interest in the asymmetric synthesis of α-amino acids and α,α-disubstituted amino acids by the alkylation of a prochiral enolate derived from glycine or an α-substituted amino acid in the presence of a chiral catalyst. Most of this work is carried out under phase-transfer conditions, with the chiral catalyst acting as a phase transfer catalyst.[1]

The first results in this area came from the group of O'Donnell and used quaternary ammonium salts derived from cinchona alkaloids to catalyse the asymmetric alkylation of a glycine derived enolate, leading to α-amino acids with moderate enantiomeric excesses.[2] The main problem with this chemistry was the inadequate enantioselectivity, but recently the groups of Lygo[3] and Corey,[4] have shown that the use of a 9-anthracenylmethyl group to quaternize the cinchona alkaloid resulted in a catalyst that exhibited significantly enhanced enantioselectivity, and allowed the synthesis of α-amino acids with >95% enantiomeric excess.[5] Attempts to extend this chemistry to enolates derived from other amino acids, thus allowing the synthesis of α,α-disubstituted amino acids were less successful due to the lower enantioselectivity observed.[6] The same catalyst can also be used to catalyse the alkylation of other enolates,[7] Michael additions,[8,9] aldol reactions,[10] and enone epoxidations.[11] It can also be used in conjunction with achiral palladium complexes to induce the asymmetric allylation of enolates.[12] Recently, polymer supported[9,13] and oligomeric[14] versions of the cinchona derived phase transfer catalysts have been developed and used for asymmetric amino acid synthesis. The catalysts have also been used under micellar conditions.[15]

Synthetic quaternary ammonium salts derived from binaphthol have been developed by Maruoka.[16] These salts have been shown to act as asymmetric phase transfer catalysts for both the alkylation and dialkylation (with two different alkylating agents) of a glycine derived imine, leading to both α-amino acids and α,α-disubstituted amino acids with excellent enantiomeric excesses. The asymmetric alkylation of β-keto-esters[17] and aldol reactions are also catalysed by these chiral ammonium salts.[18] Other groups have also investigated the use of synthetic phase transfer catalysts derived from ammonium[19] or guanidinium[20] salts and crown ethers.[21]

All the above work is based on the use of purely organic catalysts as asymmetric phase transfer catalysts. It was not until 1998 that Belokon' and Kagan first demonstrated that a metal complex could act as an asymmetric phase transfer catalyst. The sodium salt of TADDOL was found to catalyse the alkylation of alanine derivatives leading to α-methyl-α-amino acids with up to 82% enantiomeric excess.[22] It was subsequently shown that the sodium salts of both NOBIN[23] and BINOLAM[24] could act as asymmetric phase transfer catalysts for the same reaction.

Keywords: Phase-transfer-catalysis; α-Amino acid; Alkylation; Diamine.
* Corresponding author. Tel.: +44-207-848-1164; fax: +44-870-131-3783; e-mail address: michael.north@kcl.ac.uk

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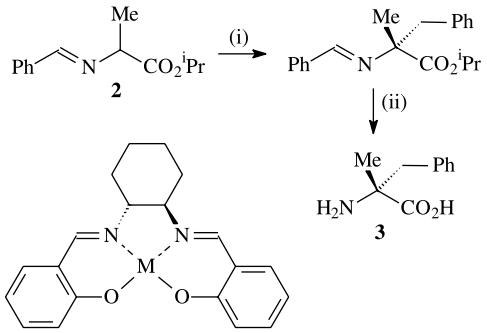
Chiral transition metal complexes have been used to catalyse a wide range of asymmetric transformations, and we have shown that they can be used to catalyse the asymmetric alkylation of amino acid enolates under phase transfer conditions. In 1999, we reported that nickel(II)salen complex **1a** (10 mol%) would catalyse the asymmetric benzylation of alanine enolate **2** leading to α-methyl phenylalanine **3** (Scheme 1) with 30% enantiomeric excess.[25] The corresponding copper(II)salen complex **1b** was found to be a far more effective catalyst and 2 mol% of this complex was sufficient to catalyse the formation of compound **3** with 88% enantiomeric excess. Complex **1b** also catalysed the asymmetric alkylation of compound **2** with other alkyl halides, giving α-methyl α-amino acids with 75–90% enantiomeric excess.[25] These reactions are carried out under solid–liquid phase transfer conditions with solid sodium hydroxide as the base, and both enantiomers of catalyst **1b** are equally readily available, thus allowing the synthesis of either enantiomer of an α-methyl α-amino acid.



1a: M = Ni **1b:** M = Cu
1c: M = Mn **1d:** M = Fe
1e: M = Co **1f:** M = Zn
1g: M = Rh **1h:** M = Pd
1i: M = Pt **1j:** M = Co-I
1k: M = Co^{+} PF_6^{-}
1l: M = Co-Na

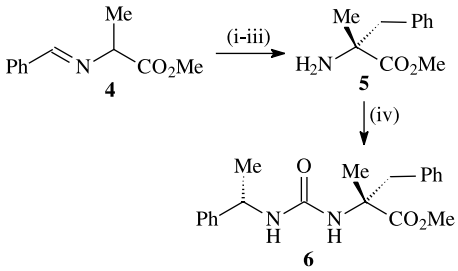
Scheme 1. Reagents: (i) **1a**,**b** (2–10 mol%)/NaOH (solid)/BnBr; (ii) H_3O^{+}/Δ.

In subsequent work, we have studied the effect that substituents on the aromatic rings of catalyst **1b** have on the enantioselectivity of the catalyst,[25,26] and optimized the reaction conditions and the structure of the imine within substrate **2**.[26] We have also demonstrated that under appropriate reaction conditions, it is possible to use the readily available methyl ester analogue **4** of substrate **2**.[27] Most recently, we have shown that the chemistry shown in Scheme 1 can be applied to amino acids other than alanine, thus allowing the synthesis of a range of non-racemic α,α-disubstituted α-amino acids.[28]

In this paper, we report the results of a study aimed at better understanding the influence of various factors on the enantioselectivity of this reaction. In particular, we have prepared catalysts from a range of transition metals and from both cyclic and acyclic chiral diamines.

2. Results and discussion

The first factor that we studied was the effect of the central transition metal. Since the nickel(II) and copper(II) complexes **1a**,**b** had already been found to be catalytically active,[25] a range of other (salen)M^{2+} complexes were prepared and tested for catalytic activity in the model reaction shown in Scheme 2. The substrate **4** used in this work does not have the optimized *para*-chlorobenzylidene imine as this optimisation had not been discovered at the start of this project.[26] Substrate **4** was subsequently used throughout the work described in this paper to allow the results to be compared. The enantiomeric excess of the α-methyl-phenylalanine methyl ester product **5** was determined by reaction with an excess of (*S*)-α-methyl benzylisocyanate to give a pair of diastereomeric ureas **6**. The diastereotopic benzylic protons ($PhCH_2$) of compounds **6** give rise to a series of four well resolved doublets in the ^1H NMR spectrum. Integration of these doublets allowed the diastereomeric excess of ureas **6** and hence the enantiomeric excess of amine **5** to be determined once the conversion of **5** to **6** had gone to completion.



Scheme 2. Reagents: (i) **1a-l** (2 mol%)/NaOH (solid)/BnBr; (ii) MeOH/AcCl; (iii) SiO_2; (*S*)-PhCH(Me)N=C=O.

Initially, first row transition metal complexes were studied. Complexes **1c-e** could be prepared and isolated by reaction of the salen ligand with the appropriate metal acetate. However, all attempts to isolate complex **1f** using zinc bromide or diethylzinc (in thf, toluene or hexane) as the metal source were completely unsuccessful.[29] Therefore, this complex was prepared in situ from the salen ligand and diethylzinc. Manganese(II)salen[30,31] and iron(II)salen[31,32] complexes **1c** and **1d** were found to be catalytically inactive (Table 1: entries 1 and 2). These complexes would not be

Table 1. The effect of the metal in complexes **1** on enantioselectivity[a]

Entry	Metal	Complex	Yield (%)	Enantioselectivity (%)[b]
1	Mn^{2+}	**1c**	15	1
2	Fe^{2+}	**1d**	34	3
3	Co^{2+}	**1e**	83	80
4[c]	Ni^{2+}	**1a**	34	30
5	Cu^{2+}	**1b**	91	81
6	Zn^{2+}	**1f**	39	1
7	Rh^{2+}	**1g**	92	14
8	Pd^{2+}	**1h**	56	1
9	Pt^{2+}	**1i**	55	0
10	Co^{3+}	**1j**	46	7
11	Co^{3+}	**1k**	66	0
12	Co^{1+}	**1l**	21	0

[a] Reactions were carried out under the conditions described in Scheme 2.
[b] The error in this measurement is estimated to be ±3%.
[c] Data taken from Ref. 25 for substrate **2** and using 10 mol% of complex **1a**.

expected to be square-planar. The 15–34% yield of essentially racemic compound **5** obtained in these reactions presumably arises from an uncatalysed background reaction as we have previously shown that even in the absence of any catalyst, racemic α-methyl-phenylalanine is formed under the reaction conditions.[33]

Cobalt(II)salen complex[34] **1e** was found to be as active a catalyst as the copper(II)salen complex **1b** (Table 1: entries 3 and 5), which is the best previously known salen complex for this reaction. To further investigate the relationship between complexes **1e** and **1b**, the X-ray structure[35] of complex **1e** was obtained for comparison with the known structure of complex **1b**.[36] The structure of complex **1e** is shown in Figure 1, and as expected the complex was found to be square-planar.[37] Comparison of the bond lengths and bond angles within the X-ray structures of complexes **1b** and **1e** revealed that the structures were essentially superimposable. The asymmetric unit of compound **1e** contains two essentially identical, independent, homochiral molecules that form discrete, face-to-face dimers in the solid state with a Co···Co distance of 3.326(1) Å. Symmetry-related dimers interact via CH···O hydrogen bonds.

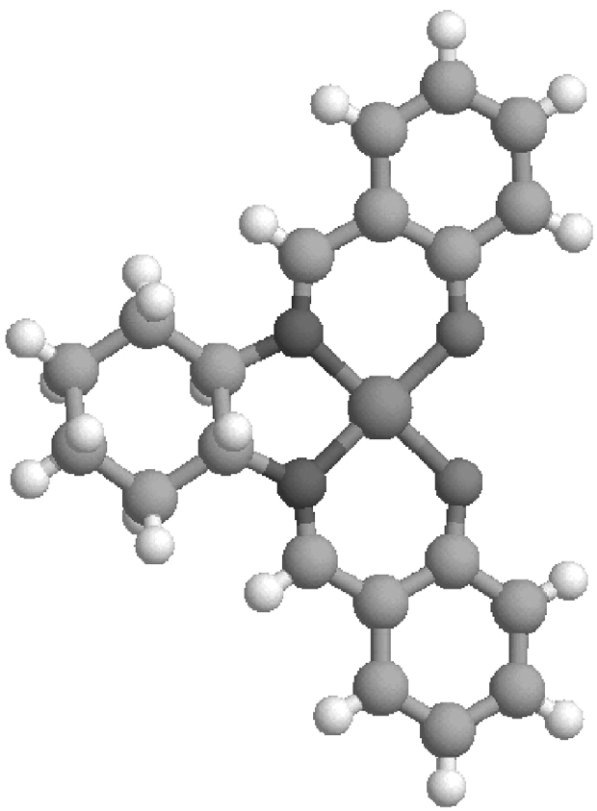


Figure 1. The X-ray structure of complex **1e**.

In situ prepared zinc(II)salen complex **1f** did not give an active catalyst (Table 1: entry 6). A survey of the Cambridge X-ray database revealed that Zn(salen) complexes tend not to be four-coordinate in the solid state. Instead, trigonal bipyramidal, five-coordinate complexes are formed by intermolecular association involving the salen oxygen atoms.[29]

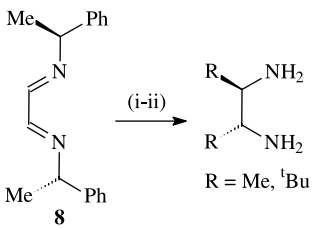
The results from the first row of transition metal M^{2+}(salen) complexes clearly show that a square-planar complex is essential for catalytic activity. It is also notable that complexes **1b** and **1e** which are both paramagnetic ($17e^-$ and $15e^-$ systems respectively) are significantly more active than the nickel(II)salen complex **1a** which is diamagnetic ($16e^-$ system), despite the fact that all three complexes are known to be square-planar.[36,38] This suggests that the mechanism may involve a single electron transfer process.

Three other M^{2+}(salen) complexes were prepared from group 9/10 metals in the second and third rows of transition metals. Rh(II)salen complex **1g** was prepared from rhodium(II) acetate and was found to be catalytically active, but gave product **5** with only 14% enantiomeric excess (Table 1: entry 7). An attempt to increase the enantioselectivity by using 10 mol% of catalyst **1g** was unsuccessful, giving product **5** with an unchanged 13% enantiomeric excess. Interestingly however, complex **1g** gave the (*S*)-enantiomer of compound **5** as the major product, whilst every other complex tested gave predominantly the (*R*)-enantiomer of the product. The reason for this difference in enantioselectivity is not known, but it may be relevant that rhodium(II)salen complexes are known to be bimetallic with a Rh–Rh bond.[39] Palladium(II)salen complex[40,41] **1h** (prepared from palladium(II) acetate) and platinum(II)salen complex[41,42] **1i** (prepared from platinum(II) chloride) were both catalytically inactive, giving racemic product **5** (Table 1: entries 8 and 9). These three results again show the superiority of complexes from group 9 over complexes from group 10 as asymmetric phase transfer catalysts. Complexes **1h** and **1i** were also tested as catalysts in conjunction with potassium hydroxide rather than sodium hydroxide as the base. Our model to explain the asymmetric induction in these reactions[25,28] envisages the formation of a bimetallic complex, with the alkali metal coordinated between the oxygen atoms of the salen ligand. Increasing the size of the transition metal within the salen complex was anticipated to increase the distance between these two oxygen atoms so that they would prefer to coordinate to a larger alkali metal. However, palladium complex **1h** gave just a 13% yield of racemic **5** under these conditions, and platinum complex **1i** gave no product. As a result of these results we concluded that only first row transition metal complexes formed useful catalysts and our subsequent work was concentrated on these species.

All of the above work was carried out with metal ions in the +2 oxidation state. Two Co(III) complexes were also prepared and tested. Iodo complex **1j** was prepared by treatment of Co(II)salen complex **1e** with iodine in dichloromethane as reported for the preparation of other iodocobalt(III)salen complexes.[43] Complex **1k** was obtained by treatment of complex **1e** with ferrocinium hexafluorophosphate in acetonitrile.[44] By analogy with the known X-ray structures[45] of other 5-coordinate Co(III)salen complexes, complex **1j** is expected to have a square-based pyramidal structure with the salen ligand forming the square base. Complex **1k**, with a non-coordinating anion will however be square-planar.[46] Both of these complexes displayed little or no catalytic activity (Table 1, entries 10 and 11).

Finally, the use of salen complexes of metals in the +1 oxidation state was investigated. Attempts to prepare the Cu(I)salen complex from copper(I) acetate and the salen ligand were unsuccessful as only the Cu(II)salen complex **1b** could be isolated from these reactions. The preparation of Co(I)salen complexes by the reduction of the corresponding Co(II)salen complexes using sodium amalgam is however a well known process.[47] Cobalt(I)salen complexes are known to be square-planar and to be capable of coordinating a sodium ion between the two phenolic oxygens.[48] Therefore, complex **1e** was treated with sodium amalgam in thf to generate the corresponding Co(I)salen complex[34] **1l** This complex was used without purification due to the known sensitivity of Co(I)salen complexes to air, but was not found to display any catalytic activity. Reactions involving complex **1l** were far less clean than those involving complexes **1b**,**e**, produced only a small amount of product and gave only racemic product (Table 1: entry 12).

Having determined that Co^{2+} and Cu^{2+} were the optimal metals, the structure of the diamine was next investigated. Four complexes (**7a**-**d**) derived from three C_2-symmetric acyclic diamines with different steric properties were prepared. The (*R*,*R*)-1,2-diphenyl-ethane-1,2-diamine needed for the preparation of complexes **7b**,**c** was commercially available[49,50] and the corresponding diamines needed for the preparation of complexes **7a**,**d** were prepared by a literature route involving the addition of the appropriate Grignard reagent to imine **8** (Scheme 3).[51,52] As the results in Table 2 show, all of these ligands formed copper(II) complexes which were less catalytically active than complex **1b**. The most active of these complex was **7a** (Table 2: entry 1) derived from (*R*,*R*)-butane-2.3-diamine, and complex **7d** was catalytically inactive (Table 2: entry 4) as indicated by the absence of any enantioselectivity. The chemical yield in this case is probably due to the uncatalysed background reaction.[33]



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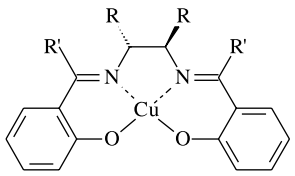
Scheme 3. Reagents: (i) RMgBr then H_3O^+; (ii) $Pd(OH)_2/HCO_2NH_4$/EtOH/Δ.

Table 2. The effect of acyclic diamines on catalytic activity[a]

Entry	Complex	Yield (%)	Enantioselectivity (%)
1	**7a**	73	36
2	**7b**	21	25
3	**7c**	54	5
4	**7d**	27	0

[a] Reactions were carried out under the conditions described in Scheme 2.



7a: R = Me; R' = H
7b: R = Ph; R' = H
7c: R = Ph; R' = Ph
7d: R = ^{t}Bu; R' = H

The R-groups in complexes **7a**-**d** can adopt locations which are either *gauche*- or *anti*- to one another as shown by the Newman projections in Figure 2. Cyclic diamines (such as (*R*,*R*)-cyclohexane-1,2-diamine) can only adopt the *gauche*-conformation, but for acyclic diamines the *anti*-conformation is generally thermodynamically more stable as it minimizes steric repulsions between the R-groups. The X-ray structure of the square-planar cobalt(II) complex derived from ligand **7a** has previously been determined[53] and shows that the methyl groups are indeed *anti* to one another.

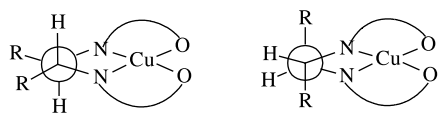


Figure 2. *gauche*- and *anti*-Conformations of salen complexes.

Complex **7b** derived from (*R*,*R*)-1,2-diphenyl-ethane-1,2-diamine was less active than complex **7a** (Table 2: compare entries 1 and 2). X-ray structures of square-planar nickel(II)salen complexes derived from this ligand have been reported in which the phenyl rings are *gauche*- or *anti*- to one another.[54,55] In contrast, the X-ray structure of the square-planar cobalt(II) complex analogous to **7c** shows that the phenyl rings on the ethylenediamine unit are in this case locked into the *anti*-conformation to avoid steric interactions with the two additional phenyl rings on the imine part of the ligand.[56] Complex **7c** was found exhibit only a very low enantioselectivity (Table 2: entry 3).

To investigate why complex **7d** was totally inactive, an X-ray structure analysis of this complex was undertaken.[57] This compound also contains two independent molecules in the asymmetric unit, although a face-to-face interaction as in **1e** is precluded by the bulk of the *tert*-butyl substituents. Intermolecular association is again via CH···O interactions and, as in **1e**, the geometry at both independent Cu(II) ions is square-planar. The structure also revealed (Fig. 3) that the *tert*-butyl groups adopted *anti*-positions on the five-membered chelate ring to minimize steric repulsions between them. The effect of this is that the *tert*-butyl groups extend over and below the copper ion as shown in the space filling model illustrated in Figure 4. This would prevent substrate **4** from complexing to the copper ion, and hence prevent complex **7d** from exhibiting any catalytic activity.

The results obtained with complexes **7a**-**d** strongly suggest that for a complex to be catalytically active, the substituents

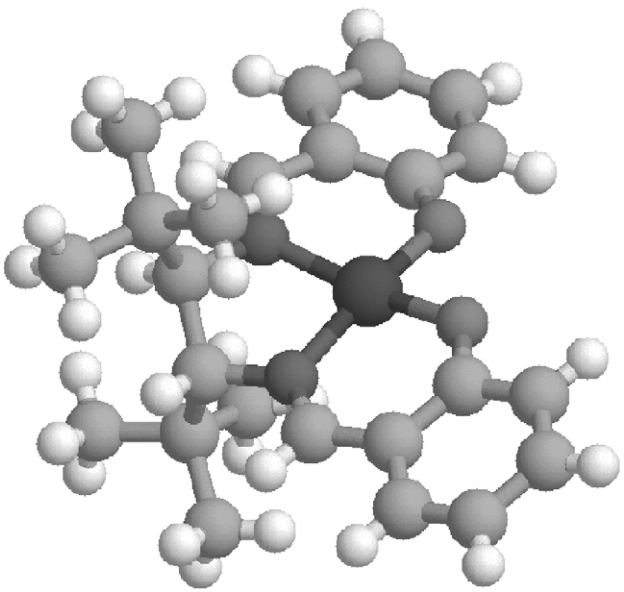


Figure 3. The X-ray structure of complex **7d**.

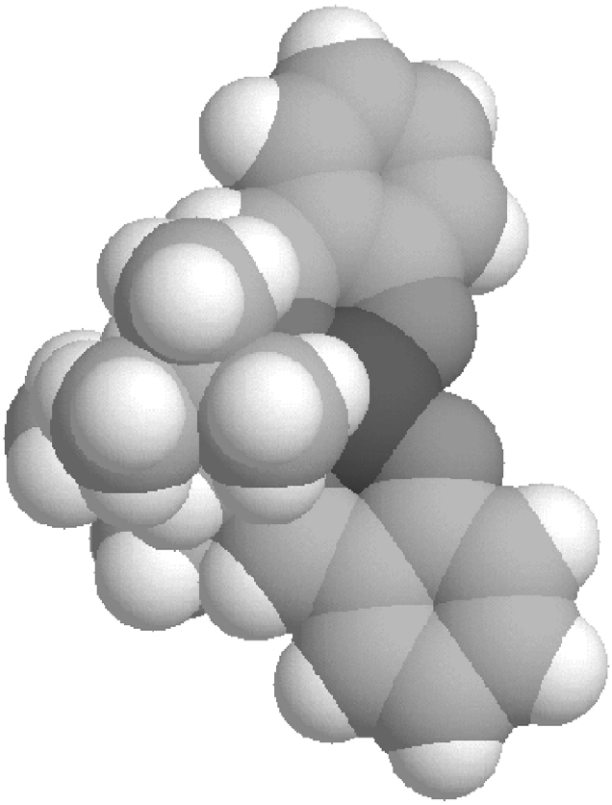
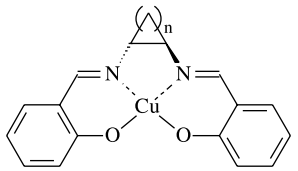


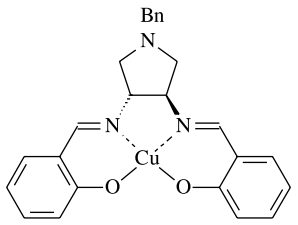
Figure 4. A space-filling model of complex **7d** showing the *tert*-butyl group protruding over the copper ion.

on the ethylenediamine part of the salen ligand must adopt a *gauche*-conformation. Complexes **7c**,**d** where this is not possible are inactive, whilst complexes **7a**,**b** which are expected to exist as an equilibrium mixture of *anti*- and *gauche*-conformations are active. Complex **7a** with small methyl substituents would be expected to have a greater percentage of molecules in the *gauche*-conformation than complex **7b** and hence to be more catalytically active. This matches the observed results.

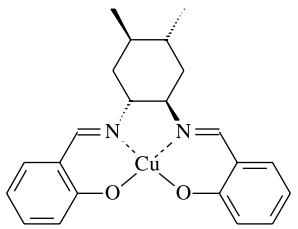
To restrict the ligands to a *gauche*-conformation whilst varying the size of the substituents within the ethylenediamine unit, a series of complexes derived from cyclic diamines was prepared. First, the systematic replacement of the cyclohexyl ring within catalyst **1b** with cyclopropyl, cyclobutyl- and cyclopentyl- rings to give complexes **9a-c** was investigated. The enantiomerically pure diamines required for this work were prepared by literature procedures.[58,59] The catalytic activity observed which should be with each of these complexes is presented in Table 3.



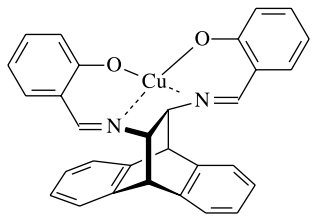
9a: n = 1
9b: n = 2
9c: n = 3



9d



9e



9f

Table 3. The effect of cyclic diamines on catalytic activity[a]

Entry	Complex	Yield (%)	Enantioselectivity (%)
1	**9a**	69	0
2	**9b**	60	0
3	**9c**	84	25
4	**9d**	59	37
5	**9e**	52	32
6	**9f**	85	32

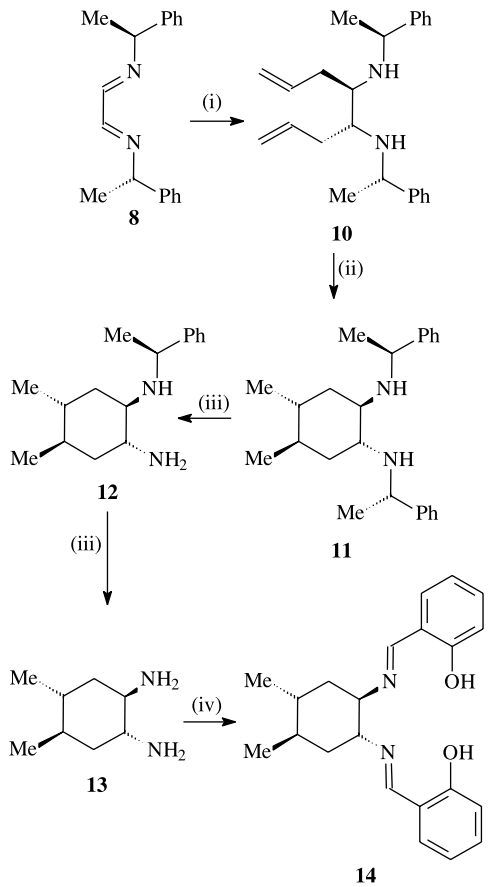
[a] Reactions were carried out under the conditions described in Scheme 2.

In the case of compounds **9a** and **9b**, whilst we were able to prepare the required enantiomerically pure 1,2-diamines, and the salen ligand, it was not possible to isolate the copper

complexes **9a**,**b**. It may be that the torsional angles around the 3- or 4-membered ring prevent the heteroatoms within the salen ligand from adopting suitable locations to form a square-planar complex. However, the crude product obtained by mixing the ligand and copper(II) bromide was tested, though no enantioselectivity was observed (Table 3: entries 1 and 2).

Cyclopentane derivative **9c** was prepared by the literature route,[59] and the corresponding *N*-benzyl pyrrolidine derived ligand was also prepared by a modification of the literature procedure.[60] Thus, *N*-benzyl-(3*S*,4*S*)-3,4-dihydroxypyrrolidine was prepared from (*R*,*R*)-tartaric acid. However, in our hands the conversion of this diol into the corresponding bis-azide by a Mitsunobu procedure[60] was problematic. In contrast, conversion of the diol to the corresponding bis-mesylate[61] and then conversion to the bis-azide using the procedure reported for 1,2-diazidocyclopentane[62] worked smoothly. Subsequent reduction of the bis-azide to the corresponding diamine, formation of the salen ligand and synthesis and isolation of complex **9d** occurred as expected. However, whilst complexes **9c** and **9d** did form active catalysts (Table 3: entries 3 and 4), the asymmetric induction observed with them was only about one third that observed with the corresponding cyclohexane derivative **1b**.

The 1,2-diamino-4,5-dimethylcyclohexane required for the synthesis of complex **9e** was prepared by a modification of a literature procedure. Addition of allylmagnesium bromide to imine **8** gave diamine[63] **10** as shown in Scheme 4. Treatment of diamine **10** with butylmagnesium chloride and catalytic bis-(cyclopentadienyl)zirconium dichloride resulted in reductive cyclisation to cyclohexane derivative[64] **11**. However, the order of addition of the reagents was found to be critical to control the stereochemistry of the cyclisation. Only when the butylmagnesium chloride and (cyclopentadienyl)zirconium dichloride were premixed followed by addition of diamine **10** was compound **11** obtained as the major stereoisomer. In our hands, all other conditions gave unreacted starting material. Hydrogenolysis of compound **11** was carried out using 20% $Pd(OH)_2$ on carbon at three atmospheres pressure of hydrogen for 24 h, and gave the partially deprotected compound **12**. Compound **12** was resubjected to the same hydrogenolysis conditions to give diamine **13**. Treatment of diamine **13** with salicylaldehyde gave the required salen ligand **14** which could be complexed to copper to give complex **9e**.



Scheme 4. Reagents: (i) allylMgBr then H_3O^+; (ii) BuMgBr (5 equiv.)/Cp_2ZrCl_2 (20 mol%); (iii) $Pd(OH)_2/C/H_2$, 3 atm; (iv) salicylaldehyde.

In complex **9e**, the formation of the chelate forces both amino groups to adopt equatorial positions on the cyclohexane ring, and this in turn means that both methyl groups are in axial positions. It was hoped that the methyl groups would be able to interact with a coordinated substrate, but disappointingly, complex **9e** only exhibited 32% enantioselectivity (Table 3: entry 5), compared to 81% for complex **1b** (Table 1: entry 5) which does not have the two methyl groups on the cyclohexane ring. The acyclic diamine derived ligands **7a**-**d** demonstrated that axial groups on the carbon adjacent to the nitrogen atoms were detrimental to the enantioselectivity of the catalysts. The result obtained with complex **9e** suggests that this effect extends all the way across the cyclohexane ring.

The enantiomerically pure anthracene derived diamine required for the preparation of complex **9f** was prepared from anthracene and fumaric acid by the literature route.[65] Condensation of this diamine with salicylaldehyde gave the required salen ligand[49] which could be complexed to copper to give complex **9f**. In complex **9f**, the cyclohexane ring is forced to adopt a boat conformation, and this was found to have a detrimental effect on the enantioselectivity of the catalyst (Table 3: entry 6) as the complex converted compound **4** into product **5** with just 32% enantiomeric excess.

3. Conclusions

Of the metal(salen) complexes studied as asymmetric phase transfer catalysts in this work, only the Cu(II) and Co(II) complexes were found to give high levels of asymmetric induction. These two complexes are both square-planar and paramagnetic. Variation of the original cyclohexane-1,2-diamine derived salen ligand did not increase the asymmetric induction. Complexes derived from acyclic diamines exist predominantly in an *anti*-conformation which may account for their reduced catalytic activity. It was not possible to isolate copper complexes of cyclopropyldiamine and cyclobutyldiamine derived ligands. The cyclopentyldiamine and cyclohexyldiamine derived ligands studied, were catalytically active, but gave lower asymmetric

induction than the parent cyclohexane diamine derived complex.

4. Experimental

4.1. General

^{1}H NMR, ^{13}C NMR, ^{19}F NMR and ^{31}P NMR spectra were recorded on a Bruker Avance 360 Spectrometer, (^{1}H 360 MHz, ^{13}C 90 MHz, ^{19}F 338 MHz and ^{31}P 145 MHz). The solvent for a particular spectrum is given in parentheses. ^{1}H and ^{13}C NMR Spectra were referenced to TMS and chemical-shift (δ) values, expressed in parts per million (ppm), are reported downfield of TMS. Chemical-shift values for ^{31}P spectra are reported downfield of phosphoric acid, and chemical-shift values for ^{19}F spectra are relative to $CFCl_3$. The multiplicity of signals is reported as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br) or a combination of any of these. For ^{13}C NMR spectra, the peak assignments were made with the assistance of DEPT experiments.

Infrared spectra were recorded on a Perkin–Elmer FT-IR Paragon 1000 spectrometer, as a thin film between NaCl plates in the reported solvent, or as KBr disks. The characteristic absorption is reported as broad (br), strong (s), medium (m) or weak (w). Low and high resolution mass spectra were recorded at the EPSRC national service at the University of Wales, Swansea, or on a Bruker Apex III FTMS or Jeol AX505W spectrometer within the chemistry department at King's College. The sample was ionized by electron ionization (EI), chemical ionisation (CI) fast atom bombardment (FAB) or electrospray ionization (ESI). The major fragment ions are reported and only the molecular ions are assigned.

Optical rotations were recorded on a Perkin–Elmer 343 polarimeter in a thermostated cell of length 1 dm at 20 °C using the sodium D-line, and a suitable solvent that is reported along with the concentration (in g/100 ml). Melting points were determined with a Buchi Melting Point apparatus N° 520092 and are uncorrected. Elemental analyses were performed by the London School of Pharmacy.

Chromatographic separations were performed with silica gel 60 (230–400 mesh) and thin-layer chromatography was performed on polyester backed sheets coated with silica gel 60 F254, both supplied by Merck. Toluene was distilled from sodium prior to use.

Crystals were mounted on a thin glass fibre using epoxy resin and cooled on the diffractometer to 120 K using an Oxford Cryostream low temperature attachment. Approximate unit cell dimensions were determined by the Nonius Collect program[66] from 5 index frames of width 2° in ϕ using a Nonius ^{Kappa}CCD diffractometer, with a detector to crystal distance of 30 mm. The Collect program was then used to calculate a data collection stratgey to 99.5% completeness for θ=27.5° using a combination of 2° ϕ and ω scans of 10–120 s deg^{-1} exposure time (depending on crystal quality). Crystals were indexed using the DENZO-SMN package[67] and positional data were refined along with diffractometer constants to give the final unit cell parameters. Integration and scaling (DENZO-SMN, Scalepack[67]) resulted in unique data sets corrected for Lorentz and polarisation effects and for the effects of crystal decay and absorption by a combination of averaging of equivalent reflections and an overall volume and scaling correction. Structures were solved using SHELXS-97[68] and developed via alternating least squares cycles and difference Fourier synthesis (SHELXL-97[68]) with the aid of the program XSeed.[69] All non-hydrogen atoms were modelled anisotropically, while hydrogen atoms are assigned an isotropic thermal parameter 1.2 times that of the parent atom (1.5 for terminal atoms) and allowed to ride. All calculations were carried out with IBM compatible PCs.

4.1.1. Manganese(II)salen complex 1c. To a solution of (*R*,*R*)-[*N*,*N*′-bis-(2′-hydroxybenzylidene)]-1,2-diamino-cyclohexane (476 mg, 1.48 mmol) in ethanol (15 ml), was added KOH (166 mg, 2.96 mmol) dissolved in ethanol (4 ml). To the resulting yellow solution was added a suspension of anhydrous manganese acetate (256 mg, 1.48 mmol) in ethanol (4 ml) and the reaction was refluxed at 100–120 °C for 2 h under a nitrogen atmosphere. The solution was allowed to reach room temperature and then concentrated in vacuo. The resulting black solid was taken up with dichloromethane, filtered and evaporated in vacuo to leave a black solid which was recrystallized from dichloromethane/hexane to afford compound **1c** (461 mg, 83%) as black crystals. Mp >250 °C. $[\alpha]_D^{20}=-1233$ (*c* 0.012, $CHCl_3$); ν_{max} (KBr) 3022 (w), 2934 (m), 2859 (w), 1632 (s), 1600 (s) and 1537 cm^{-1} (s); *m*/*z* (ESI) 375 (M^+, 100). Found (ESI) 375.0900 (M^+), $C_{20}H_{20}N_2O_2Mn$ requires 375.0880.

4.1.2. Iron(II)salen complex 1d.[32] (*R*,*R*)-[*N*,*N*′-Bis-(2′-hydroxybenzylidene)]-1,2-diamino-cyclohexane (847 mg, 2.63 mmol) and anhydrous iron(II) acetate (457 mg, 2.63 mmol) were stirred in ethanol (8 ml) at 75 °C for 1 h under a nitrogen atmosphere A dark orange solid precipitated. The mixture was allowed to cool to room temperature and then filtered and washed with hexane under a nitrogen atmosphere. The orange precipitate was purified by suspension in refluxing ethanol under a nitrogen atmosphere, followed by filtration and washing with hexane to give compound **1d** (494 mg, 50%) as an orange solid. Mp >270 °C; $[\alpha]_D^{20}=-714$ (*c* 0.017, $CHCl_3$); ν_{max} (KBr) 3024 (w), 2926 (m), 2855 (w), 1614 (s) and 1539 cm^{-1} (s); *m*/*z* (ESI) 376 (M^+, 100). Found (ESI) 376.0846 (M^+), $C_{20}H_{20}N_2O_2Fe$ requires 376.0869.

4.1.3. Cobalt(II)salen complex 1e.[34] (*R*,*R*)-[*N*,*N*′-Bis-(2′-hydroxybenzylidene)]-1,2-diamino-cyclohexane (1.61 g, 5.0 mmol) and anhydrous cobalt(II) acetate (1.25 g, 5.0 mmol) were stirred in ethanol (16 ml) at 70 °C for 1 h under an argon atmosphere. During this time an orange solid precipitated. The reaction was allowed to cool to room temperature and then filtered and washed with hexane under a nitrogen atmosphere. The orange precipitate was purified by suspension in refluxing ethanol under an argon atmosphere, followed by filtration and washing with hexane to obtain a crimson solid (543 mg, 29%). Crystals suitable for X-ray analysis were obtained by recrystallisation from hexane/dichloromethane. Mp >270 °C; $[\alpha]_D^{20}=-1420$ (*c*

0.050, $CHCl_3$); ν_{max} (KBr) 3019 (w), 2930 (w), 2855 (w), 1603 (s) and 1531 cm^{-1} (m); *m/z* (FAB) 380 (MH^+, 70%), 379 (M^+, 66), 307 (26), 154 (100), 136 (69). Crystal data: $C_{20}H_{20}CoN_2O_2$, M=379.31, red cube, 0.30×0.30×0.30 mm^3, monoclinic, space group $P2_1$ (No. 4), a=11.1089(7), b=12.3377(6), c=12.3903(10) Å, β=97.133(3)°, V=1685.05(19) $Å^3$, Z=4, D_c=1.495 g/cm^3, F_{000}=788, KappaCCD, Mo K_α radiation, λ=0.71073 Å, T=120(2) K, $2\theta_{max}$=55.0°, 10999 reflections collected, 6940 unique (R_{int}=0.0610). Final GooF=0.996, $R1$=0.0534, $wR2$=0.0871, R indices based on 5011 reflections with $I>2\sigma(I)$ (refinement on F^2), 452 parameters, 1 restraint. Lp and absorption corrections applied, μ=1.034 mm^{-1}. Absolute structure parameter=−0.009(17).[70]

4.1.4. Rhodium(II)salen complex 1g. (*R*,*R*)-[*N*,*N*′-Bis-(2′-hydroxybenzylidene)]-1,2-diamino-cyclohexane (116 mg, 0.36 mmol) and sodium methoxide (39 mg, 0.72 mmol) were dissolved in methanol (7 ml). The yellow solution was stirred at room temperature for 5 min, then $[Rh(OAc)_2]_2 \cdot 2H_2O$ (86 mg, 0.18 mmol) was added as a slurry in MeOH (2 ml). The resulting green solution was stirred and heated to 60 °C for 4 h, under an argon atmosphere. Subsequently, the dark brown mixture was allowed to cool to room temperature and then evaporated in vacuo. The crude product was dissolved in dichloromethane (7 ml) and diethyl ether (10 ml) was added until a pale brown solid precipitated. The precipitate was collected by suction filtration, washed with diethyl ether (5 ml) and dried in vacuo to leave complex **1g** (150 mg, 98%) as a pale brown solid. Mp >270 °C; $[\alpha]_D^{20}$=−8 (*c* 0.025, MeOH); ν_{max} ($CHCl_3$) 2942 (m), 2863 (w), 1635 (s), 1602 (s) and 1536 cm^{-1} (w); *m/z* (ESI) 423 (M^+, 100). Found (ESI) 423.0572 (M^+), $C_{20}H_{20}N_2O_2Rh$ requires 423.0574.

4.1.5. Palladium(II)salen complex 1h.[40] (*R*,*R*)-[*N*,*N*′-Bis-(2′-hydroxybenzylidene)]-1,2-diamino-cyclohexane (122 mg, 0.378 mmol) and sodium methoxide (49 mg, 0.91 mmol) were dissolved in methanol (29 ml). The yellow solution was stirred at room temperature for 5 min, then anhydrous palladium acetate (85 mg, 0.378 mmol) was added and the reaction stirred for 2 h. The precipitate was collected by vacuum filtration, washed with cold methanol and dried in vacuo with gentle heating for several hours to provide complex **1h** (127 mg, 79%) as a yellow solid. Mp >270 °C; $[\alpha]_D^{20}$=−504 (*c* 0.025, $CHCl_3$); ν_{max} (KBr) 3045 (w), 2932 (m), 2857 (w), 1632 (s), 1601 (s) and 1531 cm^{-1} (s); δ_H ($CDCl_3$) 1.3–2.4 (4H, m, CH_2CH_2), 3.6–3.7 (1H, m, CH–N), 6.4–7.3 (4H, m, ArCH), 7.31 (1H, s, HC=N); δ_C ($CDCl_3$) 24.9 (CH_2), 28.8 (CH_2), 72.7 (CH), 115.0 (ArCH), 121.2 (ArC), 122.2 (ArCH), 135.0 (ArCH), 135.2 (ArCH), 155.6 (CH=N), 165.9 (ArC); *m/z* (ESI) 426 (M^+, 100). Found (ESI) 426.0644 (M^+), $C_{20}H_{20}N_2O_2Pd$ requires 426.0648. Found: C, 56.4%; H, 4.5%; N, 6.3%. $C_{20}H_{20}N_2O_2Pd$ requires: C, 56.3%; H, 4.7%; N, 6.6%.

4.1.6. Platinum(II)salen complex 1i.[41] (*R*,*R*)-[*N*,*N*′-Bis-(2′-hydroxybenzylidene)]-1,2-diamino-cyclohexane (200 mg, 0.62 mmol), $PtCl_2$ (165 mg, 0.62 mmol) and NaOMe (67 mg, 1.24 mmol) were added to methanol (5 ml) stirred for 4 h at room temperature and then the solvent was removed in vacuo. The residue was first purified by chromatography on LH-20 using EtOH/toluene (1:3) as eluent to give a mixture of complex **1i** and unreacted ligand. The mixture was washed with diethyl ether (3×4 ml) to leave complex **1i** (60 mg, 19%) as a yellow solid. Mp 180–190 °C (decomp.); $[\alpha]_D^{20}$=−192 (*c* 0.017, $CHCl_3$); ν_{max} (KBr) 2932 (m), 1607 (s) and 1535 cm^1 (m); δ_H ($CDCl_3$) 1.3–2.4 (4H, m, CH_2CH_2), 3.6–3.7 (1H, m, CH–N), 6.4–7.4 (4H, m, ArCH), 7.63 (1H, s, H–CN); δ_C ($CDCl_3$) 25.0 (CH_2), 28.1 (CH_2), 74.1 (CH), 116.2 (ArCH), 122.5 (ArC), 122.7 (ArCH), 134.1 (ArCH), 134.3 (ArCH), 151.2 (CH=N), 163.8 (ArC); *m/z* (ESI) 538 ($M+Na^+$). Found (ESI) 1053.2262 ($2M+Na^+$), $C_{40}H_{40}N_4O_4Pt_2Na$ requires 1053.2237.

4.1.7. Cobalt(III)salen complex 1j. To a solution of complex **1e** (100 mg, 0.26 mmol) in dichloromethane (53 ml) was added a solution of iodine (34 mg, 0.13 mmol) in dichloromethane (1 ml). The mixture was stirred at room temperature for 1 h during which time the red colour of the solution disappeared and a brown solid precipitated. The solution was evaporated to dryness to give complex **1j** (128 mg, 96%) as a brown solid which was used without further purification. Mp 260 °C; $[\alpha]_D^{20}$=−1000 (*c* 0.001, $CHCl_3$); ν_{max} (KBr) 3052 (w), 2933 (w), 2859 (w), 1628 (s), 1595 (s) and 1535 cm^{-1} (m); δ_H (DMSO-d_6) 1.5–3.1 (4H, m, CH_2CH_2), 3.6–3.7 (1H, m, CHN), 6.5–7.6 (4H, m, ArCH), 8.03 (1H, s, HC=N); δ_C (DMSO-d_6) 24.5 (CH_2), 29.8 (CH_2), 69.9 (CH), 115.5 (ArCH), 119.3 (ArC), 123.0 (ArCH), 135.1 (ArCH), 135.5 (ArCH), 164.4 (CH=N), 165.6 (ArC). Found (ESI) 379 ($M-I^+$, 100). Found (ESI) 379.0831 ($M-I^+$), $C_{20}H_{20}N_2O_2Co$ requires 379.0857.

4.1.8. Cobalt(III)salen complex 1k. A solution of ferrocenium hexafluorophosphate (66 mg, 0.20 mmol) in acetonitrile (4 ml) was added to a solution of complex **1e** (75 mg, 0.20 mmol) in acetonitrile (4 ml) at room temperature. The mixture was stirred for 19 h and then was concentrated in vacuo. The crystalline residue was washed with hexane to remove ferrocene and dried in vacuo to afford complex **1k** (104 mg, 99%) as a black crystalline solid. Mp >250 °C; $[\alpha]_D^{20}$=−3005 (*c* 0.033, MeOH); ν_{max} (KBr): 2939 (w), 1637 (s), 1604 (m), and 1544 cm^{-1} (m); δ_H (DMSO-d_6) 1.6–2.1 (4H, m, CH_2CH_2), 3.0–3.1 (1H, m, CHN), 6.7–7.6 (4H, m, ArCH), 8.02 (1H, s, HC=N); δ_C (DMSO-d_6) 24.5 (CH_2), 29.8 (CH_2), 69.8 (CH), 115.5 (ArCH), 119.2 (ArC), 123.0 (ArCH), 135.1 (ArCH), 135.5 (ArCH), 164.4 (CH=N), 165.6 (ArC); δ_F (DMSO-d_6) −70.5 (d $^1J_{PF}$=711 Hz, PF_6); δ_P(DMSO-d_6) −143 (hept. $^1J_{PF}$=711 Hz, PF_6); *m/z* (ESI) 379 $(M-PF_6)^+$. Found (ESI) 379.0821 $(M-PF_6)^+$, $C_{20}H_{20}N_2O_2Co$ requires 379.0851.

4.1.9. Copper(II)salen complex 7a. (+)-[*N*,*N*′-Bis-(2′-hydroxybenzylidene)]-2,3-diamino-butane[53] (80 mg, 0.3 mmol), copper(II) bromide (67 mg, 0.3 mmol) and sodium methoxide (33 mg, 0.6 mmol) were dissolved in methanol (5 ml) and stirred for 18 h at room temperature. The solvent was evaporated in vacuo and the residue was purified by chromatography on LH-20 using EtOH/toluene (1:3) to give complex **7a** (74 mg, 69%), as a dark brown solid. Mp 258–260 °C; $[\alpha]_D^{20}$=−582 (*c* 0.014, $CHCl_3$); ν_{max} ($CHCl_3$) 2964 (w), 1622 (s), 1600 (m) and 1536 cm^{-1} (m); *m/z* (CI) 358 (MH^+, 55), 297 (63), 148 (89), 122 (100), 72

(61). Found (ESI) 358.0743 (MH^+), $C_{18}H_{19}N_2O_2Cu$ requires 358.0737.

4.1.10. [*N*,*N*′-Bis-(2′-hydroxyphenyl)phenylmethylidene]-(*R*,*R*)-1,2-diamino-1,2-diphenylethane and [*N*-(2′-hydroxyphenyl)phenylmethylidene]-(*R*,*R*)-1,2-diamino-1,2-diphenylethane. To a solution of (*R*,*R*)-1,2-diamino-1,2-diphenylethane (220 mg, 1.04 mmol) in ethanol (10 ml), 2-hydroxybenzophenone (410 mg, 2.07 mmol) was added at room temperature. The resulting bright yellow solution was stirred under reflux for 44 h, then it was allowed to cool to room temperature and allowed to stand overnight. The resulting precipitate was filtered, washed with cold ethanol (2 ml), dried by suction filtration and then in vacuo to leave [*N*,*N*′-bis-(2′-hydroxyphenyl)-phenylmethylidene]-(*R*,*R*)-1,2-diamino-1,2-diphenylethane[71] (300 mg, 51%) as a yellow solid. Mp 215–217 °C; $[\alpha]_D^{20}=+178$ (*c* 0.55, $CHCl_3$); ν_{max} ($CHCl_3$) 3064 (w), 3032 (w), 2913 (w) and 1606 cm^{-1} (s); δ_H ($CDCl_3$) 4.68 (1H, s, CH), 6.50–7.37 (14H, m, ArCH), 15.42 (1H, s, OH); δ_C ($CDCl_3$) 72.5 (CH), 117.9 (ArCH), 118.4 (ArCH), 120.4 (ArC), 127.4 (ArCH), 127.7 (ArCH), 128.0 (ArCH), 128.3 (ArCH), 128.5 (ArCH), 128.7 (ArCH), 128.9 (ArCH), 129.2 (ArCH), 132.4 (ArCH), 132.9 (ArCH), 134.3 (ArC), 140.3 (ArC), 163.2 (ArC), 175.4 (C═N); *m*/*z* (CI) 573 (MH^+, 5), 286 (31), 198 (73), 106 (100). Found (ESI) 573.2549 (MH^+), $C_{40}H_{33}N_2O_2$ requires 573.2536. The mother liquors from the crystallisation were evaporated in vacuo, and the resulting yellow residue was purified by chromatography using Et_2O/hexane (3:7) to give [*N*-(2′-hydroxyphenyl)phenylmethylidene]-(*R*,*R*)-1,2-diamino-1,2-diphenylethane (142 mg, 35%) as a yellow solid. Mp 61–64 °C; $[\alpha]_D^{20}=+48$ (*c* 0.5, $CHCl_3$); ν_{max} ($CHCl_3$) 3384 (w), 3062 (m), 3030 (m), 2908 (w), 1607 (s) and 1572 cm^{-1} (m); δ_H ($CDCl_3$) 1.55 (2H, brs, NH_2), 4.32 (1H, d *J*=5.5 Hz, CH), 4.39 (1H, d *J*=5.5 Hz, CH), 6.51–7.31 (19H, m, ArCH), 15.90 (1H, s, OH); δ_C ($CDCl_3$) 62.8 (CH), 72.7 (CH), 117.9 (ArCH), 118.4 (ArCH), 120.3 (ArC), 127.6 (ArCH), 127.7 (ArCH), 127.5 (ArCH), 127.9 (ArCH), 128.1 (ArCH), 128.5 (ArCH), 128.6 (ArCH), 128.8 (ArCH), 129.3 (ArCH), 132.3 (ArCH), 133.1 (ArCH), 133.9 (ArC), 141.0 (ArC), 142.6 (ArC), 163.7 (ArC), 175.4 (C═N); *m*/*z* (CI) 393 (MH^+, 20), 287 (100), 270 (99), 167 (15), 106 (55). Found (ESI) 393.1961 (MH^+), $C_{27}H_{25}N_2O$ requires 393.1961.

4.1.11. Copper(II)salen complex 7b.[50] (*R*,*R*)-[*N*,*N*′-Bis-(2′-hydroxybenzylidene)]-1,2-diamino-1,2-diphenylethane, (140 mg, 0.33 mmol), $CuBr_2$ (74 mg, 0.33 mmol) and NaOMe (36 mg, 0.67 mmol) in methanol (4 ml) were stirred for 4 h at room temperature and then the solvent was removed in vacuo. The crude residue was purified by chromatography on LH-20 using EtOH/toluene (1:3) to give complex **7b** (109 mg, 69%) as a purple solid. Mp >270 °C; $[\alpha]_D^{20}=-310$ (*c* 0.010, $CHCl_3$); ν_{max} ($CHCl_3$) 3028 (w), 1619 (s), and 1535 cm^{-1} (m); *m*/*z* (FAB) 504 ($M+Na^+$, 100%), 482 (MH^+, 69), 481 (M^+, 21). Found (ESI) 482.1053 $(MH)^+$, $C_{28}H_{23}N_2O_2Cu$ requires 482.1056. Found: C, 70.0%; H, 4.4%; N, 5.5%. $C_{28}H_{22}N_2O_2Cu$ requires: C, 69.8%; H, 4.6%; N, 5.8%.

4.1.12. Copper(II)salen complex 7c. [*N*,*N*′-Bis-(2′-hydroxyphenyl)phenylmethylidene]-(*R*,*R*)-1,2-diamino-1,2-diphenylethane[71] (173 mg, 0.3 mmol), copper(II) bromide (67 mg, 0.3 mmol) and sodium methoxide (33 mg, 0.6 mmol) were dissolved in methanol (8 ml) and stirred for 3 h at room temperature. The solvent was evaporated in vacuo and the residue was purified by chromatography on LH-20 using EtOH/toluene (1:3) to give complex **7c** (186 mg, 98%), as a brown solid. Mp >270 °C; $[\alpha]_D^{20}=-60$ (*c* 0.025, $CHCl_3$); ν_{max} (KBr) 3057 (w), 2926 (w), 1600 (m), 1568 (s) and 1521 cm^{-1} (s); *m*/*z* (CI) 634 (MH^+, 100), 573 (33), 286 (56), 106 (92). Found (ESI) 634.1680 (MH^+), $C_{40}H_{31}N_2O_2Cu$ requires 634.1676.

4.1.13. [*N*,*N*′-Bis-(2′-hydroxybenzylidene)]-(*R*,*R*)-3,4-diamino-2,2,5,5-tetramethylhexane. To a solution of (*R*,*R*)-3,4-diamino-2,2,5,5-tetramethyl-hexane[52] (270 mg, 1.6 mmol) in ethanol (20 ml), was added salicylaldehyde (380 mg, 3.2 mmol). The resulting bright yellow solution was stirred under reflux for 5 h. Subsequently the solution was allowed to reach room temperature and then evaporated in vacuo. The residue was recrystallized from hexane-isopropanol to leave the desired product (340 mg, 56%) as yellow crystals. Mp 117–119 °C; $[\alpha]_D^{20}=+185$ (*c* 0.083, $CHCl_3$); ν_{max} ($CHCl_3$) 3060 (w), 2963 (s), 2871 (m), 1626 (s) and 1582 cm^{-1} (m); δ_H ($CDCl_3$) 0.83 (9H, s, $C(CH_3)_3$), 3.31 (1H, s, C*H*–N), 6.8–7.3 (4H, m, ArCH), 8.30 (1H, s, HC═N), 13.58 (1H, s, OH); δ_C ($CDCl_3$): 28.0 (CH_3), 36.3 (CMe_3), 77.7 (CHN), 118.0 (ArCH), 118.6 (ArCH), 118.9 (ArC), 131.7 (ArCH), 132.8 (ArCH), 162.3 (ArC), 165.8 (CH═N); *m*/*z* (CI) 381 (MH^+, 100), 262 (8), 122 (12). Found (ESI) 381.2541 (MH^+), $C_{24}H_{33}N_2O_2$ requires 381.2542. Found: C, 75.9%; H, 8.6%; N, 7.2%. $C_{24}H_{32}N_2O_2$ requires: C, 75.8%; H, 8.5%; N, 7.4%.

4.1.14. Copper(II)salen complex 7d. [*N*,*N*′-Bis-(2′-hydroxybenzylidene)]-(*R*,*R*)-3,4-diamino-2,2,5,5-tetramethyl-hexane (140 mg, 0.37 mmol), copper(II) bromide (82 mg, 0.37 mmol) and sodium methoxide (40 mg, 0.74 mmol) were added to methanol (2 ml) and stirred for 3 h at room temperature. The solvent was evaporated in vacuo and the residue was purified by chromatography on LH-20 using EtOH/toluene (1:3) to give complex **7d** as a black solid. Recrystallisation from hexane-dichloromethane gave complex **7d** (111 mg, 68%) as black crystals. Mp >270 °C; $[\alpha]_D^{20}=-1200$ (*c* 0.025, $CHCl_3$); ν_{max} (KBr) 3021 (w), 2963 (s), 2870 (w), 1614 (s), and 1533 cm^{-1} (s); *m*/*z* (FAB) 464 ($M+Na^+$, 100), 442 (MH^+, 66), 350 (24), 328 (52). Found (ESI) 442.1682 (MH^+), $C_{24}H_{31}N_2O_2Cu$ requires 442.1681. Found: C, 65.1%; H, 7.0%; N, 6.2%. $C_{24}H_{30}N_2O_2Cu$ requires: C, 65.2%; H, 6.8%; N, 6.3%. Crystal data: $C_{24}H_{30}CuN_2O_2$, *M*=442.04, blue needle, 0.40×0.15×0.15 mm^3, monoclinic, space group $P2_1$ (No. 4), *a*=11.2350(4), *b*=18.1208(5), *c*=11.5127(4) Å, β=108.019(2)°, *V*=2228.88(13) $Å^3$, *Z*=4, D_c=1.317 g/cm^3, F_{000}=932, KappaCCD, Mo K_α radiation, λ=0.71073 Å, *T*=120(2) K, $2\theta_{max}$=55.0°, 14897 reflections collected, 8895 unique (R_{int}=0.0872). Final GooF=1.012, *R*1=0.0527, *wR*2=0.1067, *R* indices based on 7186 reflections with $I>2\sigma(I)$ (refinement on F^2), 535 parameters, 1 restraint. Lp and absorption corrections applied, μ=1.001 mm^{-1}. Absolute structure parameter=−0.007(12).[70]

4.1.15. (−)-(*R*,*R*)-[*N*,*N*′-Bis-(2′-hydroxybenzylidene)]-1,2-diaminocyclopropane. To a solution of (−)-*trans*-1,2-diaminocyclopropane dihydrochloride[58] (190 mg, 1.3 mmol) in dichloromethane (10 ml), salicylaldehyde (351 mg, 2.9 mmol) was added at room temperature. The

resulting bright yellow solution was stirred at reflux for 23 h, and then evaporated in vacuo to give a dark yellow syrup. The residue was dissolved in dichloromethane and hexane was added to precipitate impurities. The solution was filtered and evaporated in vacuo to give the desired compound[72,73] (148 mg, 40%) as a bright yellow solid. Mp 109–111 °C; $[\alpha]_D^{20}=-563$ (*c* 1.6, $CHCl_3$); ν_{max} ($CHCl_3$) 3057 (w), 2986 (w), 2883 (w), 1625 (s) and 1580 cm^{-1} (m); δ_H ($CDCl_3$) 1.59 (2H, t J=6.3 Hz, CH_2), 3.32 (1H, t J=6.3 Hz, CH), 6.8–6.9 (2H, m, ArCH), 7.1–7.3 (2H, m, ArCH), 8.40 (1H, s, H–CN), 12.37 (1H, brs, OH); δ_C ($CDCl_3$) 20.4 (CH_2), 50.6 (CHN), 117.3 (ArCH), 119.3 (ArC), 119.4 (ArCH), 131.5 (ArCH), 132.5 (ArCH), 160.7 (ArC), 164.0 (CH=N); *m/z* (FAB) 281 (MH^+, 50), 160 (55), 148 (100), 132 (72), 105 (80). Found (ESI) 281.1286 (MH^+) $C_{17}H_{17}N_2O_2$ requires 281.1290.

4.1.16. (+)-[*N*,*N*′-Bis-(2′-hydroxybenzylidene)]-1,2-diaminocyclobutane. To a solution of (+)-*trans*-1,2-diaminocyclobutane[59] (112 mg, 1.3 mmol) in dichloromethane (10 ml), salicylaldehyde (317 mg, 2.6 mmol) was added at room temperature. The resulting bright yellow solution was stirred at room temperature for 19 h, and then evaporated in vacuo to give the desired product[73] (233 mg, 61%) as a yellow gel. $[\alpha]_D^{20}=+565$ (*c* 1.2, $CHCl_3$); ν_{max} ($CHCl_3$) 3057 (w), 2990 (w), 2948 (w), 2875 (w), 1625 (s) and 1580 cm^{-1} (m); δ_H ($CDCl_3$) 1.9–2.3 (2H, m, CH_2CH_2), 4.0–4.1 (1H, m, CH), 6.8–7.3 (4H, m, ArCH), 8.21 (1H, s, HC=N), 13.21 (1H, brs, OH); δ_C ($CDCl_3$) 24.4 (CH_2), 69.5 (CHN), 117.4 (ArCH), 119.0 (ArC), 119.2 (ArCH), 132.1 (ArCH), 132.9 (ArCH), 161.4 (ArC), 164.2 (CH=N); *m/z* (CI) 295 (MH^+, 100), 191 (10), 148 (6), 122 (6). Found (ESI) 317.1243 $(M+Na)^+$, $C_{18}H_{18}N_2O_2Na$ requires 317.1261.

4.1.17. (−)-(*R*,*R*)-[*N*,*N*′-Bis-(2′-hydroxybenzylidene)]-1,2-diaminocyclopentane. To a solution of (−)-(*R*,*R*)-*trans*-1,2-diaminocyclopentane[59] (179 mg, 1.8 mmol) in dichloromethane (10 ml), salicylaldehyde (437 mg, 3.6 mmol) was added at room temperature. The resulting bright yellow solution was stirred at room temperature for 21 h, then evaporated in vacuo, and dried in vacuo with gentle heating for several hours to give the desired product (433 mg, 78%) as a yellow gel. $[\alpha]_D^{20}=-467$ (*c* 0.535, $CHCl_3$); ν_{max} (neat) 3057 (w), 2959 (m), 2873 (m), 1626 (s) and 1580 cm^{-1} (m); δ_H ($CDCl_3$) 1.8–2.2 (3H, m, CH_2CH_2-CH_2), 3.6–3.7 (1H, m, NCH), 6.8–7.2 (4H, m, ArCH), 8.19 (1H, s, HC=N), 13.24 (1H, s, OH); δ_C ($CDCl_3$) 22.3 (CH_2), 33.4 (CH_2), 76.9 (CHN), 117.2 (ArCH), 119.0 (ArC), 119.1 (ArCH), 131.8 (ArCH), 132.7 (ArCH), 161.3 (ArC), 165.1 (CH=N); *m/z* (CI) 308 (M^+, 56), 187 (100), 147 (14), 122 (22). Found (ESI) 309.1593 (MH^+) $C_{19}H_{21}N_2O_2$ requires 309.1598.

4.1.18. Copper(II) complex 9c. (−)-(*R*,*R*)-[*N*,*N*′-Bis-(2′-hydroxybenzylidene)]-1,2-diamino-cyclopentane (213 mg, 0.69 mmol), $CuBr_2$ (154 mg, 0.69 mmol) and NaOMe (75 mg, 1.38 mmol) were added to methanol (5 ml) and stirred for 5 h at room temperature. The solvent was evaporated in vacuo and the residue was purified by gel permeation chromatography on LH-20 using CH_2Cl_2 as eluent. Recrystallization from dichloromethane gave complex **9c** (104 mg, 41%) as small green needles. Mp >270 °C; $[\alpha]_D^{20}=-177.8$ (*c* 0.016, $CHCl_3$); ν_{max} (KBr) 2933 (w), 1639 (s), 1601 (m) and 1534 cm^{-1} (m); *m/z* (ESI) 370 (MH^+). Found (ESI) 739.1402 ($2M+H^+$), $C_{38}H_{37}N_4O_4Cu_2$ requires 739.1401.

4.1.19. Copper(II) complex 9d. (3*R*,4*R*)-[*N*,*N*′-Bis-(2′-hydroxybenzylidene)]-1-benzyl-3,4-diaminopyrrolidine[60] (65 mg, 0.16 mmol), $CuBr_2$ (36 mg, 0.16 mmol) and NaOMe (18 mg, 0.33 mmol) were added to methanol (6 ml) and stirred at room temperature for 3 h. The solvent was evaporated in vacuo and the residue was purified by gel permeation chromatography on LH-20 using EtOH/toluene (1:3) as eluent to give complex **9d** (34 mg, 45%) as a dark green solid. Mp 236–238 °C; $[\alpha]_D^{20}=-30$ (*c* 0.023, $CHCl_3$); ν_{max} (KBr) 1637 (s) and 1536 cm^{-1} (m); *m/z* (ESI) 461 (MH^+, 55), 412 (100), 387 (31). Found (ESI) 461.1158 (MH^+), $C_{22}H_{25}N_2O_2Cu$ requires 461.1159.

4.1.20. *N*,*N*′-Bis-[(*S*)-1′-phenylethyl]-(1*R*,2*R*,4*R*,5*R*)-1,2-diamino-4,5-dimethyl-cyclohexane.[64] Bis-(cyclopentadienyl)zirconium dichloride (224 mg, 0.76 mmol) and dry diethyl ether (70 ml) were added to a three necked flask under a N_2 atmosphere. *n*-Butylmagnesium chloride (2 M in Et_2O, 9.4 ml, 18.7 mmol) was added with stirring and the mixture was allowed to react for 30 min. *N*,*N*′-Bis-[(*S*)-1′-phenylethyl]-(*R*,*R*)-4,5-diamino-1,7-octadiene (1.3 g, 3.74 mmol) dissolved in dry diethyl ether (5 ml) was then added dropwise and the resulting mixture was allowed to react for 44 h at room temperature. The reaction was quenched with saturated aqueous ammonium chloride (40 ml). The aqueous layer was extracted with diethyl ether (3×40 ml) and the combined organic layers were washed with brine (70 ml), dried over magnesium sulphate and concentrated in vacuo to give an orange oil (1.3 g) which contained a 6:1 ratio of the 4,5-(*R*,*R*) and 4,5-(*R*,*S*)-diastereomers. The diastereomers were separated by column chromatography using EtOAc/hexane (1:3) as eluent. The 4,5-(*R*,*R*)-diastereomer (790 mg, 60%) eluted first as a yellow oil, followed by the 4,5-(*R*,*S*)-diastereomer (134 mg, 10%) as a yellow oil. Spectroscopic data for both diastereomers were consistent with the literature data.[64]

4.1.21. *N*-[(*S*)-1′-Phenylethyl]-(1*R*,2*R*,4*R*,5*R*)-1,2-diamino-4,5-dimethyl cyclohexane 12. A solution of *N*,*N*′-bis-[(*S*)-1′-phenylethyl]-(1*R*,2*R*,4*R*,5*R*)-1,2-diamino-4,5-dimethyl cyclohexane (350 mg, 1.0 mmol) in methanol (20 ml) was hydrogenated in the presence of 20% $Pd(OH)_2$ on carbon (150 mg) under hydrogen at three atmospheres pressure for 24 h. The reaction was filtered through Celite and concentrated in vacuo The resulting pale yellow residue was purified by chromatography using ethyl acetate/methanol (5:1) to give compound **12** (115 mg, 47%) as a colourless oil. $[\alpha]_D^{20}=-96.7$ (*c* 0.55, $CHCl_3$); ν_{max} (neat) 3301 (s), 3025 (w), 2960 (s), 2923 (s), 2872 (m) and 1584 cm^{-1} (m); δ_H ($CDCl_3$) 0.79 (3H, d J=6.3 Hz, CH_3), 0.88 (3H, d J=6.3 Hz, CH_3), 1.27 (3H, d J=6.6 Hz, CH_3), 1.3–1.5 (4H, m, 2×CH_2), 1.75 (2H, brs, NH_2), 1.77 (1H, s, NH), 2.1–2.2 (1H, m, CH), 2.6–2.7 (1H, m, CH), 3.82 (1H, q J=6.6 Hz, CH), 7.1–7.3 (5H, m, ArCH); δ_C ($CDCl_3$) 20.4 (CH_3), 20.5 (CH_3), 25.6 (CH_3), 32.9 (CH), 33.5 (CH_2), 33.8 (CH), 37.1 (CH_2), 51.3 (CH), 55.3 (CH), 56.5 (CH), 127.1 (ArCH), 127.2 (ArCH), 128.8 (ArCH), 146.3 (ArC); *m/z* (CI) 247 (MH^+, 100), 174 (10), 120 (43). Found (ESI) 247.2174 (MH^+), $C_{16}H_{27}N_2$ requires 247.2174.

4.1.22. (1*R*,2*R*,4*R*,5*R*)-1,2-Diamino-4,5-dimethyl cyclohexane 13. A solution of compound **12** (236 mg, 0.96 mmol) in methanol (6 ml) was hydrogenated in the presence of 20% $Pd(OH)_2$ on carbon (150 mg) under hydrogen at three atmospheres pressure for 90 h. The reaction was filtered through Celite and concentrated in vacuo. The resulting pale yellow residue was purified by chromatography using dichloromethane/methanol (3:1) to give compound **13** (45 mg, 33%) as a colourless oil. Spectroscopic data were consistent with the literature data.[64]

4.1.23. (1*R*,2*R*,4*R*,5*R*)-[*N*,*N*′-Bis-(2′-hydroxybenzylidene)]-1,2-diamino-4,5-dimethylcyclohexane 14. To a solution of (1*R*,2*R*,4*R*,5*R*)-4,5-dimethyl-cyclohexane-1,2-diamine[64] (35 mg, 0.25 mmol) in ethanol (6 ml), salicylaldehyde (61 mg, 0.50 mmol) was added at room temperature. The resulting bright yellow solution was refluxed for 19 h, then allowed to cool to room temperature and evaporated in vacuo. The residue was purified by column chromatography using ethyl acetate/hexane (1:2) as eluent to afford compound **14** (26 mg, 30%) as a yellow solid. Mp 93–95 °C; $[\alpha]_D^{20}=+245$ (*c* 1.3, $CHCl_3$); ν_{max} ($CHCl_3$) 2957 (w), 2926 (m), 2875 (m), 1630 (s) and 1582 cm^{-1} (m); δ_H ($CDCl_3$) 0.95 (3H, d *J*=6.0 Hz, CH_3), 1.5–1.7 (2H, m, CH_2), 1.7–1.9 (1H, m, CH), 3.4–3.5 (1H, m, CH), 6.8–6.9 (2H, m, ArCH), 7.1–7.3 (2H, m, ArCH), 8.32 (1H, s, HC=N), 13.51 (1H, brs, OH); δ_C ($CDCl_3$) 20.4 (CH_3), 33.8 (CH), 37.2 (CH_2), 70.0 (CHN), 117.3 (ArCH), 119.1 (ArCH), 119.2 (ArC), 131.8 (ArCH), 132.8 (ArCH), 161.5 (ArC), 164.6 (CH=N); *m*/*z* (CI) 351 (MH^+, 100%), 247 (9), 232 (10), 122 (39). Found (ESI) 351.2063 (MH^+), $C_{22}H_{27}N_2O_2$ requires 351.2067.

4.1.24. Copper(II) complex 9e. Ligand **14** (25 mg, 0.07 mmol), $CuBr_2$ (16 mg, 0.07 mmol) and NaOMe (8 mg, 0.142 mmol) were added to methanol (2 ml) and stirred at room temperature for 5 h. The solvent was evaporated in vacuo and the residue was purified by gel permeation chromatography on LH-20 using CH_2Cl_2/MeOH (1:1) as eluent. Recrystallization from dichloromethane/methanol gave complex **9e** (28 mg, 96%) as small purple needles. Mp >250 °C; $[\alpha]_D^{20}=-451$ (*c* 0.014, $CHCl_3$); ν_{max} ($CHCl_3$) 2931 (w), 1630 (s), 1602 (m) and 1540 cm^{-1} (m); *m*/*z* (EI) 411 (M^+, 2), 132 (25), 91 (22), 44 (100). Found (ESI) 412.1204 (MH^+), $C_{22}H_{25}N_2O_2Cu$ requires 412.1207.

4.1.25. (+)-(11*S*,12*S*)-11,12-Diamino-9,10-dihydro-9,10-ethano-anthracene dihydrochloride.[65] (11*S*,12*S*)-9,10-Dihydro-9,10-ethanoanthracene-11,12-diacid chloride[65] (2.00 g, 6.04 mmol) dissolved in toluene (15 ml) was added dropwise to a cooled (ice bath) solution of sodium azide (1.37 g, 21.18 mmol) in water (15 ml). The mixture was stirred between 0 °C and room temperature for 4 h. The organic layer was separated and washed with dilute sodium hydrogen carbonate (15 ml) and water (2×10 ml), dried over anhydrous magnesium sulfate and filtered into a 50 ml round bottom flask to give a solution of the corresponding bis-azide. A reflux condenser and extra toluene (15 ml) were added to the flask, and the solution was stirred and heated to 80 °C for 1 h. Subsequently, the reaction was cooled to room temperature to give a solution of bis-isocyanate. To this solution was added 6 N HCl (6 ml). The mixture was stirred and heated to 80 °C for 3 h and stirred at room temperature overnight. The two layers were separated and the aqueous phase was washed with toluene (2×10 ml). The aqueous phase was then concentrated in vacuo to give (+)-(11*S*,12*S*)-diamino-9,10-dihydro-9,10-ethano-anthracene dihydrochloride (970 mg, 40%) as a brownish solid. Mp >250 °C; $[\alpha]_D^{20}=+14$ (*c* 0.25, $CHCl_3$); ν_{max} (KBr) 3406 (m), 2878 (br), 1578 (m) and 1527 cm^{-1} (m); δ_H (CD_3OD) 3.66 (1H, brs, CH), 4.79 (1H, brs, CH), 7.3–7.4 (2H, m, ArCH), 7.5–7.6 (2H, m, ArCH); δ_C (CD_3OD) 48.0 (CH), 56.6 (CH), 126.8 (ArCH), 127.9 (ArCH), 129.5 (ArCH), 129.7 (ArCH), 138.1 (ArC), 141.3 (ArC); *m*/*z* (EI) 237 ($(M-HCl-Cl)^+$, 100).

4.1.26. (11*S*,12*S*)-[*N*,*N*′-Bis-(2′-hydroxybenzylidene)]-11,12-diamino-9,10-dihydro-9,10-ethanoanthracene. To a solution of (+)-(11*S*,12*S*)-11,12-diamino-9,10-dihydro-9,10-ethanoanthracene dihydrochloride (280 mg, 0.9 mmol) in ethanol (20 ml), were added sodium methoxide (98 mg, 1.8 mmol) and salicylaldehyde (221 mg, 1.8 mmol). The resulting solution was stirred under reflux for 3 h. The solution was allowed to cool to room temperature and then evaporated in vacuo. The yellow residue was taken up in dichloromethane (20 ml) and washed with water (15 ml) and brine (15 ml). The organic layer was dried over anhydrous magnesium sulphate and evaporated to dryness to leave the desired compound (220 mg, 54%) as a yellow solid. Mp 102–104 °C; $[\alpha]_D^{20}=+250$ (*c* 1.4, $CHCl_3$); ν_{max} ($CHCl_3$) 3024 (w), 2879 (w), 1628 (s) and 1579 cm^{-1} (m); δ_H ($CDCl_3$) 3.45 (1H, s, CH), 4.23 (1H, s, CH), 6.7–6.8 (2H, m, ArCH), 7.1–7.3 (6H, m, ArCH), 8.21 (1H, s, HC=N), 12.41 (1H, s, OH); δ_C ($CDCl_3$) 52.0 (CH), 77.5 (CH), 117.5 (ArCH), 118.9 (ArC), 119.2 (ArCH), 124.6 (ArCH), 126.1 (ArCH), 127.1 (ArCH), 127.2 (ArCH), 131.9 (ArCH), 133.0 (ArCH), 140.2 (ArC), 140.7 (ArC), 161.2 (ArC), 164.9 (CH=N); *m*/*z* (ESI) 445 (MH^+, 100). Found (ESI) 445.1907 (MH^+), $C_{30}H_{25}N_2O_2$ requires 445.1911.

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