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Influence of aromatic substituents on metal(II)salen catalysed, asymmetric synthesis of α-methyl α-amino acids

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Abstract—The influence of substituents on both the aromatic rings of the catalyst, and the benzylidene unit of the substrate are investigated in the (salen)copper(II) catalysed asymmetric benzylation of alanine derivatives. Catalysts with electron-donating, and electron-withdrawing substituents of various sizes and at various locations on the aromatic rings of the salen ligand were prepared, but all exhibited inferior enantioselectivity to the parent (salen)copper(II) complex. In contrast, the introduction of halogenated substituents onto the aromatic ring of the *N*-benzylidene alanine methyl ester substrate was found to enhance the enantioselectivity of the alkylation with a *para*-chloro substituent giving optimal results. A new procedure for the preparation of the catalysts which avoids the need for chromatography on sephadex LH20 is reported, and the optimal catalyst obtained in this way was found to be a cobalt(salen) complex.

1. Introduction

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 has increased significantly in recent years. The most effective way of carrying out this process is to use a chiral catalyst under phase-transfer conditions, with the chiral catalyst also acting as a phase transfer catalyst.[1]

O'Donnell was the first to show that quaternary ammonium salts derived from cinchona alkaloids would catalyse the asymmetric alkylation of a glycine derived enolate, leading to non-racemic α-amino acids.[2] Recently, the groups of Lygo[3] and Corey,[4] have optimized this process and shown that the use of a 9-anthracenylmethyl group to quaternize the cinchona alkaloid results in a highly enantioselective catalyst which allows 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.[6] Quaternized cinchona alkaloids can also be used to catalyse the alkylation of other enolates,[7] Michael additions,[8,9] aldol reactions,[10] and enone epoxidations.[11] They 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 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 glycine derived imines, 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 reported 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] Belokon' and Kagan have subsequently shown that the sodium salt of NOBIN[23] could act as an extremely rapid and enantioselective phase transfer catalyst for the same reaction. Nájera has recently reported that the sodium salt of BINOLAM is also an effective phase-transfer catalyst.[24]

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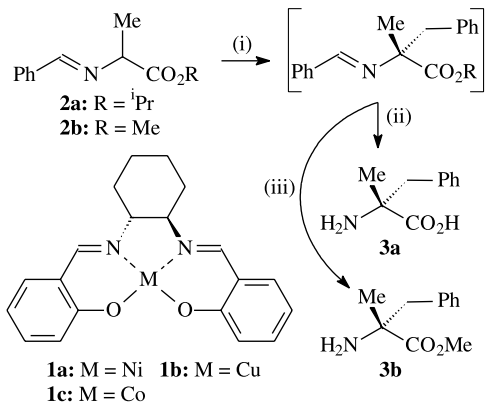
Chiral transition metal complexes have been used to catalyse a wide range of asymmetric transformations, and we have developed the asymmetric alkylation of amino acid enolates under phase transfer conditions catalysed by salen complexes of transition metals. In 1999, we reported that nickel(II)salen complex **1a** (10 mol%) would catalyse the asymmetric benzylation of alanine enolate **2a** leading to α-methyl phenylalanine **3a** (Scheme 1) with 30% enantiomeric excess.[25] The corresponding copper(II)salen complex **1b** was also studied and was found to be a far more effective catalyst. Just 2 mol% of complex **1b** was sufficient to catalyse the formation of compound **3a** with 88% enantiomeric excess. Recently, we have screened a wide range of other metal(salen) complexes for the alkylation of substrate **2b**, but whilst the Co(II)salen complex **1c** was found to be as active as complex **1b**, no superior catalyst was found.[26]



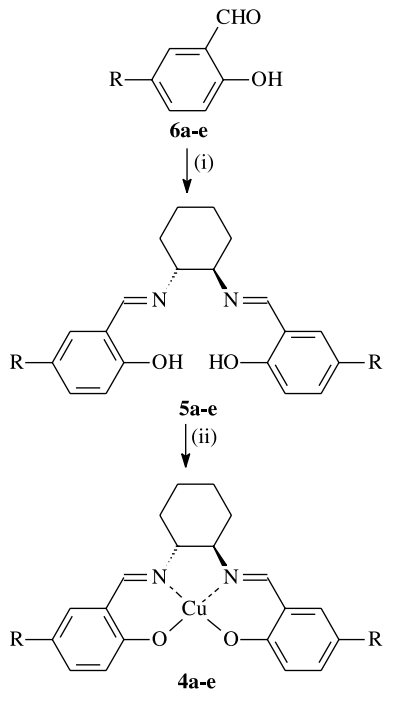
Scheme 1. Reagents: (i) **1a–c** (2–10 mol%)/NaOH (solid)/BnBr; (ii) H_3O^+/Δ; (iii) (R=Me), MeOH/AcCl then SiO_2.

Complex **1b** also catalysed the asymmetric alkylation of compound **2a** 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. In subsequent work, we have also demonstrated that under appropriate reaction conditions, it is possible to use the readily available methyl ester substrate **2b**.[27] In addition, 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]

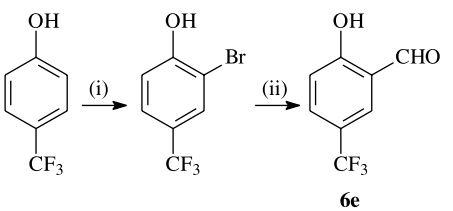
In this paper, we report the results of a study aimed at better understanding and optimizing the influence of various factors on the enantioselectivity of this reaction. In particular, the effect that substituents on the aromatic rings of catalyst **1b** have on the enantioselectivity of the catalyst are reported[25,29] In addition, the influence of the structure of the imine within substrate **2b** on the enantioselectivity of the reaction is studied.[29] Finally, a method for the preparation of the catalysts which avoids the use of size-exclusion chromatography on sephadex LH20 is described.

2. Results and discussion

Based on precedent from our work on asymmetric cyanohydrin synthesis using titanium(salen) complexes,[30] we expected that introduction of substituents at positions 3- and/or 5- of the aromatic rings of catalyst **1b** would enhance the enantioselectivity of the catalyst. These two positions (*ortho* and *para* to the phenol respectively) both allow the substituent to exert an electronic effect on the copper ion. However, we have previously shown that for the reaction shown in Scheme 1, introduction of a large *tert*-butyl group into the 3-position of the aromatic rings had a very negative impact on the enantioselectivity of the resulting catalyst.[25] Therefore, we initially investigated the synthesis and use of 5-substituted salen complexes **4a–e**. Compounds **4a–e** were prepared from the appropriate aldehyde via the corresponding salen ligands **5a–e** as shown in Scheme 2. Aldehydes **6b** and **6c** were commercially available, aldehydes **6a** and **6d** were prepared by literature routes,[31,32] and aldehyde **6e**[33] was prepared from 4-trifluoromethylphenol as shown in Scheme 3.[34]



Scheme 2. Reagents: (i) (*R*,*R*)-cyclohexane diamine/NaOMe; (ii) $CuBr_2$/NaOMe.



Scheme 3. Reagents: (i) Br_2; (ii) BuLi/DMF.

Catalysts **4a–e** were screened for catalytic activity in the alkylation of substrate **2b** with benzyl bromide to give α-methyl phenylalanine methyl ester **3b** as shown in Scheme 1. The enantiomeric excess of compound **3b** was readily determined by ^{1}H NMR analysis of the derived α-methylbenzyl ureas as previously reported.[25–29] The chemical yields and enantioselectivities observed using these catalysts are summarized in Table 1.

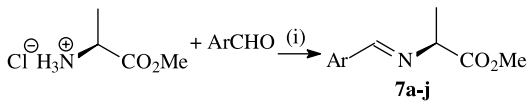
Table 1. Effect of 5-substituents on the enantioselectivity of catalysts **4a–e**

Entry	R	Yield (%)	ee (%)
1	^{t}Bu (**4a**)	39	80
2	OMe (**4b**)	78	45
3	NO_2 (**4c**)	60	0
4	F (**4d**)	54	42
5	CF_3 (**4e**)	68	25

The introduction of a large *tert*-butyl group into position 5 of the aromatic rings (**4a**) had no significant effect on the level of asymmetric induction observed using the catalyst (Table 1: entry 1). In contrast, complex **4b** containing a strongly electron donating group in the 5-position displayed significantly reduced asymmetric induction (Table 1: entry 2). Reasoning that if electron donating groups reduced the asymmetric induction, electron withdrawing groups might increase the asymmetric induction, the synthesis of complex **4c** containing nitro groups in the 5-position was undertaken. Unfortunately, whilst ligand **5c** could be prepared without difficulty, copper complex **4c** was totally insoluble and impossible to purify. When the catalytic activity of the crude complex was tested, no asymmetric induction was observed (Table 1: entry 3). The chemical yield obtained in this case is probably due to an uncatalysed background reaction.

To overcome the solubility problems observed with complex **4c**, the synthesis of fluorinated complexes **4d** and **4e** was undertaken and both complexes were obtained without difficulty. The 5-fluoro substituents in complex **4d** are inductively strongly electron withdrawing, but mesomerically strongly electron donating and the complex was found to exhibit very similar asymmetric induction to complex **4b** (Table 1: entry 4). In contrast, the trifluoromethyl groups in complex **4e** can only exhibit an inductively electron withdrawing effect, and this complex was found to be an even worse catalyst (Table 1: entry 5). Thus, the introduction of either electron donating or electron withdrawing substituents onto the 5-positions of complex **1b** was found to be detrimental for the asymmetric induction observed when the complexes were used as asymmetric phase transfer catalysts.

Having found no advantage in introducing substituents onto the aromatic rings of catalyst **1b**, the effect of substituents on the imine of substrate **2b** was investigated. Substrates **7a–j** were prepared from (*S*)-alanine methyl ester and the appropriate aldehyde as shown in Scheme 4. The alkylation of each of these substrates was carried out using benzyl bromide as the electrophile under the conditions shown in Scheme 1. The chemical yields and enantiomeric excesses of the α-methyl phenylalanine methyl ester **3b** obtained in each case are reported in Table 2.



7a-j

a: Ar = 4-$O_2NC_6H_4$; **b:** Ar = 4-$MeOC_6H_4$
c: Ar = 4-ClC_6H_4; **d:** Ar = 3-ClC_6H_4
e: Ar = 2-ClC_6H_4; **f:** Ar = 4-FC_6H_4
g: Ar = 4-BrC_6H_4; **h:** Ar = 4-IC_6H_4
i: Ar = 1-naphthyl; **j:** Ar = 2- naphthyl

Scheme 4. Reagents: (i) $Et_3N/MgSO_4$.

Table 2. Effect of imine structure on the enantioselectivity of the alkylation of substrates **7a–j**

Entry	Ar	Yield (%)	ee (%)
1	4-$O_2NC_6H_4$ (**7a**)	50	65
2	4-$MeOC_6H_4$ (**7b**)	79	71
3	4-ClC_6H_4 (**7c**)	71	92
4	3-ClC_6H_4 (**7d**)	53	81
5	2-ClC_6H_4 (**7e**)	43	70
6	4-FC_6H_4 (**7f**)	44	84
7	4-BrC_6H_4 (**7g**)	95	81
8	4-IC_6H_4 (**7h**)	67	86
8	1-Naphthyl (**7i**)	89	79
9	2-Naphthyl (**7j**)	62	77

Initially, the influence of electronic effects on the enantioselectivity was studied by the preparation of the 4-nitro **7a** and 4-methoxy **7b** substituted imines. It was anticipated that a strongly electron withdrawing group in the 4-position would acidify the α-proton and therefore possibly lower the enantioselectivity by increasing the rate of the uncatalysed background reaction. This was borne out by the observed 16% reduction in enantioselectivity (Table 2: entry 1) compared to the use of substrate **2b** under identical conditions (81% ee). In contrast however, an electron donating methoxy substituent was expected to increase the enantioselectivity of the reaction by reducing the acidity of the α-proton and hence reducing the rate of the background reaction. A possible reduction in chemical yield as a result of the lower acidity of the α-proton was also anticipated. In practice however (Table 2: entry 2), the chemical yield remained high and the enantioselectivity was reduced compared to substrate **2b**. This may indicate that the background reaction is not a significant factor when a catalyst is present and some other factor or factors are responsible for controlling the asymmetric induction.

Halo substituents offer the opportunity to introduce inductively electron withdrawing substituents onto the imine and to have this offset to some extent by a mesomerically electron donating effect. Therefore, a series of compounds **7c**, **f–h** were prepared in which a halogen was introduced at the 4-position of the imine. In each case, the enantioselectivity was at least as high as that observed using substrate **2b** (Table 2: entries 3, 6–8) and in the best case (the 4-chloro substituted derivative **7c**), a 10% increase in enantioselectivity to 91% was observed (Table 2: entry 3). The order of effectiveness of a 4-halo substituent was Cl>I>F>Br. The reason behind this ordering is not apparent, but the enantioselectivities observed with the bromo-, fluoro- and iodo- substituents are all within 5% of one another and this may be within the experimental error of

±3%. Thus, it appears that a 4-chloro substituent provides the optimal balance of electron withdrawing and electron donating effects to achieve the highest enantioselectivity and retain a good chemical yield. The importance of the chloro-substituent being in the 4-position was demonstrated by the preparation of the corresponding 3-chloro and 2-chloro derivatives **7d**,**e** respectively. The 3-chloro derivative which cannot exhibit any mesomeric effect gave an identical enantioselectivity to that observed using substrate **2b** (Table 2: entry 4). The 2-chloro derivative gave a lower enantioselectivity than that observed using substrate **2b** (Table 2: entry 5), and steric effects may be important in this case. To further probe the influence of steric effects, the synthesis of two naphthyl derivatives **7i**,**j** was undertaken. These two substrates both gave enantioselectivities that were comparable with, or just slightly lower than, substrate **2b** (Table 2: entries 8 and 9), suggesting that steric effects (at least in the plane of the aromatic ring) are not a significant factor in determining the enantioselectivity of the reaction.

In general, the effect of introducing substituents onto the imine on the enantioselectivity of the reaction was not as marked as the effect of introducing substituents onto the catalyst. However, in contrast to the results obtained with substituted catalysts, it was possible to both increase and decrease the enantioselectivity of the reaction compared to substrate **2b** (81% ee) by using an appropriately substituted imine.

Having successfully optimized the structure of the substrate, we returned to studies aimed at optimizing the structure of catalyst **1b**, this time using the benzylation of substrate **7c** as the test reaction. As a result of our related work in this area,[25–29] we have developed a working model to explain the mode of action of catalyst **1b**.[25,28] This model is shown in Figure 1. The key feature of the model is the formation of a hetero-polymetallic complex involving both copper(II) and sodium ions, with the latter coordinated by the salen oxygens, a process for which there is ample literature precedent.[35] In addition, our studies on changing the nature of the transition metal ion,[26] and in particular the fact that only the paramagnetic complexes derived from Cu(II) and Co(II) displayed high levels of asymmetric induction suggested that the reaction might proceed by a radical or radical anion mechanism.

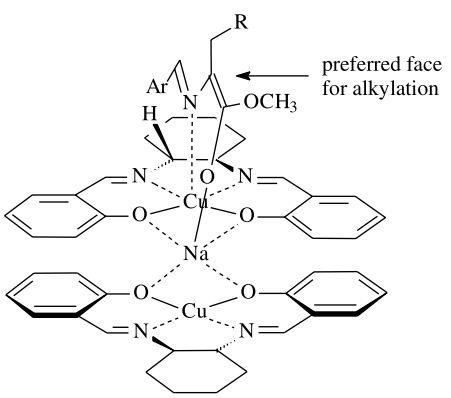
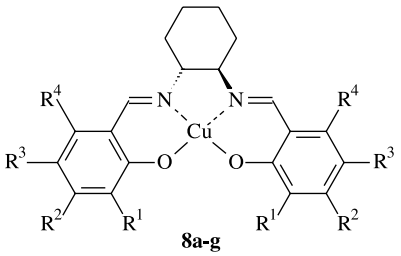


Figure 1. A model to explain the mode of action of catalyst **1b**.

Based on this model and mechanistic hypothesis, we decided to prepare a series of electron rich copper(II)salen complexes bearing hydroxy or methoxy substituents. It was hoped that if the substituents were located in the 3-position, then they would be able to assist with the coordination of the sodium ion and hence enhance the catalytic activity. In addition, there is literature precedent for hydroxyl substituents stabilizing radical anion formation in salen ligands.[36] Therefore, complexes **8a–f** were prepared and complex **4b** was also included in this study as was complex **8g**. The latter complex allowed us to investigate the effect of an alkyl group at the 4-position of the salen ring as this had not previously been studied. All of the aldehydes needed for the preparation of complexes **8a–g** are commercially available and were converted into the corresponding salen ligands by the route shown in Scheme 2. Copper complexes **8a–g** were then prepared by one of two methods. For complexes **8a**,**d**,**e**, the salen ligand was treated with copper(II) bromide and the resulting copper complex purified by gel permeation chromatography on sephadex LH-20 in the same way as for complexes **1b** and **4a**,**b**,**d**,**e**. However, during the course of this work the sephadex LH-20 required for the purification of complexes prepared in this way became commercially unavailable. Therefore, for complexes **8**,**b**,**c**,**f**,**g**, an alternative synthesis was developed which uses copper(II) acetate as the copper source. This method had the advantage that the copper complex could be purified simply by washing with suitable solvents (see Section 4 for details).



8a-g

a: R^1 = OH; R^2 = R^3 = R^4 = H
b: R^2 = OH; R^1 = R^3 = R^4 = H
c: R^3 = OH; R^1 = R^2 = R^4 = H
d: R^1 = OMe; R^2 = R^3 = R^4 = H
e: R^2 = OMe; R^1 = R^3 = R^4 = H
f: R^4 = OMe; R^1 = R^2 = R^3 = H
g: R^2= Me; R^1 = R^3 = R^4 = H
4b: R^3 = OMe; R^1 = R^2 = R^4 = H

The results of catalytic studies using copper complexes **8a–g** and **4b** in conjunction with substrate **7c** are summarized in Table 3. Previous work had suggested that

Table 3. Effect of oxygen or methyl substituents on the enantioselectivity of catalysts **4b** and **8a–g**

Entry	Complex	Yield (%)	ee (%)
1	**8a**	79	5
2	**8b**	46	4
3	**8c**	59	3
4	**8d**	39	14
5	**8e**	89	75
6	**4b**	61	52
7	**8f**	78	67
8	**8g**	56	74

a *tert*-butyl substituent in the 3-positions (R^1) would have a severely detrimental effect on the catalytic activity of the catalyst.[25] It was hoped that the much smaller size of a hydroxy or methoxy group combined with their sodium coordinating ability would overcome this steric effect. However, as entries 1 and 4 in Table 3 show, complexes **8a** and **8d** exhibited very poor levels of asymmetric induction. It is likely that the chemical yield observed in these cases is largely due to an uncatalysed alkylation as we have previously shown that significant formation of α-methyl phenylalanine occurs under the conditions of Scheme 1, even if the catalyst is omitted.[28]

The other two catalysts containing hydroxyl groups (**8b** and **8c**) also showed negligible levels of asymmetric induction (Table 3: entries 2 and 3). Catalysts **8a–c** will almost certainly form bis-sodium salts in situ, and this may prevent the formation of the bimetallic complex shown in Figure 1 and hence account for the lack of catalytic activity.

The methoxy containing catalysts **8d–f** and **4b** were all much more enantioselective than the corresponding hydroxy derivatives, even when the methoxy groups are in the 3-positions (R^1) (Table 3: compare entries 1 and 4). However, the highest chemical yield and asymmetric induction was observed with catalyst **8e** in which the methoxy groups are in the 4-positions (R^2) (Table 3: entry 5). In this position, the methoxy groups cannot coordinate the sodium ion in the model shown in Figure 1 and cannot exert any other obvious steric or electronic effect on the catalysis. It is notable that the second best results (Table 3: entry 7) were obtained with catalyst **8f** with the methoxy groups in the 6-position (R^4), the other position on the aromatic ring where the substituent cannot exert an apparent steric or electronic effect. Catalysts **8e** and **8f** were both significantly more active and enantioselective than catalyst **4b** (Table 3: entry 6) in which the methoxy group is *para* to the coordinating oxygen and so can exert a mesomeric electronic effect on the copper ion. Catalyst **8g** with methyl rather than methoxy groups in the R^4-positions showed essentially identical enantioselectivity to catalyst **8e**, suggesting that the enantioselectivity is not connected to the presence of an oxygen atom.

Since the catalysts used during this work were prepared by two different routes and since the method reported for the preparation of catalyst **1b** was no longer viable due to the commercial unavailability of sephadex LH20, it was decided to carry out a direct comparison of catalysts prepared by both synthetic routes. Two catalysts, **1b** and **8e**, were chosen for this study. Samples of both catalysts were prepared from the appropriate salen ligand using copper bromide/sodium methoxide followed by purification by chromatography on sephadex LH20 and by use of copper acetate followed by isolation of the catalyst by precipitation and purification by washing. The results obtained when the resulting catalysts were used to induce the asymmetric benzylation of substrate **7c** are compared in Table 4.

In the case of catalyst **1b**, the catalyst prepared using the copper acetate procedure was noticeably less enantioselective than the catalyst prepared by the copper bromide procedure (Table 4: entries 1 and 2). This may be partly due to the catalyst prepared from copper acetate being less pure due to the lack of a chromatographic purification, and use of an increased mol% of the catalyst did increase the enantioselectivity slightly (Table 4: entries 3 and 4). However, it was still not possible to match the enantioselectivity obtained using the catalyst prepared from copper bromide and increasing the mol% of catalyst above 4 mol% was severely detrimental to both the enantioselectivity and the chemical yield (Table 4: entry 5). The enantioselectivity of catalyst **1b** prepared using copper acetate could be further slightly increased by recrystallizing the catalyst from dichloromethane (Table 4: entry 6). This process was used in the literature to obtain crystals of complex **1b** suitable for X-ray analysis.[37] However, the recrystallization is very slow and low yielding and so not synthetically useful.

Table 4. Effect of method of preparation on the enantioselectivity of catalysts **1b** and **8e**

Entry	Catalyst (mol%)	Preparation	Yield (%)	ee (%)
1	**1b** (2)	$CuBr_2$	71	92
2	**1b** (2)	$Cu(OAc)_2$	94	78
3	**1b** (3)	$Cu(OAc)_2$	61	82
4	**1b** (4)	$Cu(OAc)_2$	78	81
5	**1b** (6)	$Cu(OAc)_2$	28	64
6	**1b**[a] (2)	$Cu(OAc)_2$	83	84
7	**8e** (2)	$CuBr_2$	89	75
8	**8e** (2)	$Cu(OAc)_2$	89	83
9	**8e** (3)	$Cu(OAc)_2$	59	80
10	**1c** (2)	$Co(OAc)_2$	89	85

[a] Catalyst was additionally recrystallized from dichloromethane.

In contrast, catalyst **8e** was found to be more enantioselective when prepared using copper acetate than when prepared using copper bromide (Table 4: entries 7 and 8). It may be that the purification by washing is more successful in the case of catalyst **8e** than catalyst **1b**. Increasing the amount of catalyst **8e** above the standard 2 mol% was found to have a detrimental effect on both the enantioselectivity and the chemical yield (Table 4: entry 9).

We have previously reported that Co(salen) complex **1c** (prepared using cobalt acetate) was as enantioselective as copper(salen) complex **1b** (prepared using copper bromide). This comparison was carried out using substrate **2b** and the enantioselectivities were 81 and 80% for catalysts **1b** and **1c** respectively.[26] Therefore, we decided to see if the enantioselectivity observed with catalyst **1c** could be further enhanced by the use of substrate **7c**. Treatment of substrate **7c** with benzyl bromide under the standard conditions (Scheme 1) using 2 mol% of complex **1c** as catalyst resulted in the formation of α-methyl phenylalanine methyl ester **3b** in 89% yield and 85% enantiomeric excess (Table 4: entry 10). This result is the best obtainable with any of the catalysts studied without the need for purification on sephadex LH20.

3. Conclusions

The enantioselectivity of (salen)Cu complexes as catalysts for the asymmetric benzylation of alanine derivatives was found to be strongly influenced by substituents on the aromatic rings of the salen ligand. All of the substituents

studied at any location on the aromatic rings had a negative effect on the enantioselectivity. In contrast, substituents on the aromatic ring of the *N*-arylidene alanine methyl ester substrate could have either a positive or negative effect. Optimal results were obtained using a *para*-chlorobenzylidene imine.

The mode of preparation of the catalyst was also found to influence its enantioselectivity. The best result (92% ee) was obtained when the catalyst was prepared using copper bromide and purified by chromatography on sephadex LH20. An alternative procedure using copper acetate and purification by washing with various solvents gave a less enantioselective (78% ee) catalyst derived from the unsubstituted salen ligand, though the enantioselectivity of the catalyst could be increased to 84% by further purification by recrystallization. In contrast however, for catalyst **8e** derived from the 4-methoxy-salen ligand, the copper acetate route was found to give a more enantioselective (83% ee) catalyst than the copper bromide procedure (75% ee). The most enantioselective catalyst (85% ee) which did not need purification by sephadex LH20 however was complex **1c** derived from cobalt acetate.

4. Experimental

^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a Bruker Avance 360 Spectrometer, (^{1}H 360 MHz, ^{13}C 90 MHz, and ^{19}F 338 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 ^{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 ionization with ammonia as the reagent gas (CI), fast atom bombardment (FAB) or electrospray ionization (ES). 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.

4.1. 2-Hydroxy-5-trifluoromethylbenzaldehyde[33] 6e

In a three-neck flask under an argon atmosphere, 2-bromo-4-trifluoromethylphenol[34] (0.95 g, 4.2 mmol) was dissolved in THF (40 mL). The resulting solution was stirred and cooled to −60 °C and then *n*-BuLi (3.4 mL of a 2.5 M solution in hexane) was added dropwise. The reaction temperature was maintained at −60 °C for 1 h. Dimethyl formamide (1.6 mL, 21.1 mmol) was then added dropwise at the same temperature, stirred for another 5 min at −60 °C, and then the mixture was allowed to increase its temperature slowly until it reached room temperature and was stirred overnight. The reaction was hydrolysed with diluted hydrochloric acid and extracted 3 times with dichloromethane. The combined organic layers were dried and evaporated in vacuo to dryness to give a yellow oil which was chromatographed using dichloromethane/hexane (2:1) as eluent to give aldehyde **6e** (239 mg, 30%) as a white solid. Mp 59–60 °C; $\nu_{max}(CHCl_3)$ 3156 (s), 2960 (w), 2856 (w), 1665 (s), 1632 (m), 1596 (m), and 1496 cm^{-1} (m); $\delta_H(CDCl_3)$ 7.0–7.8 (3H, m, ArCH), 9.88 (1H, s, HCO), 11.23 (1H, s, OH); $\delta_C(CDCl_3)$ 119.1 (ArCH), 120.3 (ArC), 122.9 (q $^2J_{CF}$=34 Hz, Ar*C*CF$_3$), 124.0 (q $^1J_{CF}$=272 Hz, CF_3), 131.4 (q $^3J_{CF}$=4 Hz, ArCH), 133.8 (q $^3J_{CF}$=3 Hz, ArCH), 164.3 (ArC), 196.2 (HCO); $\delta_F(CDCl_3)$ −62.4 (CF_3); *m*/*z* (EI) 190 (M^+, 100), 189 (100), 172 (19), 161 (27), 144 (20). Found: C, 50.70%; H, 2.70%; $C_8H_5O_2F_3$ requires: C, 50.54%; H, 2.65%.

4.2. General procedure for the preparation of salen ligands

To a stirred mixture of aldehyde (20.0 mmol) and (1*R*,2*R*)-diaminocyclohexane dihydrochloride (1.87 g, 10.0 mmol) in methanol (37 mL) and ethanol (37 mL) was added a solution of NaOMe (5 mL of a 4.65 N solution) at room temperature. The resulting bright yellow solution was stirred under reflux overnight, then allowed to cool to room temperature, filtered and evaporated in vacuo. The yellow residue was taken up in dichloromethane (80 mL), filtered, then the organic layers were washed with water (2×30 mL) and brine (30 mL). The combined aqueous layers were back extracted with dichloromethane. The combined organic layers were dried and evaporated in vacuo to leave the desired ligand.

4.2.1. (1*R*,2*R*)-[*N*,*N*′-Bis-(2′-hydroxy-5′-*tert*-butylbenzylidene)]-1,2-diaminocyclohexane[38] 5a. Obtained as a pale yellow solid in 70% yield. Mp 115–116 °C; $[\alpha]_D^{20}$=−184 (*c* 0.9, $CHCl_3$); ν_{max}(KBr) 2959 (s), 2863 (m), 1632 (s), and 1492 cm^{-1} (s); $\delta_H(CDCl_3)$ 1.16 (9H, s, $C(CH_3)_3$), 1.3–1.8 (4H, m, CH_2CH_2), 3.2–3.3 (1H, m, CHN), 6.7–6.9 (1H, m, ArCH), 7.2–7.3 (3H, m, ArCH), 8.18 (1H, s, HC=N); $\delta_C(CDCl_3)$ 23.2 (CH_2), 30.4 (CH_3), 32.2 (CH_2), 32.9 (CMe_3), 71.8 (CHN), 115.2 (ArCH), 116.9 (ArC), 126.9 (ArCH), 128.4 (ArCH), 140.2 (ArC), 157.6 (ArC), 164.0 (HC=N).

4.2.2. (1*R*,2*R*)-[*N*,*N*′-Bis-(2′-hydroxy-5′-methoxy-benzylidene)]-1,2-diaminocyclohexane 5b. Obtained as a yellow solid in 88% yield. Mp 118–120 °C; $[\alpha]_D^{20}=-306$ (*c* 1.0, $CHCl_3$); ν_{max}($CHCl_3$) 2936 (m), 2860 (w), 1636 (s), and 1592 cm^{-1} (s); δ_H($CDCl_3$) 1.5–2.0 (4H, m, CH_2CH_2), 3.3–3.4 (1H, m, CHN), 3.72 (3H, s, OCH_3), 6.66 (1H, dd *J*=2.7 Hz, ArCH), 6.85 (1H, s, ArCH), 6.86 (1H, d *J*=2.7 Hz, ArCH), 8.21 (1H, s, HC═N), 12.83 (1H, s, OH); δ_C($CDCl_3$) 24.6 (CH_2), 33.5 (CH_2), 56.3 (OCH_3), 73.2 (CHN), 115.2 (ArCH), 117.9 (ArCH), 118.7 (ArC), 119.8 (ArCH), 152.4 (ArC), 155.5 (ArC), 164.9 (HC═N); *m*/*z* (CI) 383 (MH^+, 100), 249 (8). Found (ES) 383.1957, $C_{22}H_{27}N_2O_4$ (MH^+) requires 383.1971.

4.2.3. (1*R*,2*R*)-[*N*,*N*′-Bis-(2′-hydroxy-5′-nitro-benzylidene)]-1,2-diaminocyclohexane[38,39] 5c. Obtained as a yellow solid in 77% yield. Mp 198–200 °C; $[\alpha]_D^{20}=-27$ (*c* 1.0, $CHCl_3$); ν_{max}(KBr) 2926 (m), 1639 (s), 1538 (m), and 1484 cm^{-1} (m); δ_H($CDCl_3$) 1.4–1.5 (1H, m, CH_2), 1.6–1.8 (1H, m, CH_2), 1.9–2.0 (2H, m, CH_2), 3.3–3.5 (1H, m, CH–N), 6.8–6.9 (1H, m, ArCH), 8.0–8.10 (2H, m, ArCH), 8.28 (1H, s, HC═N); δ_C($CDCl_3$) 24.3 (CH_2), 33.1 (CH_2), 72.4 (CHN), 117.5 (ArC), 118.7 (ArCH), 128.3 (ArCH), 128.5 (ArCH), 139.9 (ArC), 164.1 (HC═N), 167.7 (ArC).

4.2.4. (1*R*,2*R*)-[*N*,*N*′-Bis-(2′-hydroxy-5′-fluoro-benzylidene)]-1,2-diaminocyclohexane 5d. Obtained as yellow crystals in 36% yield after recrystallization from hexane–isopropanol. Mp 121–123 °C; $[\alpha]_D^{20}=-494$ (*c* 0.4, $CHCl_3$); ν_{max}($CHCl_3$) 2938 (m), 2862 (m), 1636 (s) and 1589 cm^{-1} (m); δ_H($CDCl_3$) 1.4–1.5 (1H, m, CH_2), 1.6–1.7 (2H, m, CH_2), 1.8–1.85 (2H, m, CH_2), 3.2–3.3 (1H, m, CHN), 6.7–6.9 (3H, m, ArCH), 8.12 (1H, s, HC═N), 12.90 (1H, br s, OH); δ_C($CDCl_3$) 24.5 (CH_2), 33.3 (CH_2), 73.1 (CHN), 116.9 (d $^2J_{CF}$=23 Hz, ArCH), 118.2 (d $^3J_{CF}$=7 Hz, ArC), 118.7 (d $^3J_{CF}$=7 Hz, ArCH), 119.7 (d $^2J_{CF}$=23 Hz, ArCH), 155.7 (d $^1J_{CF}$=237 Hz, ArCF), 157.4 (d $^4J_{CF}$=1 Hz, ArCO), 164.1 (d $^4J_{CF}$=2 Hz, HC═N); δ_F($CDCl_3$) −126.3 (ArC–F); *m*/*z* (CI) 359 (MH^+, 100), 237 (7). Found (ES) 381.1372, $C_{20}H_{20}N_2O_2F_2Na$ ($M+Na^+$) requires 381.1385.

4.2.5. (1*R*,2*R*)-[*N*,*N*′-Bis-(2′-hydroxy-5′-trifluoromethyl-benzylidene)]-1,2-diaminocyclohexane 5e. Obtained as a yellow solid in a yield of 77%. Mp 120–122 °C; $[\alpha]_D^{20}=-250$ (*c* 0.4, $CHCl_3$); ν_{max}($CHCl_3$) 2936 (w), 1622 (s), and 1541 cm^{-1} (m); δ_H($CDCl_3$) 1.4–2.0 (4H, m, CH_2CH_2), 3.3–3.4 (1H, m, CHN), 6.9–7.4 (3H, m, ArCH), 8.22 (1H, s, HC═N), 13.64 (1H, s, OH); δ_C($CDCl_3$) 23.0 (CH_2), 31.9 (CH_2), 71.5 (CHN), 116.6 (ArCH), 116.9 (ArC), 120.0 (q $^2J_{CF}$=33 Hz, Ar*C*CF_3), 123.0 (q $^1J_{CF}$=271 Hz, CF_3), 127.7 (q $^3J_{CF}$=4 Hz, ArCH), 128.1 (q $^3J_{CF}$=3 Hz, ArCH), 162.7 (ArC), 162.9 (HC═N); δ_F($CDCl_3$) −62.0 (CF_3); *m*/*z* (CI) 459 (MH^+, 100), 190 (6), 52 (30). Found (ES) 481.1356, $C_{22}H_{20}N_2O_2F_6Na$ ($M+Na^+$) requires 481.1321.

4.2.6. (1*R*,2*R*)-[*N*,*N*-Bis-(2′-hydroxy-3′-methoxy-benzylidene)]-1,2-diaminocyclohexane.[40] Obtained as a yellow gel in 57% yield using the general procedure but with only a three hour reflux and ethyl acetate rather than dichloromethane used to extract the product. $[\alpha]_D^{20}=-490$ (*c* 0.05, $CHCl_3$); ν_{max}($CHCl_3$) 2937 (w), 2861 (w), 2254 (w), 1629 (s), and 1464 cm^{-1} (s); δ_H($CDCl_3$) 1.4–1.9 (4H, m, CH_2CH_2), 3.2–3.3 (1H, m, CHN), 3.80 (3H, s, OCH_3), 6.32 (1H, t *J*=7.75 Hz, ArCH), 6.71 (1H, dd *J*=7.75, 1.6 Hz, ArCH), 6.78 (1H, dd *J*=7.7, 1.7 Hz, ArCH), 8.17 (1H, s, HC═N); *m*/*z* (CI) 383 (M^+, 10), 242 (12), 210 (100), 193 (95), 170 (50). Found (ES) 405.1805, $C_{22}H_{26}N_2O_4Na$ ($M+Na^+$) requires 405.1785.

4.2.7. (1*R*,2*R*)-[*N*,*N*-Bis-(2′-hydroxy-4′-methoxy-benzylidene)]-1,2-diaminocyclohexane. Obtained as a yellow gel in 92% yield using the general procedure but with only a three hour reflux and ethyl acetate rather than dichloromethane used to extract the product. $[\alpha]_D^{20}=-1477$ (*c* 0.015, MeOH); ν_{max}($CHCl_3$) 3388 (br), 2935 (w), 1625 (s), 1580 (m), and 1514 cm^{-1} (m); δ_H($CDCl_3$) 1.3–2.1 (4H, m, CH_2CH_2), 3.2–3.3 (1H, m, CHN), 3.79 (3H, s, OCH_3), 6.33 (1H, dd *J*=8.6, 2.4 Hz, ArCH), 6.37 (1H, d *J*=2.4 Hz, ArCH), 7.01 (1H, d *J*=8.6 Hz, ArCH), 8.11 (1H, s, HC═N), 13.83 (1H, br s, OH); δ_C($CDCl_3$) 24.6 (CH_2), 33.5 (CH_2), 55.7 (OCH_3), 72.0 (CHN), 101.5 (ArCH), 106.6 (ArCH), 112.6 (ArC), 133.1 (ArCH), 163.8 (ArC), 164.1 (HC═N), 165.3 (ArC); *m*/*z* (CI) 383 (MH^+, 100), 249 (14), 152 (11). Found (ES) 383.1927, $C_{22}H_{27}N_2O_4$ (MH^+) requires 383.1965.

4.2.8. (1*R*,2*R*)-[*N*,*N*-Bis-(2′-hydroxy-6′-methoxy-benzylidene)]-1,2-diaminocyclohexane. Obtained as a yellow solid in 79% yield using the general procedure but with only a three hour reflux and ethyl acetate rather than dichloromethane used to extract the product. Mp 156–157 °C; $[\alpha]_D^{20}=-42.5$ (*c* 0.035, $CHCl_3$); ν_{max}($CHCl_3$) 2937 (w), 2360 (w), 2252 (w), 1624 (s), 1578 (m), and 1446 cm^{-1} (s); δ_H($CDCl_3$) 1.4–2.0 (4H, m, CH_2CH_2), 3.3–3.4 (1H, m, CHN), 3.73 (3H, s, OCH_3), 6.21 (1H, d *J*=8.2 Hz, ArCH), 6.48 (1H, d *J*=8.4 Hz, ArCH), 7.17 (1H, t *J*=7.7 Hz, ArCH), 8.70 (1H, s, HC═N), 14.37 (1H, s, OH); δ_C($CDCl_3$) 24.6 (CH_2), 33.5 (CH_2), 55.9 (OCH_3), 72.5 (CHN), 99.9 (ArCH), 108.3 (ArC), 110.5 (ArCH), 133.6 (ArCH), 160.0 (ArC), 161.3 (HC═N), 164.4 (ArC); *m*/*z* (CI) 384 (MH^+, 100), 249 (17), 152 (11). Found (ES) 383.1944, $C_{22}H_{27}N_2O_4$ (MH^+) requires 383.1965. Found (ES) 405.1764, $C_{22}H_{26}N_2O_4Na$ ($M+Na^+$) requires 405.1784.

4.2.9. (1*R*,2*R*)-[*N*,*N*-Bis-(2′,3′-dihydroxybenzylidene)]-1,2-diaminocyclohexane. To a stirred mixture of 2,3-dihydroxybenzaldehyde (2.0 g, 14.48 mmol) in methanol (100 mL) was added a solution of (1*R*,2*R*)-diaminocyclohexane dihydrochloride (1.35 g, 7.24 mmol) and sodium methoxide (0.78 g, 14.48 mmol) in methanol (100 mL) at room temperature. The resulting bright yellow solution was stirred under reflux for 2 h. Subsequently it was allowed to cool to room temperature and then evaporated in vacuo. The yellow residue was dissolved in dichloromethane (3×50 mL). The organic layers were washed with water (4×50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo to give a yellow gel. Crystallization from ethyl acetate and hexane at 4 °C overnight, gave an orange solid which was washed with hexane (2×10 mL) to obtain the desired compound (1.64 g 64%) as an orange solid. Mp 120–121 °C; $[\alpha]_D^{20}=-876$ (*c* 0.5, $CHCl_3$); ν_{max}($CHCl_3$) 3352 (br), 2937 (w), 2253 (w), and 1631 cm^{-1} (s); δ_H($CDCl_3$) 1.3–2.0 (4H, m, CH_2CH_2), 3.3–3.4 (1H, m, CHN), 6.56 (1H, t *J*=7.7 Hz, ArCH), 6.63 (1H, dd *J*=7.7, 1.6 Hz, ArCH), 6.85 (1H, dd *J*=7.7, 1.6 Hz, ArCH), 8.12 (1H, s, HC═N); δ_C($CDCl_3$) 24.5 (CH_2), 33.3

(CH_2), 71.3 (CHN), 117.2 (ArC), 117.0 (ArCH), 118.2 (ArCH), 122.7 (ArCH), 145.8 (ArC), 152.6 (ArC), 165.2 (HC═N); *m/z* (CI) 355 (MH^+, 3), 100 (15), 98 (100), 96 (20), 94 (12). Found (ES) 355.1653, $C_{20}H_{23}N_2O_4$ (MH^+) requires 355.1652.

4.2.10. (1*R*,2*R*)-[*N*,*N*-Bis-(2′,4′-dihydroxybenzylidene)]-1,2-diaminocyclohexane. To a stirred mixture of 2,4-dihydroxybenzaldehyde (2.0 g, 14.48 mmol) in methanol (100 mL) was added a solution of (1*R*,2*R*)-diaminocyclohexane dihydrochloride (1.35 g, 7.24 mmol) and sodium methoxide (0.78 g, 14.48 mmol) in methanol (100 mL) at room temperature. The resulting bright yellow solution was stirred under reflux for 2 h. The reaction mixture was cooled to room temperature and the yellow precipitate collected by filtration, washed with methanol (3×10 mL) and dried in vacuo to leave the desired compound (2.31 g, 90%) as a yellow solid. Mp >400 °C; $[\alpha]_D^{20}=-139$ (*c* 0.015, DMSO); ν_{max}(KBr) 2934 (w), 2524 (br), 1855 (br), and 1634 cm^{-1} (s); δ_H(DMSO-d_6) 1.4–1.9 (4H, m, CH_2CH_2), 3.28 (1H, m, CHN), 6.10 (1H, d *J*=2.1 Hz, ArCH), 6.21 (1H, dd *J*=8.5, 2.1 Hz, ArCH), 7.08 (1H, d *J*=8.5 Hz, ArCH), 8.27 (1H, s, HC═N), 9.99 (1H, br s, OH), 13.67 (1H, s, OH); δ_C(DMSO-d_6) 24.1 (CH_2), 33.1 (CH_2), 70.9 (CHN), 101.7 (ArCH), 107.2 (ArCH), 111.5 (ArC), 133.5 (ArCH), 161.9 (ArC), 164.1 (ArC), 164.4 (HC═N); *m/z* (CI) 355 (MH^+, 22), 235 (35), 189 (54), 136 (29), 115 (100). Found (ES) 355.1640, $C_{20}H_{23}N_2O_4$ (MH^+) requires 355.1652.

4.2.11. (1*R*,2*R*)-[*N*,*N*-Bis-(2′,5′-dihydroxybenzylidene)]-1,2-diaminocyclohexane.[41] To a stirred mixture of 2,5-dihydroxybenzaldehyde (2.0 g, 14.48 mmol) in methanol (100 mL) was added a solution of (1*R*,2*R*)-diaminocyclohexane dihydrochloride (1.35 g, 7.24 mmol) and sodium methoxide (0.78 g, 14.48 mmol) in methanol (100 mL) at room temperature. The resulting bright yellow solution was stirred under reflux for 2 h. Subsequently it was allowed to cool to room temperature and then evaporated in vacuo. The brown residue was dissolved in dichloromethane (3×50 mL) and filtered. The organic layers were washed with water (100 mL), dried ($MgSO_4$) and evaporated in vacuo to give a brown gel. The residue was crystallized from diethyl ether and hexane and the yellow precipitate was collected by filtration, washed with hexane (2×10 mL) and dried in vacuo to give the desired compound (795 mg, 31%) as a yellow solid. Mp 123–124 °C; $[\alpha]_D^{20}=-312$ (*c* 0.5, MeOH); ν_{max}(KBr) 3363 (br), 2935 (w), 1638 (s), and 1592 cm^{-1} (m); δ_H(DMSO-d_6) 1.4–1.9 (4H, m, CH_2CH_2), 6.6–6.7 (3H, m, ArCH), 8.94 (1H, s, HC═N), 9.20 (1H, s, OH), 12.46 (1H, s, OH); δ_C(CD_3OD) 25.7 (CH_2), 34.4 (CH_2), 74.1 (CHN), 120.2 (ArC), 118.1 (ArCH), 118.4 (ArCH), 121.5 (ArCH), 150.8 (ArC), 155.8 (ArC), 166.7 (HC═N); *m/z* (CI) 355 (MH^+, 81), 235 (100). Found (ES) 355.1645, $C_{20}H_{23}N_2O_4$ (MH^+) requires 355.1652.

4.3. General procedure for the preparation of copper(salen) complexes using copper bromide

To a solution of a chiral salen ligand (1.0 mmol) in methanol (5 mL) were added $CuBr_2$ (0.223 g, 1.0 mmol) and NaOMe (0.23 mL of a 4.6 N solution in MeOH). The resulting mixture was stirred for 3 h at room temperature and then the solvent was removed in vacuo. The crude residue was purified by gel permeation chromatography on LH-20 using EtOH/toluene (1:3) as eluent.

4.4. General procedure for the preparation of copper(salen) complexes using copper acetate

Solutions of the appropriate salen ligand (0.83 mmol) in ethanol (20 mL) and cuprous acetate monohydrate (0.17 g, 0.83 mmol) in water (2 mL) were mixed and refluxed under vigorous stirring for 2 h. After this time, the resulting solution was cooled to room temperature, filtered and the precipitate washed successively with water, methanol and diethyl ether (3×10 mL) to give the desired compound.

4.4.1. [(1*R*,2*R*)-[*N*,*N*-Bis-(2′-hydroxybenzylidene)]-1,2-diaminocyclohexanato]copper(II) 1b. Obtained as a purple solid in 82% yield using the copper acetate procedure. Mp >400 °C; $[\alpha]_D^{20}=-877$ (*c* 0.0219, $CHCl_3$); ν_{max}(KBr) 2931 (w), 1589 (s), and 1534 cm^{-1} (s); *m/z* (CI) 384 (29), 324 (34), 323 (100), 320 (32), 239 (28), 123 (28), 94 (47), 69 (27). Found (ES) 406.0729, $C_{20}H_{20}N_2O_2CuNa$ ($MH+Na^+$) requires 406.0713.

4.4.2. [(1*R*,2*R*)-[*N*,*N*′-Bis-(2′-hydroxy-5′-*tert*-butylbenzylidene)]-1,2-diaminocyclohexanato]copper(II) 4a. Obtained as a brown solid in a yield of 87% using the copper bromide procedure. Mp >270 °C; $[\alpha]_D^{20}=-604$ (*c* 0.013, $CHCl_3$); ν_{max}($CHCl_3$) 3018 (w), 2951 (s), 2861 (m), 1620 (s), 1525 (s), and 1470 cm^{-1} (s); *m/z* (ES) 496 (MH^+, 100), 331 (49). Found (ES) 496.2183, $C_{28}H_{37}N_2O_2Cu$ (MH^+) requires 496.2151.

4.4.3. [(1*R*,2*R*)-[*N*,*N*′-Bis-(2′-hydroxy-5′-methoxybenzylidene)]-1,2-diaminocyclohexanato]copper(II) 4b. Obtained as a brown solid in 79% yield using the copper bromide procedure. Mp >250 °C; $[\alpha]_D^{20}=-600$ (*c* 0.005, $CHCl_3$); ν_{max}($CHCl_3$) 2931 (m), 1634 (s), 1614 (m), 1538 (m), and 1468 cm^{-1} (s); *m/z* (CI) 444 (MH^+, 19), 383 (100), 232 (24), 151 (57). Found (ES) 444.1112, $C_{22}H_{25}N_2O_4Cu$ (MH^+) requires 444.1110.

4.4.4. [(1*R*,2*R*)-[*N*,*N*′-Bis-(2′-hydroxy-5′-nitro-benzylidene)]-1,2-diaminocyclohexanato]copper(II) 4c. Obtained using the copper bromide procedure without chromatography as an insoluble solid which was used without further purification. ν_{max}(KBr) 3062 (w), 2940 (w), 2862 (w), 1633 (m), 1601 (s), 1550 (m), and 1494 cm^{-1} (m).

4.4.5. [(1*R*,2*R*)-[*N*,*N*′-Bis-(2′-hydroxy-5′-fluoro-benzylidene)]-1,2-diaminocyclohexanato]copper(II) 4d. Obtained as a brown solid in a yield of 26% using the copper bromide procedure. Mp >270 °C; $[\alpha]_D^{20}=-640$ (*c* 0.025, $CHCl_3$); ν_{max}(KBr) 2942 (w), 1632 (s), 1538 (m), and 1462 cm^{-1} (s); *m/z* (ES) 420 (MH^+, 100), 140 (7). Found (ES) 420.0700, $C_{20}H_{19}N_2O_2F_2Cu$ (MH^+) requires 420.0711.

4.4.6. [(1*R*,2*R*)-[*N*,*N*′-Bis-(2′-hydroxy-5′-trifluoromethylbenzylidene)]-1,2-diaminocyclohexanato]copper(II) 4e. Obtained as a purple solid in a yield of 30% using the copper bromide procedure. Mp >270 °C. $[\alpha]_D^{20}=-352$ (*c* 0.013, $CHCl_3$); ν_{max}(KBr) 2936 (w), 2861 (w), 1633 (s), 1620 (s), and 1542 cm^{-1} (m); *m/z* (FAB) 520 (M^+, 48), 307 (19), 289 (12), 154 (100), 136 (69), 107 (27), 77 (33).

Found: C, 50.80%; H, 3.77%; N, 5.14%; $C_{22}H_{18}N_2O_2F_6Cu$ requires C, 50.82%; H, 3.49%; N, 5.39%.

4.4.7. [(1*R*,2*R*)-[*N*,*N*-Bis-(2′3′-dihydroxy-benzylidene)]-1,2-diaminocyclohexanato]copper(II) 8a. Obtained as a brown solid in 67% yield using the copper bromide procedure. Mp >400 °C; $[\alpha]_D^{20}=-1096$ (*c* 0.016, $CHCl_3$); ν_{max}(KBr) 3394 (br), 2933 (m), 2859 (w), 1626 (s), and 1551 cm^{-1} (m); *m*/*z* (ES) 438 (M+Na^+, 100), 281 (20), 227 (22), 179 (32). Found (ES) 416.0779, $C_{20}H_{21}N_2O_4Cu$ (MH^+) requires 416.0797. Found (ES) 438.0601, $C_{20}H_{20}N_2O_4CuNa$ (M+Na^+) requires 438.0611.

4.4.8. [(1*R*,2*R*)-[*N*,*N*-Bis-(2′4′-dihydroxy-benzylidene)]-1,2-diaminocyclohexanato]copper(II) 8b. Obtained as a brown solid in 83% yield using the copper acetate procedure. Mp >400 °C; $[\alpha]_D^{20}=-958$ (*c* 0.009, DMSO); ν_{max}(KBr) 3109 (br) 2934 (w), 1621 (s), and 1542 cm^{-1} (s); *m*/*z* (ES) 438 (M+Na^+, 100), 416 (MH^+, 63), 415 (86), 178 (17). Found (ES) 416.0783, $C_{20}H_{21}N_2O_4Cu$ (MH^+) requires 416.0791. Found (ES) 438.0601, $C_{20}H_{20}N_2O_4CuNa$ (M+Na^+) requires 438.0611.

4.4.9. [(1*R*,2*R*)-[*N*,*N*-Bis-(2′5′-dihydroxy-benzylidene)]-1,2-diaminocyclohexanato]copper(II) 8c. Obtained as a green/brown solid in 74% yield using the copper acetate procedure. Mp >400 °C; $[\alpha]_D^{20}=-957$ (*c* 0.011, $CHCl_3$); ν_{max}(KBr) 3375 (w), 2934 (w), 1621 (s), and 1542 cm^{-1} (s); *m*/*z* (ES) 416 (MH^+, 100). Found (ES) 416.0797, $C_{22}H_{21}N_2O_4Cu$ (MH^+) requires 416.0791.

4.4.10. [(1*R*,2*R*)-[*N*,*N*-Bis-(2′-hydroxy-3′-methoxy-benzylidene)]-1,2-diaminocyclohexanato]copper(II) 8d. Obtained as a red/brown solid in 94% yield using the copper bromide procedure. Mp 289–290 °C; $[\alpha]_D^{20}=-606$ (*c* 0.032, $CHCl_3$); ν_{max}(KBr) 3504 (br), 2932 (m), 1627 (s), and 1545 cm^{-1} (m); *m*/*z* (ES) 466 (M+Na^+, 100), 413 (10), 195 (30). Found (ES) 466.0990, $C_{22}H_{24}N_2O_4CuNa$ (M+Na^+) requires 466.0924.

4.4.11. [(1*R*,2*R*)-[*N*,*N*-Bis-(2′-hydroxy-4′-methoxy-benzylidene)]-1,2-diaminocyclohexanato]copper(II) 8e. Obtained as a brown solid in 75% yield using the copper bromide procedure and as a dark purple solid in 64% yield using the copper acetate procedure. Data for the product obtained using copper bromide. Mp >400 °C; $[\alpha]_D^{20}=-529$ (*c* 0.035, $CHCl_3$); ν_{max}(KBr) 3434 (br), 2933 (m), 1626 (s), and 1551 cm^{-1} (s); *m*/*z* (CI); 444 (MH^+, 52), 383 (98), 139 (100), 125 (41), 98 (96). Found (ES) 444. 1110, $C_{22}H_{25}N_2O_4Cu$ (MH^+) requires 444.1105. Data for the product obtained using copper acetate. Mp >400 °C; $[\alpha]_D^{20}=-968$ (*c* 0.022, $CHCl_3$); ν_{max}(KBr) 2933 (w), 1605 (s), and 1530 cm^{-1} (s); *m*/*z* (ES) 444 (MH^+, 100). Found (ES) 444. 1100, $C_{22}H_{25}N_2O_4Cu$ (MH^+) requires 444.1105.

4.4.12. [(1*R*,2*R*)-[*N*,*N*-Bis-(2′-hydroxy-6′-methoxy-benzylidene)]-1,2-diaminocyclohexanato]copper(II) 8f. Obtained as a brown solid in 79% yield using the copper acetate procedure. Mp 315–316 °C; $[\alpha]_D^{20}=-1074$ (*c* 0.005, $CHCl_3$); ν_{max}(KBr) 3424 (br), 3019 (m), 1637 (s), and 1544 cm^{-1} (m);. *m*/*z* (CI) 444 (MH^+, 20), 383 (67), 323 (17), 145 (18). Found (ES) 466. 0938, $C_{22}H_{24}N_2O_4CuNa$ (M+Na^+) requires 466.0924.

4.4.13. [(1*R*,2*R*)-[*N*,*N*-Bis-(2′-hydroxy-4′-methyl-benzylidene)]-1,2-diaminocyclohexanato]copper(II) 8g. Obtained as a brown solid in 64% yield using the copper acetate procedure. Mp 195–196 °C; $[\alpha]_D^{20}=-704$ (*c* 0.0135, $CHCl_3$); ν_{max}(KBr) 3406 (br), 2927 (m), 1609 (s), and 1527 cm^{-1} (m); *m*/*z* (ES) 412 (MH^+, 100). Found (ES) 412. 1200, $C_{22}H_{25}N_2O_4Cu$ (MH^+) requires 412.1207.

4.5. General procedure for the preparation of alanine Schiff bases

To a stirred suspension of alanine methyl ester hydrochloride (1.20 g, 7.20 mmol) in dichloromethane (10 mL), triethylamine (1.00 mL, 7.20 mmol), the appropriate aldehyde (7.20 mmol) and a small amount of $MgSO_4$ were added. The reaction mixture was stirred overnight at room temperature after which it was filtered and the solvent removed in vacuo. The residue was the taken up in diethyl ether (10 mL) and washed with Na_2CO_3(aq) (7×5 mL). The combined organic phases were then dried over $MgSO_4$ and evaporated to dryness to leave the desired product.

4.5.1. *para*-Nitrobenzylidene imine 7a. Obtained as an orange oil in 85% yield. $[\alpha]_D^{20}=+0.8$ (*c* 1.0, $CHCl_3$); ν_{max}(neat) 3107 (m), 2951 (m), 2854 (m), 1732 (s), 1601 (s), and 1518 cm^{-1} (s); δ_H($CDCl_3$) 1.58 (3H, d *J*=7 Hz, CH_3), 3.79 (3H, s, OCH_3), 4.25 (1H, q *J*=7 Hz, NCH), 7.97 (2H, d *J*=9 Hz, ArCH), 8.28 (2H, d *J*=9 Hz, ArCH), 8.44 (1H, s, HC=N); δ_C($CDCl_3$) 15.9 (CH_3), 52.6 (OCH_3), 68.5 (NCH), 124.4 (ArCH), 129.6 (ArCH), 141.8 (ArC), 149.8 (ArC), 161.4 (HC=N), 173.0 (CO_2); *m*/*z* (ES) 237 (MH^+, 50), 207 (100). Found (ES) 237.0873, $C_{11}H_{13}N_2O_4$ (MH^+) requires 237.0875.

4.5.2. *para*-Methoxybenzylidene imine[42] 7b. Obtained as a pale yellow oil in 78% yield. δ_H($CDCl_3$) 1.44 (3H, d *J*=7 Hz, CH_3), 3.67 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 4.02 (1H, q *J*=7 Hz, NCH), 6.84 (2H, d *J*=9 Hz ArCH), 7.64 (2H, d *J*=9 Hz, ArCH), 8.44 (1H, s, HC=N).

4.5.3. *para*-Chlorobenzylidene imine[43] 7c. Obtained as a yellow oil in 61% yield. δ_H($CDCl_3$) 1.47 (3H, d *J*=7 Hz, CH_3), 3.70 (3H, s, OCH_3), 4.11 (1H, q *J*=7 Hz, NCH), 7.45 (2H, d *J*=9 Hz, ArCH), 7.76 (2H, d *J*=9 Hz, ArCH), 8.22 (1H, s, HC=N).

4.5.4. *meta*-Chlorobenzylidene imine 7d. Obtained as a yellow oil in 68% yield. $[\alpha]_D^{20}=+0.6$ (*c* 1.0, $CHCl_3$); ν_{max} (neat) 3064 (w), 2984 (m), 2953 (m), 2871 (m), 1740 (s), 1645 (s), and 1570 cm^{-1} (s); δ_H($CDCl_3$) 1.42 (3H, d *J*=7 Hz, CH_3), 3.64 (3H, s, OCH_3), 4.04 (1H, q *J*=7 Hz, NCH), 7.21–7.31 (2H, m, ArCH), 7.49 (1H, m, ArCH), 7.71 (1H, s, ArCH), 8.16 (1H, s, HC=N); δ_C($CDCl_3$) 19.4 (CH_3), 52.0 (OCH_3), 67.7 (CH), 127.0 (ArCH), 128.0 (ArCH), 129.9 (ArCH), 131.1 (ArC), 134.8 (ArC), 137.5 (ArCH), 159.1 (HC=N), 172.7 (CO_2); *m*/*z* (CI) 228 (M(^{37}Cl)H^+, 30), 226 (M(^{35}Cl)H^+, 100), 166 (18). Found (EI) 225.0555, $C_{11}H_{12}NO_2^{35}Cl$ (M^+) requires 225.0557.

4.5.5. *ortho*-Chlorobenzylidene imine 7e. Obtained as a yellow oil in 67% yield. $[\alpha]_D^{20}=-0.1$ (*c* 1.0 $CHCl_3$); ν_{max}(neat) 3067 (w), 2986 (m), 2950 (m), 2890 (m), 1743 (s), 1636 (s), and 1592 cm^{-1} (m); δ_H($CDCl_3$) 1.45 (3H, d

J=7 Hz, CH_3), 3.67 (3H, s, OCH_3), 4.12 (1H, q J=7 Hz, NCH), 7.13–7.37 (3H, m, ArCH), 8.00 (1H, d J 7 Hz, ArCH), 8.66 (1H, s, HC=N); $\delta_C(CDCl_3)$ 18.4 (CH_3), 51.1 (OCH_3), 67.9 (NCH), 126.3 (ArCH), 127.4 (ArCH), 128.6 (ArCH), 130.6 (ArCH), 131.7 (ArC), 134.0 (ArC), 158.0 (HC=N), 171.6 (CO_2); *m/z* (CI) 226 (MH^+, 100). Found (ES) 226.0630, $C_{11}H_{13}NO_2^{35}Cl$ (MH^+) requires 226.0635.

4.5.6. *para*-Fluorobenzylidene imine 7f. Obtained as a yellow oil in 68% yield. $[\alpha]_D^{20}$=+26.1 (*c* 1.0, $CHCl_3$); ν_{max}(neat) 2986 (m), 2952 (m), 2872 (m), 1740 (s), 1644 (s), and 1501 cm^{-1} (s); $\delta_H(CDCl_3)$ 1.42 (3H, d J=7 Hz, CH_3), 3.64 (3H, s, OCH_3), 4.03 (1H, q J=7 Hz, NCH), 6.97 (2H, t J=9 Hz, ArCH), 7.7–7.8 (2H, m, ArCH), 8.18 (1H, s, HC=N); $\delta_C(CDCl_3)$ 20.0 (CH_3), 52.7 (OCH_3), 68.4 (CHN), 116.1 (ArCH), 116.3 (ArC), 131.0 (ArCH), 162.1 (HC=N), 166.3 (ArCF), 173.5 (CO_2); *m/z* (CI) 210 (MH^+, 100), 150 (20). Found (ES) 210.0927, $C_{11}H_{13}NO_2F$ (MH^+) requires 210.0930.

4.5.7. *para*-Bromobenzylidene imine[43,44] 7g. Obtained as a yellow oil in 74% yield. $\delta_H(CDCl_3)$ 1.42 (3H, d J=7 Hz, CH_3), 3.65 (3H, s, OCH_3), 4.04 (1H, q J=7 Hz, NCH), 7.43 (2H, d J=8.5 Hz, ArCH), 7.54 (2H, d J=8.5 Hz, ArCH), 8.16 (1H, s, HC=N).

4.5.8. *para*-Iodobenzylidene imine 7h. Obtained as a yellow oil in 72% yield from a reaction carried out following the general procedure with exclusion of light. $[\alpha]_D^{20}$=−0.1 (*c* 1.0, $CHCl_3$); ν_{max}(neat) 2983 (m), 2984 (m), 2870 (m), 1740 (s), 1642 (s), and 1585 cm^{-1} (s); $\delta_H(CDCl_3)$ 1.41 (3H, d J=7 Hz, CH_3), 3.64 (3H, s, OCH_3), 4.11 (1H, q J=7 Hz, NCH), 7.45 (2H, d J=9 Hz, ArCH), 7.76 (2H, d J=9 Hz, ArCH), 8.13 (1H, s, HC=N); $\delta_C(CDCl_3)$ 15.7 (CH_3), 52.7 (OCH_3), 68.3 (NCH), 98.3 (ArC), 130.4 (ArCH), 135.5 (ArCI), 137.9 (ArCH), 162.3 (HC=N), 173.1 (CO_2); *m/z* (CI) 318 (MH^+, 60), 192 (100). Found (EI) 316.9916 $C_{11}H_{12}NO_2I$ (M^+) requires 316.9913.

4.5.9. 1-Naphthylidene imine 7i. Obtained as a pale yellow oil in 90% yield. $[\alpha]_D^{20}$=+0.8 (*c* 1.0 $CHCl_3$); ν_{max}(neat) 3048 (m), 2984 (m), 2871 (m), 1740 (s), 1636 (s), 1590 (s), and 1509 cm^{-1} (s); $\delta_H(CDCl_3)$ 1.49 (3H, d J=7 Hz, CH_3), 3.64 (3H, s, OCH_3), 4.09 (1H, q J=7 Hz, NCH), 7.35–7.81 (7H, m, ArCH), 8.82 (1H, s, HC=N); $\delta_C(CDCl_3)$ 20.1 (CH_3), 52.7 (OCH_3), 69.3 (NCH), 124.7 (ArCH), 125.6 (ArCH), 126.2 (ArC), 127.4 (ArCH), 128.9 (ArC), 129.1 (ArCH), 129.7 (ArCH), 131.7 (ArCH), 135.7 (ArC), 161.4 (HC=N), 173.0 (CO_2); *m/z* (EI) 241 (M^+, 25), 182 (100), 166 (40), 154 (95), 139 (60), 127 (50). Found (ES) 242.1181, $C_{15}H_{16}NO_2$ (MH^+) requires 242.1181.

4.5.10. 2-Naphthylidene imine[45] 7j. Obtained as a yellow solid in 72% yield. $\delta_H(CDCl_3)$ 1.69 (3H, d J=7 Hz, CH_3), 3.89 (3H, s, OCH_3), 4.32 (1H, q J=7 Hz, NCH), 7.6–7.7 (2H, m, ArCH) 8.0–8.2 (5H, m, ArCH), 8.59 (1H, s, HC=N).

4.6. General procedure for the benzylation of *N*-arylidene (*S*)-alanine methyl esters

Imine **2b** or **7a–j** (0.88 mmol), powered sodium hydroxide (0.146 g, 3.66 mmol), catalyst **1b**,**c**, **4a–e**, or **8a–f** (2 mol%), dry toluene (2.5 mL) and benzyl bromide (0.126 mL, 1.06 mmol) were added to round bottomed flask under argon. The mixture was allowed to stir overnight at room temperature. MeOH (2 mL) and acetyl chloride (0.44 mL) were then added, and the reaction stirred for a further 4 h at room temperature under argon. The solvent was removed in vacuo and the residue was added to a silica gel column and eluted first with ethyl acetate (3×100 mL) and then with a mixture of ethyl acetate and ethanol (4:1) to give α-methyl phenylalanine methyl ester. If necessary, the amino ester was filtered through aluminium oxide to remove the last traces of copper salts.

4.7. Determination of the enantiomeric excess of α-methyl phenylalanine methyl ester

(*S*)-1-Phenylethyl isocyanate (1–2 drops, excess) was added to an NMR sample (in $CDCl_3$) of α-methyl phenylalanine methyl ester. The solution was left until the reaction was complete (usually overnight). The diastereomeric excess of the urea and hence the enantiomeric excess of the α-methyl phenylalanine methyl ester was determined by integration of the methylene proton region of the ^1H NMR spectrum of the urea.

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