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Chiral salen–metal complexes as novel catalysts for the asymmetric synthesis of α-amino acids under phase transfer catalysis conditions

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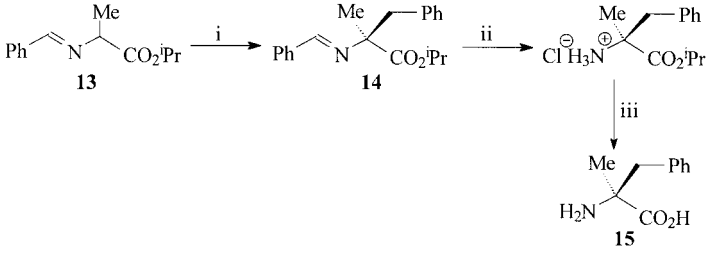
Abstract—Chiral salen–metal complexes have been tested as catalysts for the *C*-alkylation of Schiff's bases of alanine and glycine esters with alkyl bromides under phase-transfer conditions (solid sodium hydroxide, toluene, ambient temperature, 1–10 mol% of the catalyst). The best catalyst, which was derived from a Cu(II) complex of (1*R*, 2*R* or 1*S*,2*S*)-[*N*,*N*′-bis(2′-hydroxybenzylidene)]-1,2-diaminocyclohexane, gave α-amino and α-methyl-α-amino acids with enantiomeric excesses of 70–96%.

1. Introduction

Asymmetric catalysis is rapidly becoming an important tool for both small scale laboratory syntheses[1] and large scale industrial productions of enantiomerically enriched compounds.[1a,b,c] Amongst the many chiral catalysts, metal complexes feature prominently. This is partly due to their unique ability to fix the mutual orientation of chiral ligands and substrates in the coordination sphere of the complex and thus provide the necessary chiral template for chiral recognition in the transition state of the reaction.[1a,b,c] Another industrially important reaction, asymmetric phase-transfer-catalysis (PTC) of CH-acid alkylation, proceeds via ion-pair formation and usually relies on the use of chiral, quaternary ammonium salts derived from cinchona alkaloids to promote the enantioselective version of the reactions.[2] The ion-pair interactions inside the loose ion pairs, formed by the carbanions and quaternary ammonium ions however, are difficult to employ in rationally designed, stereochemically controlled, electrophilic attack on the carbanion. In spite of recent progress in the field,[3] it is still not possible to predict in advance, which reaction conditions will give good enantioselectivity in a particular reaction.

Recently, some of us reported the use of TADDOL [(4*S*,5*S*)-2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxalane-4,5-dimethanol] and NOBIN (2-hydroxy-2′-amino-1,1′-binaphthyl) to promote the asymmetric PTC *C*-alkylation of Schiff's bases of alanine esters with enantiometric excesses as high as 82%.[4] In this reaction, TADDOL functioned as a chelating agent for the alkali ions and thus made the ion-pair (formed by the corresponding carbanion and



Scheme 1. *Reagents*: (i), $PhCH_2Br$/**1**-**12**/$PhCH_3$/solid NaOH; (ii), HCl (aqueous), ambient temperature/ (iii), 6N HCl (aqueous) reflux.

Keywords: phase-transfer-catalysis; copper; Schiff-bases; asymmetric-catalysis; amino-acid.

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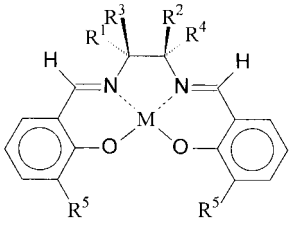
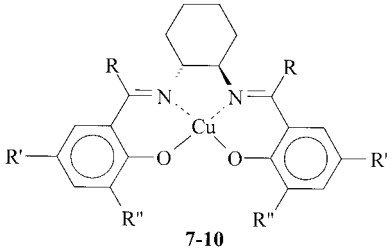
alkali ions) soluble in organic solvents. This modification combined the synthetic simplicity of the PTC approach, with the advantages of catalysis by metal complexes. We expected that other types of preformed chiral metal complexes might function in the same way: activating the ion-pair by complexation of an alkali ion and/or forming a complex with the carbanion itself. Our earlier attempts to realize this principle, using positively charge complexes, met with only limited success.[5a] We believed that neutral chiral salen complexes known for their propensity of chelating additional metal ions[6] might be better catalysts of asymmetric PTC alkylation of CH-acids. In this manuscript, we report the use of chiral salen–metal complexes **1**–**12** as phase transfer catalysts for the asymmetric synthesis of α-amino acids. Preliminary results of a part of this work were published earlier.[5b]



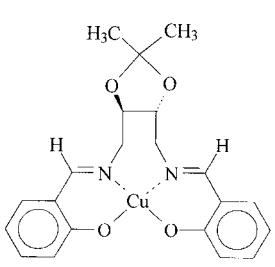
1-6

1 $R^1 = CH_2CH_2S^+Me_2$; $R^2 = R^3 = R^4 = R^5 = H$; M = Ni(II)
2 $R^1 = CH_2CH_2SMe$; $R^2 = R^3 = R^4 = R^5 = H$; M = Ni(II)
3 R^1-$R^2 = (CH_2)_4$; $R^3 = R^4 = R^5 = H$; M = Ni(II)
4 R^1-$R^2 = (CH_2)_4$; $R^3 = R^4 = R^5 = H$; M = Cu(II)
5 R^1-$R^2 = (CH_2)_4$; $R^3 = R^4 = H$; $R^5 = {}^t$Bu; M = Cu(II)
6 $R^1 = R^2 = H$; R^3-$R^4 = (CH_2)_4$; $R^5 = H$; M = Cu(II)



7-10

7 R'= ^{t}Bu; R=R"= H
8 R'=R"= ^{t}Bu; R= H
9 R'= R"=H; R= CH_3
10 R'=Br; R= R"= H



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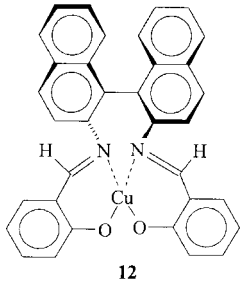

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2. Results

As a model reaction, the alkylation of Schiff's base **13** (derived from benzaldehyde and *R*,*S*-alanine isopropyl ester) with benzyl bromide under PTC conditions (solid NaOH/toluene) was chosen (Scheme 1). The advantages of using this substrate were the stability to racemization of product **14** and the importance of amino acids containing quaternary α-carbon atoms.[7]

The reaction was conducted in toluene at ambient temperature, using solid MOH (or NaH) to activate the substrate (usually 0.1 g in 4 ml of solvent) and chiral salen–metal complexes (**1**–**12**) as promoters of the reaction (substrate/catalyst ration from 10 /1 to 100/1). After 24 h, the reaction was quenched with dilute hydrochloric acid and the liberated amino ester was hydrolysed. The enantiomeric excess of the resulting α-methyl-phenylalanine **15** was established by chiral GLC, and the experimental results are summarized in Table 1.

Analysis of the results indicated that in the absence of a transition metal, the salen ligands did not produce any asymmetric induction in the product (Table 1, run 1). In other words, the disodium salt of the ligand, which would from under the PTC condition, was not an efficient asymmetric catalyst of the alkylation reaction under the reaction conditions. Catalyst **1**, derived from Ni(II) and a positively charged Schiff's base was also quite inefficient (Table 1, run 2), which may be due to the poor solubility of **1** in toluene. The removal of one methyl group from the $(Me)_2S^+$-moiety of **1** to give ligand **2**, improved the performance of the catalyst (Table 1, run 3), bringing the enantiomeric excess of the product to 31% at a ratio of substrate/catalyst of 10/1. Complex **3**, the Ni(II) complex of a Schiff's base derived from (1*R*,2*R*)-[*N*,*N*′-bis(2′-hydroxybenzylidene)]-1,2-diaminocyclohexane, was also catalytically active, giving the same level of asymmetric induction at the same concentration of the catalyst (Table 1, run 4). The performance of the catalyst was greatly improved when the Ni(II) ion in **3** was substituted by a Cu(II) ion to give complex **4**, with the enantiometric excess of the final product reaching 85% (Table 1, run 5). The introduction of *tert*-butyl groups into the 3′-position of the salen moiety of the catalyst to give complex **5** was counterproductive, with the enantiomeric excess of the product dropping to 6% (Table 1, run 6). On the other hand, introduction of a *tert*-Bu substituent into position 5′ (catalyst **7**) decreased the enantiomeric excess to a much lesser degree (Table 1, run 18). Finally, the introduction of two *tert*-Bu groups in positions 3′ and 5′ (catalyst **8**) reduced the enantiomeric excess of the reaction to zero (Table 1, run 19). In other cases of catalysis using salen ligands, the introduction of substituents at the 3′-position greatly improved the enantioselectivity of the catalyst.[8]

The reaction could be scaled up to 5 g of substrate **13**, employing complex **4** as a catalyst without any significant decrease in the enantiomeric excess of the reaction but with lower yield (Table 1, run 7). If the ratio of sodium hydroxide/substrate was chosen in the range 1.2–2.0, the chemical yield of the product was low (20–50%, Table 1, runs 1–7). One reason for this might be the consumption of sodium hydroxide in a side reaction such as hydrolysis of the substrate. This was corroborated by the drop in the chemical yield to 4% when aqueous sodium hydroxide was used (Table 1, run 8). An almost quantitative chemical yield could be achieved using *tert*-butyl *N*-benzylidene-alaninate

Table 1. Asymmetric alkylation of Schiff's base **13** by benzyl bromide mediated by salen–metal complexes in toluene at ambient temperature under PTC conditions

Run	Catalyst	Mol % of the catalyst	Base, equiv.	e.e. (%) (configuration)[a]	Yield (%)[a]
1	Free ligand of catalyst **6**	10	NaOH, 1.2	0.5	50
2	**1**	10	NaOH, 1.5	1 (*S*)	50
3	**2**	10	NaOH, 1.5	31 (*R*)	44
4	**3**	10	NaOH, 1.2	30 (*R*)	34
5	**4**	10	NaOH, 1.2	85 (*R*)	40
6	**5**	10	NaOH, 1.2	6 (*R*)	47
7[b]	**4**	10	NaOH, 1.2	80 (*R*)[c]	20
8[d]	**6**	2	NaOH, 2.0	80 (*S*)	4
9[e]	**4**	10	NaOH, 1.2	46 (*R*)	91
10	**4**	10	NaH, 1.2	89 (*R*)	82
11[b]	**6**	1	NaOH, 3.0	92 (*S*)[c]	71[c]
12	**6**	2	NaOH, 3.5	88 (*S*)	91
13	**4**	2	NaOH, 4.0	76 (*R*)	99
14[f]	**6**	2	NaOH, 3.0	53 (*S*)	95
15	**6**	2	LiOH, 2.0	0	7
16	**6**	2	KOH, 2.0	63 (*S*)	87
17[g]	**6**	2	NaOH, 1.2	90 (*S*)	48
18	**7**	10	NaOH, 3.0	65 (*R*)	80
19	**8**	10	NaOH, 3.0	0	80
20	**9**	10	NaOH, 3.0	3 (S)	76
21	**10**	10	NaOH, 3.0	3(S)	61
22	**11**	10	NaOH, 3.0	6(S)	22
23	**12**	10	NaOH, 3.0	8(S)	90

The concentration of the substrate was 0.2–0.3 M [usually 0.110 g (0.5 mmol) of substrate in 4 ml of the solvent, unless indicated otherwise]. The reaction was conducted for 24 h under an argon atmosphere, solid MOH was used as base unless indicated otherwise, and the ratio of benzyl bromide to **13** was 1.2–2.

[a] The enantiomeric excess of α-methyl-phenyalanine was determined by GLC of the *N*-trifluoroacetyl derivative of its propyl-ester, and the chemical yield was determined by ^{1}H NMR spectroscopy using leucine as an internal standard.

[b] The experiment was scaled up to 5 g of **13** in 100 ml of toluene.

[c] After crystallization, the enantiomeric excess of α-methyl-phenylalanine was increased to 98% and the yield decreased to 61%.

[d] Aqueous NaOH (50%) was used as a base.

[e] The substrate was derived from the *tert*- Bu ester of *R*,*S*-alanine.

[f] The experiment was conducted in an open vessel without any Ar atmosphere.

[g] The catalyst recovered from the previous experiments was used.

as a hydrolytically stable substrate (Table 1, run 9). Alternatively, use of 1.2 equiv. of sodium hydride gave a good chemical yield and satisfactory enantiomeric excess (Table 1, run 10). Finally, increasing the amount of solid sodium hydroxide to 3.5 equiv. improved the chemical yield without compromising the enantiomeric excess of the product (Table 1, runs 11,12) even if the amount of the catalyst was decreased to 1% (Table 1, run 11). Further increase in the amount of sodium hydroxide to 4.0 equiv. decreased the enantiomeric excess of the product from 88 to 76% (Table 1, run 13). It was necessary to carry out these reactions under an inert atmosphere, as an attempt to conduct the reaction in an open vessel resulted in a low enantiomeric excess of the product (Table 1, run 14). Sodium hydroxide was found to be the base of choice since lithium hydroxide was inefficient (Table 1, run 15) and use of potassium hydroxide gave a low enantiomeric excess (Table 1, run 16). Catalysts **6** or **4** could be recovered and successfully reused in the reaction (Table 1, run 17).

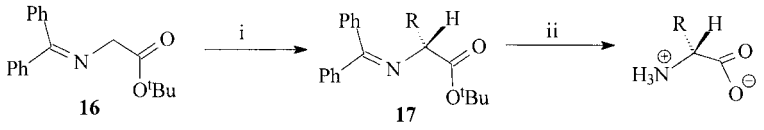
Generally, any modification of the catalyst's salen moiety resulted in a decreased enantiomeric excess of the reaction. The introduction of an electronegative Br-substituent at the *para*-position (catalyst 10) was also detrimental for the catalytic activity with the enantiomeric excess of the product being close to zero (Table 1, run 21). Catalyst **9**, differing from complex **4** by the methyl substituents at the C=N bonds, was active in the reaction, but lost its asymmetry inducing properties (Table 1, run 20). Both catalysts **11** and **12** derived from (*S*,*S*)-1,3-oxa-2,2-dimethyl-4,5-diaminomethylcyclopentane and (*R*)-2,2′-diamino-1,1′-dinaphthyl, respectively, catalysed the reaction, but the asymmetric induction was very low 6 and 8% in both cases (Table 1, runs 22, 23). A complex of Cu(II) of the Schiff's base derived from (*R*,*R*)-1,2-diaminocyclohexane and pyridine-2-aldehyde was not a very efficient catalyst and did not induce any enantioselectivity in the reaction.

Thus, catalyst **4** (or its enantiomer **6**) was the catalyst of

Table 2. Alkylation of substrate **13** with different alkylating agents catalysed by **4**

Run	Alkylating agent	Chemical yield (%)	e.e.(%) (configuration)
1	1-Chloromethylnaphthalene	52	88 (*R*)
2	Allyl bromide	40	90 (*R*)
3	EtBr	25	13 (*R*)
4	EtI	58	75 (*R*)

The experimental conditions are the same as in Table 1, run 12.



Scheme 2. (i) RX, solid NaOH, catalyst **4**, toluene, 48 h; (ii) aqueous HCl.

choice in the set of the complexes **1**–**12** under study. It was of interest to broaden the scope of the reaction by including other alkylating agents and/or other substrates in the reaction under the optimal conditions of run 12 of Table 1. Table 2 summarizes the results of the alkylation of the alanine derivative **13** with other alkylating agents. As can be seen from the data, allyl bromide and 1-naphthylmethyl bromide reacted with **13** with good enantioselectivity and moderate chemical yield (Table 2, runs 1,2). Ethyl bromide proved to be a slow reacting alkylating agent, but ethyl iodide was reasonably active, giving 2-amino-2-methyl butyric acid with an enantiomeric excess close to 75% (Table 2, runs 3,4).

Alkylation of the glycine derivative **16** was conducted according to Scheme 2 under the optimal conditions (Table 1, run 12) and the results are summarized in Table 3. The amino acids could be recovered from the reaction mixture either by direct hydrolysis, or the intermediate Schiff's base could first be purified on SiO_2. As can be seen from the results, benzyl bromide, allyl bromide, and naphthylmethyl bromide participated in the catalyst **4** mediated alkylation of **16** and the resulting α-amino acids had enantiomeric excesses in the 70–80% range (Table 3, runs 1–3). There was no racemization of the intermediate Schiff's base **17** during the reaction, as no decrease in the enantiomeric excess of the amino acids was observed as the time of the reaction was increased (Table 3, runs 6, 7). The cation of the base was important and NaOH was found the base of choice (Table 3, runs 1, 8, 9) exactly as in the case of the substrate **13**.

3. Discussion

The decrease in the enantioselectivity of the alkylation reaction with the introduction of a *tert*-butyl group *ortho* to the phenol oxygen atoms is highly unusual for other chiral salen complex catalysed reactions.[8] One possible explanation might be the paramount importance of the phenol oxygen atoms of the salen ligand for the asymmetric course of the reaction, with any steric hindrance of the approach to them making an achiral route more competitive. As the detrimental effect of the introduction of an electronegative Br-substituent in the *para*-position indicates (Table 1, run 21) it is the nucleophilicity of the coordinated metal atoms which is essential for the asymmetric reactivity of the catalyst. The data of Table 1 indicate that both the nature of the central atoms of the catalysts (Table 1, runs 4, 5) and the cations of the base (Table 1, runs 15, 16; Table 2, runs 8,9) were important for high enantioselectivity of alkylation to be observed. In addition, the conformation of the salen ligands is crucial for both the magnitude and direction of the asymmetric induction (compare catalysts **4**, **11** and **12**).

Table 3. Alkylation of substrate **16** (Scheme 2) with different alkylating agents catalysed by **4**

Run	Alkylating agent	Chemical yield (%)	e.e. (configuration)
1	$PhCH_2Br$	>95	80 (*R*)
2	Allyl bromide	>90	81 (*R*)
3	1-Chloromethylnaphtalene	>95	77 (*R*)
4	CH_3I	12	7 (*R*)
5	$(CH_3)_2CHI$	20	9 (*R*)
6	$PhCH_2Br$ (4 h)	88	75 (*R*)
7	$PhCH_2Br$ (20 h)	>90	78 (*R*)
8	$PhCH_2Br$ (KOH)	>95	60 (*R*)
9	$PhCH_2Br$ (LiOH)	0	–

The experimental conditions are the same as in Table 1, run 12.

To further investigate the nature of the catalytically active species, the presence of any non-linear effects was investigated. As the plot of enatiomeric purity of the ligand versus the enantiomeric purity of the product (Fig. 1) indicated, there were positive non-linear effects[9] observed for the alkylation of both substrates with benzyl bromide catalysed by **4** or **6**. In other words more than one salenCu(II) complex participated in the transition state of the alkylation and a complex of (*S*,*S*)/(*S*,*S*)-type was a better catalyst than that of (*S*,*S*)/(*R*,*R*)-configuration.

Scheme 3 presents a hypothetical mechanism of the reaction in which the ion pair derived from the substrate and MOH forms on the surface of the solid MOH. Then, the ion pair and the catalyst form a hydrophobic complex, which is transferred to the solution. The key feature of the mechanism is the formation of a mixed complex of two (or more) salen Cu(II) complexes united by a cation of the base and with the deprotonated substrate occupying the apical coordination site of one of the Cu(II) ions of the complexes. These features of the catalytic complex can account for the influence of the metal cations and the nature of the chiral ligands on the enantioselectivity of the reaction. Further alkylation of the coordinated carbanion occurs in the complex followed by the liberation of the catalyst.

There is a possibility that the initial alkylation of the complex occurs on one of the phenolic oxygens of the salen ligand in the catalytic complex, with the formation of an alkylating agent which then intramolecularly attacks the coordinated carbanion. Evidence to support this hypothesis comes from an experiment employing (1*R*,2*R*)-bis-(*N*,*N*′-2′-benzyloxybenzylidene)-1,2-diaminocyclohexane, which was capable of alkylating substrate **13** in the presence of NaOH and $CuBr_2$ to form (*R*)-**15** with an enantiomeric purity of 40%.

4. Conclusions

This work has resulted in the development of a new class of asymmetric phase-transfer catalysts for the alkylation of alanine and glycine enolates. The optimal catalyst is a

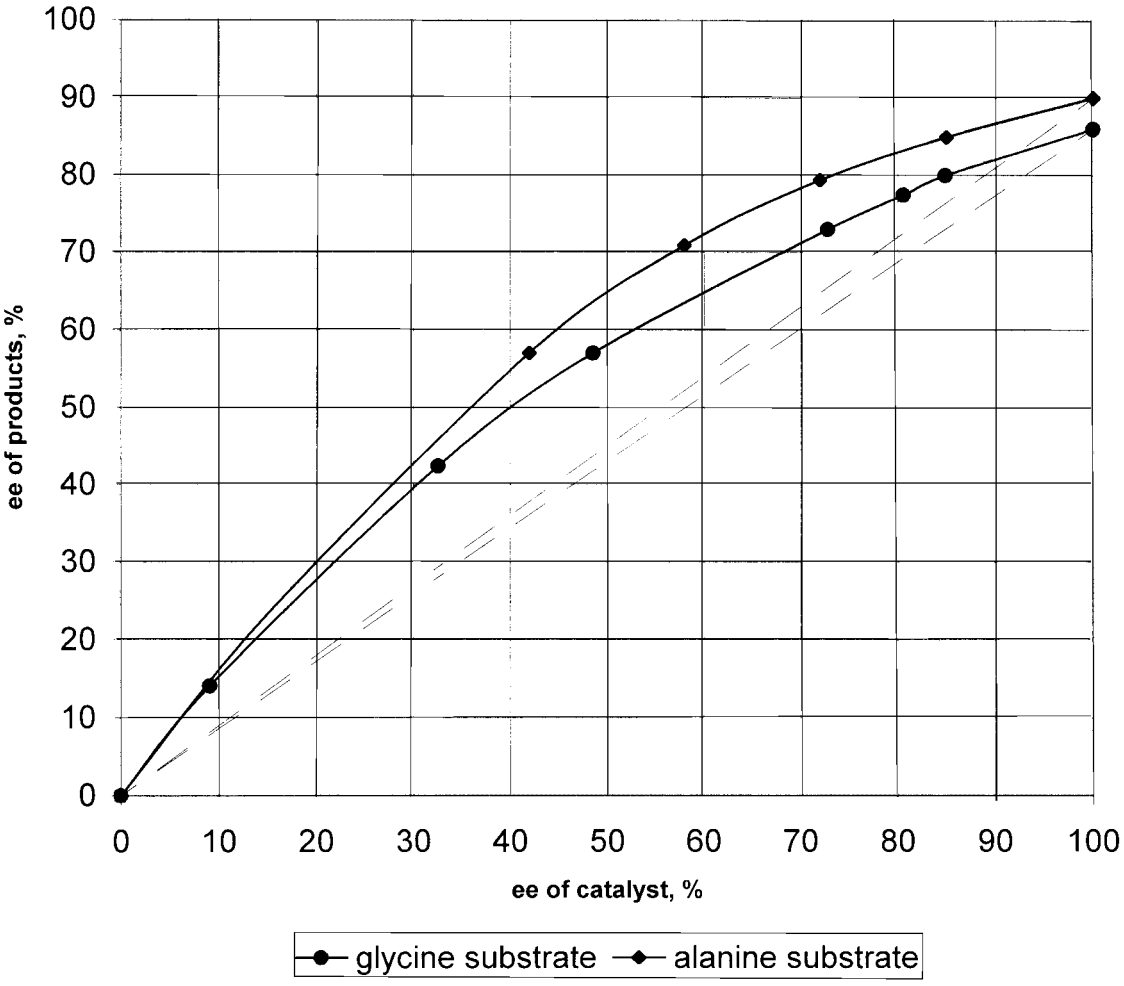
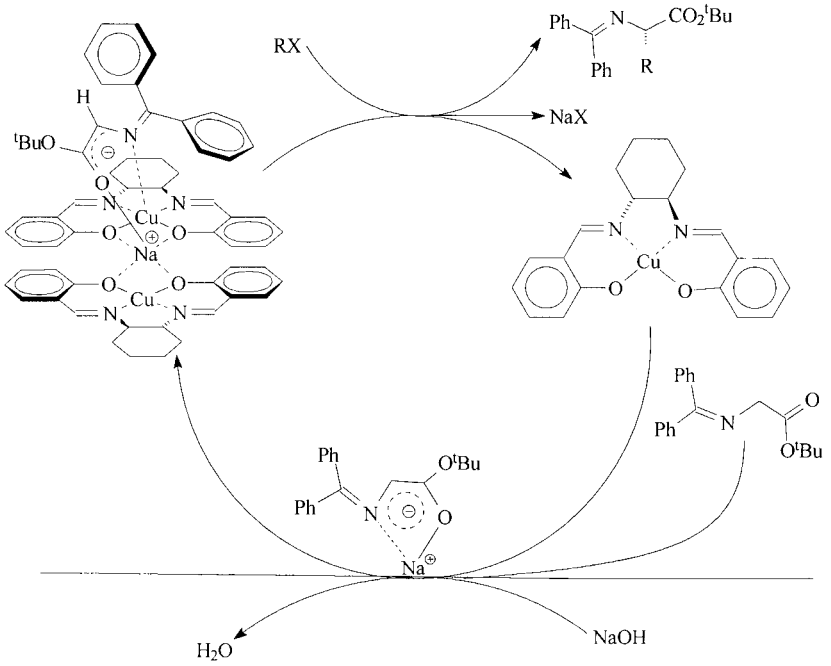


Figure 1. Positive non-linear effects in the alkylations of substrate **13** and **16** catalysed by **4** with different degrees of enantiomeric purity.



Scheme 3. A mechanism for PTC alkylation of substrate **16** catalysed by a salen Cu(II) complex.

(salen)Cu(II) derivative which produces the alkylated product with up to 92% enantiomeric excess. Preliminary mechanistic studies have shown that the introduction of substituents onto the aromatic rings of the salen ligand is detrimental to the activity of the catalyst, and that the active form of the catalyst is not monomeric. Our work on developing the synthetic applications of this chemistry and in understanding the origin of the catalytic activity is continuing, and further results will be reported in due course.

5. Experimental

5.1. General

^{1}H NMR spectra were recorded on a Bruker WP-200 instrument at 200 MHz with TMS (δ=0.00) as an internal standard and $CDCl_3$ as a solvent (unless indicated otherwise). Optical rotations were measured with a Perkin–Elmer-241 polarimeter in a thermostated cell at 25°C. Toluene was distilled from sodium prior to use. Enantiomeric analyses of amino acids were performed by GLC on their *N*-trifluoroacetyl *n*-propyl esters using a Chirasil-L-Val type phase on a fused silica capillary column 40 m×0.23 mm ID, film 0.12 μm, column temperature 125°C, and He carrier-gas at 1.80 bar. *N*-(Diphenylmethylene)glycine *tert*-butyl ester, 5-*t*-butyl-salicilaldehyde, 3,5-di-*t*-lbutyl-salicilaldehyde, (*R*)-(+)-2,2′-diamino-1,1′-binaphthalene and alkyl halides were available from Aldrich, (4*S*, 5*S*)-4,5-di(aminomethyl)-2,2-dimethyldioxalane was available from ACROS Chimica; all reagents were used without additional purification.

5.1.1. (1*R*, 2*R*)-diaminocyclohexane. This was resolved according to the literature procedure[10] and had satisfactory elemental analysis and $[\alpha]_D^{25}=-15$ (c=5, aq. 1N HCl), {lit.[11] $[\alpha]_D^{25}=-15.8$}.

5.1.2. (1*S*, 2*S*)-diaminocyclohexane. This was resolved in the same manner, using the enantiomeric tartaric acid.

5.1.3. (1*R*, 2*R*)-[*N*,*N*′-bis(2′-hydroxybenzylidene)]-1,2-diaminocyclohexane. This and all the other Schiff's bases were synthesized according to a literature procedure.[10]

5.1.4. Schiff's bases of (*R*,*S*)-alanine. These were synthesized from benzaldehyde and the appropriate amino esters, as described earlier.[12] *tert*-Butyl *N*-benzylidene-(*R*,*S*)-alaninate was obtained as a colourless oil with bp 105–107°C/1.5 mm Hg in 58% yield. δ_H 1.48 (s, 9H, $(CH_3)_3$), 1.50 (d, J=6.3 Hz, 3H, CH_3), 4.02 (q, J=6.3 Hz, 1H, CH), 7.34–7.86 (m, 5H, Ph), 8.3 (s, 1H, CH=N); ν_{max} 1650, 1740 cm^{-1}. Isopropyl *N*-benzylidene-(*R*,*S*)-alaninate was obtained as a colourless oil with bp 120–121°C/2 mm Hg in 71% yield. n_D^{15} 1.5168. δ_H 1.23 (d, J=6.2 Hz, 3H, CH_3), 1.27 (d, J=6.2 Hz, 3H, CH_3), 1.51 (d, J=7.1 Hz, 3H, CH_3), 4.09 (q, J=7.1 Hz, 1H, CH), 5.05 (m, 1H, OCH), 6.3–7.3 (m, 5H, Ph), 8.29 (s, 1H, CH=N); ν_{max} 1644, 1735 cm^{-1}.

5.1.5. 2-*O*-Benzyloxy-benzaldehyde (*O*-Benzyl-salicylaldehyde). To a solution of salicylaldehyde (10 ml, 0.096 mol) in DMF (25 ml) was slowly added NaH (60% suspension in oil) (4 g, 0.1 mol) whilst maintaining the reaction temperature below 55°C followed by the dropwise addition of benzyl bromide (12 ml, 17.3 g; 0.1 mol). The stirring was continued for another 4 h and then H_2O (75 ml) and benzene (30 ml) were added to the mixture. The organic layer was separated, washed with H_2O (3×20 ml) and concentrated in vacuo. The crude solid material was twice washed with H_2O and after drying additionally washed with hexane and dried in air. Yield 39% (7.9 g). δ_H 5.21 (s, 2H, OCH_2Ph), 7.0–7.95 (m, 9H, Ar), 10.6 (s, 1H, CHO).

5.1.6. (1*R*, 2*R*)-[*N*,*N*′-bis-(2′-benzyloxybenzylidene)]-1,2-diaminocyclohexane. To a solution of (*R*,*R*)-cyclohexanediamine tartrate (1 g, 0.38 mmol) and K_2CO_3 (1.05 g, 0.76 mmol) in H_2O (5 ml) were added ethanol (20 ml) and the reaction mixture was heated until the solution became transparent. Then, *O*-benzyl-salicylaldehyde (1.62 g, 0.76 mmol) was added to the mixture. The reaction mixture was refluxed for 2 h and put into a freezer overnight. The precipitated oil was separated and hexane (40 ml) was added to it. The mixture was refluxed for 20 min and the hot hexane solution separated from the residue. The solution was concentrated in vacuo and the resulting oil was used without additional purification. Yield 53% (1.0 g). $[\alpha]_D^{25}=+231$ (c=0.39, $CHCl_3$). δ_H 1.51 (m, 2H, CH_2), 1.86 (m, 6H, CH_2), 3.47 (m, 2H,>CH–N=), 5.03 (s, 4H, $PhCH_2O$), 6.8–8.0 (m, 18H, Ar), 8.75 (s, 2H, CHN).

5.1.7. (4*S*, 5*S*)-1,3-oxa-2,2-dimethyl-[*N*,*N*′-bis(2′-hydroxybenzylidene)]-4,5-diaminometycyclopentane. $MgSO_4$ (2 g) was suspended in a solution of (4*S*,5*S*)-4,5-di(aminomethyl)-2,2-dimethyldioxalane (0.3 g, 1.88 mmol) and salicylaldehyde (0.46 g, 3.75 mmol) in dry benzene (20 ml). The reaction mixture was stirred for 6 h, the inorganic salts filtered off and the filtrate evaporated in vacuo. The resulting oil solidified after standing for 2 days. The solid Schiff's base was used without additional purification. δ_H 1.34 (s, 6H, $2CH_3$), 3.83 (m, 4H, CH_2N=), 4.18 (m, 2H, >CHO), 7.21–7.34 (m, 8H, Ar), 8.35 (s, 2H, CH=N), 12.9 (s, 2H, OH).

5.1.8. (*R*)-[*N*,*N*′-bis-(2″-hydroxybenzylidene)]-2,2′-diamino-1,1′-binaphthalene. (*R*)-2,2′-Diamino-1,1′-binaphthalene (0.2 g, 0.702 mmol) was dissolved in absolute ethanol (30 ml), then salicylaldehyde (0.172 g, 1.408 mmol) was added and the mixture refluxed with stirring for 5 h. After adding water (2 ml), a precipitate was formed which was filtered, washed with absolute ethanol (5 ml), and dried in air. Yield 87% (0.32 g). Mp 256°C. $[\alpha]_D^{25}=-455$ (c=1, $CHCl_3$). Found: C, 82.89; H, 5.01; N, 5.52. Calculated for $C_{34}H_{24}N_2O_2$: C, 82.91; H, 4.91; N, 5.69.

5.1.9. (1*S*,2*S*)-[*N*,*N*′-bis-((2′-pyridine)-methylene)]-1,2-diaminocyclohexane. (1*S*,2*S*)-1,2-Diaminocyclohexane (1 g, 8.77 mmol) was dissolved in methanol (5 ml) and 2- pyridine carboxaldehyde (1.88 g, 17.55 mmol) was added. The stirring was continued for another 5 h. The precipitated product was filtered, recrystallized from hexane/methanol and dried in air. Yield 2.2 g (86%). Mp 127–129°C. $[\alpha]_D^{25}=+85.44$ (c=1, $CHCl_3$); δ_H 1.95 (m, 4H, $-CH_2-CH_2$), 3.55 (m, 2H,>CH–N=), 7.17–8.55 (m, 8H, Ar), 8.33 (s, 2H, CH=N). Found: C, 74.14; H, 7.24; N, 19.25. Calculated for $C_{18}H_{20}N_4$: C, 73.94; H, 6.89; N, 19.16.

5.1.10. Cu(II) complex 4. To a solution of (1*R*,2*R*)-[*N*,*N*′-bis(2′-hydroxybenzylidene)]-1,2-diaminocyclohexane (1.32 g, 4.1 mmol) in MeOH (20 ml) were added $CuBr_2$ (0.92 g, 4.1 mmol) and NaOMe (0.9 ml of 4.6 N solution in MeOH). The reaction mixture was stirred for 3 h at ambient temperature and then the solvent was removed in vacuo. The complex was purified by chromatography on LH-20 (EtOH/C_6H_6 1:3). Yield 1 g (63%); mp 315–319°C (dec.); $[\alpha]_D^{25}=-917$ (c=0.048, $CHCl_3$). Found: C, 62.97; H, 5.43; N, 7.47. Calculated for $C_{20}H_{20}N_2O_2Cu$: C, 62.57; H, 5.25; N, 7.30.

5.1.11. Cu(II) complex 6. This was synthesized as described for complex **4** in a chemical yield of 68%. Mp 313–31°C (dec.); $[\alpha]_D^{25}=+915$ (c=0.04, $CHCl_3$). Found: C, 61.78; H, 5.27; N, 7.21. Calculated for $C_{20}H_{20}N_2O_2Cu\times0.25H_2O$: C, 61.84; H, 5.32; N, 7.21.

5.1.12. Cu(II) complex 5. This was synthesized as described for complex **4** in a chemical yield of 75%. Mp 256–257°C; $[\alpha]_D^{25}=-237$ (c=0.04, $CHCl_3$). Found: C, 67.61; H, 7.50; N, 5.45. Calculated for $C_{28}H_{36}N_2O_2Cu$: C, 67.78; H, 7.31; N, 5.65.

5.1.13. Cu(II) complex of (1*R*, 2*R*)-[*N*,*N*′ bis(2′-hydroxy-5′-*t*-butyl-benzylidene)]-1,2-diaminocyclohexane 7. This was synthesized as described for complex **4** with additional purification using LH-20 in benzene/i-propyl alcohol (3:1) in a chemical yield of 75%. Mp dec. >260°C without melting; $[\alpha]_D^{25}=-613$ (c=0.04, $CHCl_3$). Found: C, 67.51; H, 7.14; N, 5.61. Calculated for $C_{28}H_{36}N_2O_2Cu$: C, 67.78; H, 7.31; N, 5.65.

5.1.14. Cu(II) complex of (1*R*,2*R*)-[*N*,*N*′-bis(2′-hydroxy-3′,5′-di-*t*-butyl-benzylidene)]-1,2-diamino-cyclohexane 8. This was synthesized as described for complex **4** in a chemical yield of 85 %. Mp dec. >280°C without melting; $[\alpha]_D^{25}=-275$ (c=0.04, $CHCl_3$). Found: C, 71.24; H, 8.56; N, 4.55. Calculated for $C_{36}H_{52}N_2O_2Cu$: C, 71.07; H, 8.62; N, 4.60.

5.1.15. Cu(II) complex of (4*S*,5*S*)-1,3-oxa-2,2-dimiethyl-[*N*,*N*′-bis(2′hydroxybenzylidene)]-4,5-diaminomethycyclopentane 11. To a solution of the Schiff's base of salicylaldehyde and (4*S*,5*S*)-1,3-oxa-2,2-dimethyl-4,5-diaminomethycyclopentane (0.1 g, 0.27 mmol) in methanol (5 ml) were added $Cu(OAc)_2\times H_2O$ (0.053 g, 0.265 mmol) and the reaction mixture was stirred under reflux for 2 h. The precipitated complex was washed with methanol and dissolved in benzene (10 ml). The solution was filtered and the complex precipitated by the addition of methanol and dried in air. Yield 65%. Mp 228–230°C, $[\alpha]_D^{25}=-462$ (c=0.52, $CHCl_3$). Found: C, 58.58; H, 5.21; N, 6.55. Calculated for $C_{21}H_{20}N_2O_4Cu$: C, 58.66; H, 5.16; N, 6.52.

5.1.16. Cu(II) complex of (*R*)-[*N*,*N*′-bis(2″-hydroxybenzylidene)]-2,2′-diamino-1,1′-binaphthalene 12. To a stirring solution of $Cu(OAc)_2\times H_2O$ (0.061 g, 0.305 mmol) in methanol (5 ml) was added (*R*)-1,1′-(2,2′-diamino)binaphthalene (0.15 g, 0.305 mmol) after which the reaction mixture was stirred for 1 h. The precipitate of complex **12** was washed with methanol (2×5 ml), dried in air and used without additional purification. Mp 277–280°C. $[\alpha]_D^{25}=+775$ (c=0.04, $CHCl_3$). Found: C, 73.46; H, 3.82; N, 4.98. Calculated for $C_{34}H_{22}N_2O_2Cu$: C, 73.70; H, 4.00; N, 5.06.

5.1.17. Cu(II) complex of (1*R*,2*R*)-[*N*,*N*′-bis-(2′-benzyloxybenzylidene)]-1,2-diaminocyclohexane. This was synthesized in situ by dissolving (1*R*,2*R*)-[*N*,*N*′-bis-(2′-benzyloxybenzylidene)]-1,2-diaminocyclohexane (0.137 g, 0.27 mmol) in methanol (2 ml) followed by the addition of $CuBr_2$ (0.060 g, 0.27 mmol). The reaction mixture was stirred at room temperature for 4 h after which time the inorganic salts were filtered off and the brown solution concentrated in vacuo. The brown solid complex was used in alkylation reactions without any purification.

5.1.18. Cu(II) complex of (1*S*,2*S*)-[*N*,*N*′-bis-((2′-pyridine)-methylene)]-1,2-diaminocyclohexane. (1*S*,2*S*)-[*N*,*N*′-bis-((2′-pyridine)-methylene)]-1,2-diaminocyclohexane (0.050 g, 0.17 mmol) and $CuBr_2$ (0.038 g, 0.17 mmol) were mixed and stirred for 8 h. The reaction product was filtered, washed with methanol, benzene and ether, and then dried in air. Yield 87% (0.093 g). Mp 228–230°C. $[\alpha]_D^{25}=+168$ (c=1, $CHCl_3$). Found: C, 34.45; H, 3.02; N, 8.92. Calculated for $C_{18}N_4Br_2Cu\times0.5CuBr_2$: C, 34.46; H, 3.21; N, 8.93.

5.1.19. Ni(II) complex 3. This was synthesized as described for **4**, starting with $Ni(NO_3)_2\times6H_2O$ in a yield of 60%. Mp >345°C (dec); $[\alpha]_D^{25}=-610$ (c=0.04, $CHCl_3$); δ_H 1.31–2.39 (m, 8H, $CH_2CH_2CH_2CH_2$), 3.29 (m, 2H, CHN=), 6.47–7.19 (m, 8H, Ph), 7.24 (s, 2H, PhCH=N). Found: C, 62.50; H, 5.36; N, 6.99. Calculated for $C_{20}H_{20}N_2O_2Ni\times0.5H_2O$: C, 62.38; H, 5.41; N, 7.27.

5.1.20. Ni(II) complex 2. This was prepared from the corresponding Schiff's base[10b] and $Ni(NO_3)_2\times6H_2O$ as described for **4** in a yield of 58%. Mp 224–225°C; $[\alpha]_D^{25}=-1350$ (c=0.0011, $CHCl_3$); δ_H 2.02 (s, 3H, CH_3S), 1.8–2.5 (m, 4H, CH_2CH_2S), 2.84 and 3.20 (AB part of ABX system, 2H, CH_2N=), 4.05 (X part of ABX system, 1H, CHN=), 6.36–7.12 (m, 8H, Ph), 7.15 (s, 1H, PhCH=N–), 7.20 (s, 1H, PhCH=N–). Found: C, 57.40; H, 5.53; N, 6.93. Calculated for $C_{19}H_{20}N_2O_2NiS$: C, 57.10; H, 5.05; N, 7.02.

5.1.21. Ni(II) complex 1 (as an iodide). To complex **2** (0.99 g, 2.5 mmol) in CH_2Cl_2 (4 ml) at room temperature was added MeI (1.6 ml. 3.65 g, 25.7 mmol). The reaction mixture was stirred for 18 h at ambient temperature, then complex **1** was separated by filtration, washed with CH_2Cl_2 (2×3 ml) and dried in air. Yield 1.25 g (92%). Mp 152–155°C; $[\alpha]_D^{25}=-1042$, (c=0.037, $CHCl_3$); δ_H (CD_3OD) 2.34–3.54 (m, 6H, CH_2N=, $CH_2CH_2S^+$), 2.98 (s, 3H, SCH_3), 3.00 (s, 3H, SCH_3), 3.83 (m, 1H, CHN=), 6.62–7.29 (m, 8H, Ph), 7.78 (s, 1H, CH=N), 7.86 (s, 1H, CH=N). Found: C, 44.29; H, 4.22; N, 5.18. Calculated for $C_{20}H_{23}N_2O_2NiSI$: C, 44.40; H, 4.28; N, 5.18.

5.1.22. Catalytic asymmetric alkylation procedure. A flask, containing catalyst **1**–**12** (3.3 mg, 0.0086 mmol) was flame dried and filled with argon. NaOH (40 mg, 1 mmol), toluene (2 ml) and substrate **13** or **16** (110 mg, 0.5 mmol), were added to the flask under argon. The reaction mixture was deoxygenated at −78°C under vacuum and then, under argon, a solution of 0.1 ml of alkyl halide in

2 ml of toluene was added with stirring. The temperature was allowed to rise to room temperature and the stirring was continued for another 5–12 h. Then, the mixture was filtered and the filtrate treated as described earlier for recovery of the α-amino acids.[4] The procedure for the alkylation of **16** differed, as sometimes the final product of the alkylation, the corresponding benzophenone Schiff's bases, could be purified by TLC (SiO_2, acetone/hexane, 1/8). The isolated amino acids were analysed by chiral GLC without any purification. In the case of scale up experiments α-methyl-α-phenylalanine was additionally recrystallized from PrOH/H_2O, to obtain almost enantiomerically pure amino acid (yield 2.58 g. 61%) with $[\alpha]_D^{25}=-17.2$ ($c=1$, H_2O) lit.[4,13] +17.8 ($c=0.2$, H_2O); −17.8 ($c=0.2$, H_2O). The catalyst could be recovered in 30–50% yield from the solid precipitate by washing it with water, after which procedure the catalyst could be collected as the remaining insoluble material.

5.1.23. Non-linear effects. These were investigated employing the same procedure, using the mixture of the appropriate amounts of **4** and **6** catalysts.

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