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The influence of imine structure, catalyst structure and reaction conditions on the enantioselectivity of the alkylation of alanine methyl ester imines catalyzed by Cu(ch-salen)

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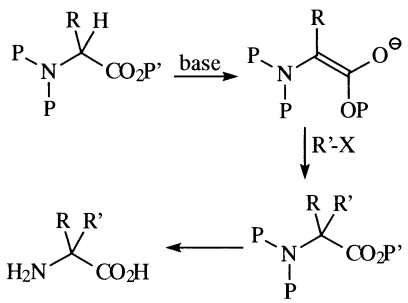
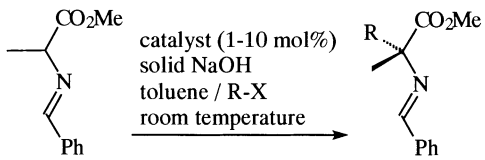
Abstract—Systematic variation of the substrate structure has shown that the most effective substrates for Cu(ch-salen)-catalyzed asymmetric enolate alkylation reactions carried out under phase-transfer conditions are the *para*-chlorophenyl imines of amino esters. The other reaction parameters (solvent and stirring speed) have also been optimized. The introduction of substituents onto the aryl rings of the salen ligand was found not to have a beneficial effect on the enantioselectivity of the reaction. © 2001 Elsevier Science Ltd. All rights reserved.

α,α-Disubstituted amino acids are important components of a number of pharmaceuticals and potential pharmaceuticals.[1] The most attractive route to the synthesis of these compounds is to start from a naturally occurring α-monosubstituted amino acid and to introduce the second side-chain through alkylation of an enolate (Scheme 1). In the simplest case, the stereochemical information contained in the original amino acid will be lost during formation of the enolate, leading to the formation of a racemic product.[2] This can be avoided by the use of a chiral auxiliary attached to the amino or acid component of the original amino acid,[3] or by the use of a chiral catalyst/base system to ensure that the amino acid enolate is coordinated within a chiral environment during the alkylation reaction. The latter process is attractive in terms of reducing the number of synthetic steps and cost of the process, and has been achieved by conducting the reaction under phase-transfer conditions in the presence of a chiral phase-transfer catalyst. Most commonly, the chiral phase-transfer reagent is an ammonium salt derivative of a cinchona alkaloid,[4] though recently, excellent results have been obtained with a synthetic quaternary ammonium salt.[5]



Scheme 1.

In recent papers, we have shown that a variety of metal complexes can also be used as chiral phase-transfer reagents. Initially, sodium taddolate was found to be effective,[6] and more recently sodium-NOBIN[7] and a copper salen complex[8] **1a** were found to give excellent results when applied to the benzylidene imine of alanine esters in the presence of solid sodium hydroxide in toluene at room temperature (Scheme 2). The great advantage of the salen based system is the ease with which the structure of the ligand can be varied by the introduction of substituents onto the aromatic rings to



Scheme 2.

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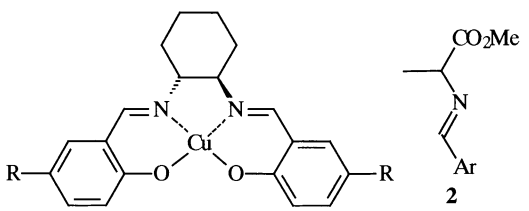
Table 1. Influence of the structure of the aryl group of **2** on the enantioselective alkylation reaction

Structure of aryl group	Chemical yield (%)	ee (%)[a]
Ph	91	81
1-Naphthyl	89	79
2-Naphthyl	62	77
4-$MeOC_6H_4$	79	71
4-$O_2NC_6H_4$	50	65
4-FC_6H_4	44	84
4-ClC_6H_4	71	92
4-BrC_6H_4	95	81
4-IC_6H_4	67	86
2-ClC_6H_4	43	70
3-ClC_6H_4	53	81

[a] Enantiomeric excesses are accurate to ±3%.

produce the optimal catalytic activity. However, before embarking on a study to optimize the catalyst, we elected to ensure that the structure of the substrate was optimal and that the reaction conditions were optimized. The use of a readily prepared and inexpensive methyl ester was highly desirable, and the amino acid side-chain had to be left variable, so the scope for optimization was limited to the structure of the imine. In this paper, the influence of the structure of the imine group on the enantioselectivity of the reaction shown in Scheme 2 with copper complex **1a** as catalyst is discussed, along with the influence of the solvent and stirring speed on the enantioselectivity. Then, the effect of introducing substituents onto the aromatic rings of the salen ligand is reported.



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1: a R=H; b R=*tert*-Bu; c R=OMe
d R=NO_2; e R=F; f R=CF_3

A range of aryl imines **2** of alanine methyl ester were prepared and alkylated under standard conditions[8] using 2 mol% of complex **1a** as an asymmetric phase-transfer catalyst, finely powdered sodium hydroxide (3.5 equiv.) as base, and benzyl bromide as alkylating agent. All reactions were carried out in toluene at ambient temperature in an argon atmosphere. Reactions were worked up with silica gel to cleave the imine, giving α-methyl phenylalanine methyl ester as the isolated product. The enantiomeric excess was determined by treatment of this amino ester with an excess of 1-phenylethylisocyanate followed by NMR analysis as previously described.[8] The results of this study are given in Table 1.

Changing the benzylidene imine to a larger imine, 1-naphthyl or 2-naphthyl did not have a beneficial effect on the enantiomeric excess of the product. Since steric effects did not seem to be important in this region of the substrate, the influence of electronic effects was investigated. The introduction of an electron-withdrawing substituent in the *para*-position of the benzylidene imine should increase the acidity of the alanine α-proton, and an electron-donating substituent should decrease the acidity of this proton. This is important since a control experiment had shown that even in the absence of catalyst **1a**, *N*-benzylidene alanine methyl ester was converted into racemic *N*-benzylidene-α-methyl phenylalanine methyl ester in 56% yield under our standard conditions. Hence, it was anticipated that an electron-rich imine might be beneficial by suppressing the uncatalyzed reaction. In the event however, both an electron-donating (OMe) and an electron-withdrawing (NO_2) substituent were detrimental to the enantioselectivity of the reaction.

More success was obtained when the use of halogenated aryl imines was investigated. A *para*-fluoro substituent had a small positive effect on the enantioselectivity, and this improved significantly when the fluorine atom was changed to chlorine. Curiously, a *para*-bromo substituent completely reversed the beneficial effect of the fluoro- or chloro-substituent, giving identical results to the benzylidene imine. Finally, an iodo substituent again increased the enantioselectivity, giving results comparable to a fluoro substituent. Since a chloro substituent seemed to be optimal, the effect of its location was investigated. If the chloro substituent was located in the *meta*-position of the aryl ring, then the enantioselectivity was identical to the benzylidene imine, whilst locating the chloro group in the *ortho*-position had even more detrimental effect on the enantioselectivity. These studies indicate that the optimal structure for the aryl group is *para*-chlorophenyl.

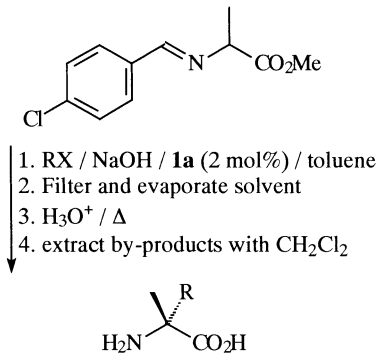
At present, it is not clear why 4-halo substituents should be beneficial in the imine. The halo group is inductively electron withdrawing which should increase the acidity of the alanine α-proton, but is also mesomerically electron donating. It may be that a combination of these two electronic effects and other factors can explain the order of effectiveness as Cl>I = F>Br.

Having optimized the substrate when benzyl bromide was used as the electrophile, the effect of this optimization on other electrophiles was investigated (Table 2). Allyl and propargyl bromides were chosen because of the relatively low enantioselectivity observed using these alkylating agents with the benzylidene imine. To further demonstrate the utility of the chemistry, and to avoid solubility problems associated with purifying the methyl esters of these rather hydrophilic amino acids, they were converted directly into the amino acids by modifying the work-up as previously described (Scheme 3).[8] A sample was then re-esterified using methanolic HCl for enantiomeric excess determination. In contrast, 1-bromomethylnaphthalene was chosen since it had previously been found to be a good substrate for the *N*-benzylidene imine, and produced a hydrophobic amino ester. The data in Table 2 show that the *para*-chlorophenyl imine substrate is always as effective or

Table 2. Alkylation of imine **2** (Ar = 4-chlorophenyl) with various electrophiles

Alkylating agent	Yield (%)	ee (%)[a]	ee obtained with benzylidene imine
1-Bromomethylnaphthalene	93	84	86
Allyl bromide	67	69	72
Propargyl bromide	82	58	43

[a] Enantiomeric excesses were determined by ^{1}H NMR spectroscopy after reaction of the amino acid methyl ester with excess 1-phenylethylisocyanate and are accurate to ±3%.



Scheme 3.

more effective (within the limits of experimental error) than the benzylidene imine containing substrate.

The effect of solvent on yield and enantioselectivity was also investigated using the *para*-chlorophenyl imine of alanine methyl ester with benzyl bromide as the alkylating agent. However, as Table 3 illustrates, whilst good chemical yields were obtained in both THF and hexane, only toluene gave a high level of asymmetric induction. Hence, it appears that a non-polar aromatic solvent is necessary to obtain high enantiomeric excesses.

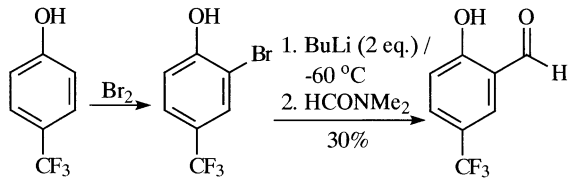
Finally, the influence of stirring rate on the chemical yield and enantioselectivity was studied, again using the reaction of the *para*-chlorophenyl imine of alanine methyl ester with benzyl bromide. The enantiomeric excess was found not to vary significantly with stirring speed, though the chemical yield was highest at a stirring rate of about 500 rpm. A lower rate of stirring (100 rpm) gave a very low chemical yield, presumably due to inadequate agitation of the heterogeneous reaction mixture, whilst a higher rate of stirring (1,000 rpm) gave a low yield due to solid being expelled from the reaction solution.

Having optimized the substrate and reaction conditions, the effect of substituents on the aryl rings of the salen ligand was investigated. Previous work had already shown that the introduction of a *tert*-butyl group into the *ortho*- (relative to phenol) position of the aryl ring had a seriously detrimental effect on the enantioselectivity of the catalyst. Hence, the substituents were located in the *para*-position of the aryl rings where they would be able to exhibit an electronic effect but would not be expected to interfere with the coordination of substrates to the copper ion. Five substituents with different steric and electronic properties were chosen, giving complexes **1b–f**. The copper complexes were all prepared from the corresponding salen ligands and copper bromide as previously reported for complex **1a**.[8] The salen ligands were prepared from the appropriate *para*-substituted salicylaldehyde and cyclohexane diamine.[8] The only salicylaldehyde that was not a known compound was 2-hydroxy-5-trifluoromethyl benzaldehyde **3**, which was prepared from 4-trifluoromethyl phenol as shown in Scheme 4. Thus, bromination of 4-trifluoromethyl phenol gave 2-bromo-4-trifluoromethyl phenol[9] which could be lithiated and reacted with dimethylformamide to give the desired aldehyde.[10]

Table 3. Influence of solvent on the asymmetric alkylation reaction

Solvent	Yield (%)	ee (%)[a]
Toluene	71	92
THF	66	39
Dichloromethane	45	44
Petroleum ether (40–60)	0	
Hexane	74	20

[a] Enantiomeric excesses were determined by ^{1}H NMR spectroscopy after reaction of the amino acid methyl ester with excess 1-phenylethylisocyanate and are accurate to ±3%.



Scheme 4.

Complex **1d** was found to be highly insoluble and so was used without purification. The other copper complexes could all be purified by size exclusion chromatography as previously described. The results obtained when complexes **1b–f** were used as asymmetric phase-transfer catalysts for the alkylation of *N*-benzylidene alanine methyl ester with benzyl bromide are presented in Table 4. Complex **1b** gave the same level of asymmetric induction as the unsubstituted complex **1a**, confirming that there was no detrimental (or advantageous) steric effect associated with these complexes. Surprisingly however, both electron-donating **1c** and electron-withdrawing **1d–f** substituents had a severely detrimental effect on the enantioselectivity of the catalyst. It should be noted that even in the absence of any

Table 4. Influence of ligand structure on the enantioselectivity of the alkylation of *N*-benzylidene alanine methyl ester

Complex	Yield (%)	ee (%)[a]
1b	39	80
1c	78	45
1d	60	0
1e	54	42
1f	68	25

[a] Enantiomeric excesses were determined by ^{1}H NMR spectroscopy after reaction of the amino acid methyl ester with excess 1-phenylethylisocyanate and are accurate to ±3%.

catalyst, a 56% yield of racemic product is obtained. Hence, the unpurified complex **1d** may not exert any catalytic influence on the reaction. The enantioselectivities observed for the other complexes may also be being affected to various extents (depending on the relative reaction rates) by the competing uncatalyzed reaction, thus masking the true influence of the substituent. Hence, it appears that the optimal electronic properties of the ligand are met by an unsubstituted or alkyl substituted salen complex.

Further work is needed to understand exactly why these reaction conditions are optimal. It is possible that a combination of steric and electronic effects determine the optimal structure of the imine, and that π–π interactions between the substrate, catalyst and solvent are also involved in optimizing the enantioselectivity. The preference for no substituents to be present on the aryl rings of the catalyst is consistent with an oligomeric form of the catalyst being the active species; this is also consistent with the observation of a non-linear effect during these reactions as reported earlier.[8]

In conclusion, we have shown that the structure of the imine within the substrate has a significant influence on the enantioselectivity of asymmetric phase-transfer alkylation reactions of alanine methyl ester with a *para*-chlorophenyl imine being optimal. The reaction solvent and rate of stirring have also been optimized. Attempts to optimize the structure of the salen ligand have indicated that the initial choice of an unsubstituted aryl ring provides optimal steric and electronic properties to the ligand under the reaction conditions.

Acknowledgements

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