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Catalytic, asymmetric synthesis of α,α-disubstituted amino acids

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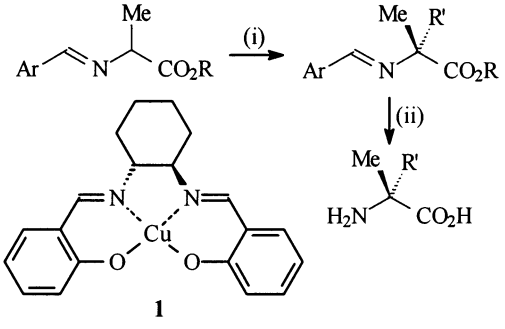
Abstract—Copper(salen) complex **1** has been found to catalyse the asymmetric alkylation of enolates derived from a variety of amino acids. There is a clear relationship between the size of the side chain in the substrate and the enantioselectivity of the process, so that the enantioselectivity decreases in the order alanine>aminobutyric acid>allylglycine>leucine>phenylalanine>valine. A transition state model which accounts for the influence of the size of the side chain on the enantioselectivity of the reactions is presented.

α,α-Disubstituted amino acids are components of a number of potential pharmaceuticals,[1] and when incorporated into peptides result in the formation of unusual conformations such as the 3_{10}-helix.[2] Whilst a number of chiral auxiliary based methods are available for the asymmetric synthesis of α,α-disubstituted amino acids,[3] a catalytic method would have significant financial and practical advantages. In recent papers, we have shown that copper(salen) complex **1** is capable of catalysing the asymmetric alkylation of alanine enolates under very mild reaction conditions as shown in Scheme 1.[4–6]



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Scheme 1. *Reagents and conditions*: (i) NaOH/R′X/**1** (2 mol%), toluene, rt; (ii) H_3O^+.

This reaction leads to α-methyl-α-amino acids with high enantiomeric excesses (up to 92%). Optimal results are obtained using a *para*-chlorobenzylidene imine,[6] and the chemistry is compatible with the use of methyl ester substrates.[5] Lygo has shown that cinchona alkaloid derivatives can be used to catalyse similar reactions,[7] and Maruoka has used synthetic, C_2-symmetric ammonium salts to prepare both α-substituted and α,α-disubstituted amino acids with high enantiomeric excesses.[8] The use of TADDOL[9] and NOBIN[10] complexes to accomplish the asymmetric alkylation of alanine enolates has also been reported. Of these systems, only the Maruoka catalyst has been demonstrated to work with substrates derived from amino acids other than glycine and alanine. In this paper, we report our results on the extension of the methodology shown in Scheme 1 to amino acids other than alanine.

It was expected that the introduction of large substituents into the substrate would lead to a reduction in the rate of the alkylation reaction which might result in catalyst decomposition during the reactions. However, initial results using *N*-benzylidene alanine isopropyl ester as substrate and benzyl bromide as the alkylating agent showed that under the standard reaction conditions, the enantiomeric excess of the product did not vary with % conversion (91% ee at 10–90% conversion). This indicated that catalyst **1** was completely stable during the reaction and hence that the longer reaction times which may be required for more hindered substrates should not result in the formation of product with reduced enantiomeric excess.

Keywords: α,α-disubstituted amino acid; enolate alkylation; asymmetric catalysis; copper(salen) complex.

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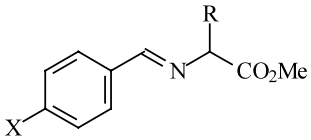
To extend the scope of the chemistry shown in Scheme 1, we first investigated the alkylation of the enolate derived from aminobutyric acid derivative **2**. As shown in Table 1 (entries 1–7), this slight increase in the size of the side chain did have a detrimental effect upon both the enantioselectivity and the rate of reaction. However, by increasing the reaction time to 2 days (compare entries 3 and 4 or 5 and 6) or by increasing the concentration of the alkylating agent (compare entries 5 and 7) where necessary, it was still possible to obtain α-ethyl α-amino acids with 79–82% enantiomeric excess with both allylic and benzylic alkyl halides.[11] All enantiomeric excesses were determined by reaction of the α,α-disubstituted amino esters with (*S*)-1-phenylethyl isocyanate and subsequent analysis of the diastereomeric adducts by ^{1}H NMR spectroscopy as previously reported.[5,6]



2: R = CH_2CH_3; X = Cl
3: R = CH_2CHMe_2; X = Cl
4: R = CH_2Ph; X = Cl
5: R = $CHMe_2$; X = Cl
6: R = $CH_2CH{=}CH_2$; X = H
7: R = CH_3; X = H

Leucine derivative **3** is a more hindered substrate which contains a branch at the γ-carbon. The alkylation of this substrate was considerably more problematical than the alkylation of compound **2** as shown in Table 1 (entries 8–15). Under the standard conditions with benzyl bromide as the alkylating agent, no reaction occurred (entry 8). However, by increasing the amount of catalyst to 10 mol% (entry 9) and the reaction time to 7 days (entry 10), it was possible to obtain the α-benzyl leucine derivative in moderate yield and enantiopurity. The same conditions were also found to be optimal when *para*-nitrobenzyl bromide was used as the alkylating agent (entry 12), though in this case use of a higher concentration of the alkylating agent allowed the reaction time to be reduced to one day with only a small reduction in enantioselectivity (entry 13). The amount of catalyst could also be reduced to 2 mol% with little change in the enantioselectivity, though at the expense of a lower chemical yield (entry 14). The smaller alkylating agent allyl bromide, also reacted with substrate **3** in the presence of 10 mol% of the catalyst to give α-allyl leucine in moderate yield but with only low enantiomeric excess after one day (entry 15).

The next amino acid to be studied as a substrate for the alkylation reaction was phenylalanine since in this case the side chain contains a branch at the β-position. The results are shown in Table 1 (entries 16–24). Using the standard amounts of alkylating agent and catalyst (entries 16 and 17), a moderate yield of α-allyl phenyl-

Table 1. Alkylation of amino acid derivatives **2–6**

Entry	Substrate	Alkylating agent (equiv.)	Catalyst (mol%)	Time (days)	Yield (%)	Enantiomeric excess (%)
1	**2**	Allyl bromide (1.2)	2	1	46	80
2	**2**	Allyl bromide (2.4)	2	1	54	70
3	**2**	Benzyl bromide (1.2)	2	1	39	80
4	**2**	Benzyl bromide (1.2)	2	2	91	82
5	**2**	*para*-Nitrobenzyl bromide (1.2)	2	1	23	78
6	**2**	*para*-Nitrobenzyl bromide (1.2)	2	2	83	79
7	**2**	*para*-Nitrobenzyl bromide (2.4)	2	1	95	75
8	**3**	Benzyl bromide (1.2)	2	1	0	
9	**3**	Benzyl bromide (1.2)	10	1	41	27
10	**3**	Benzyl bromide (1.2)	10	7	54	55
11	**3**	*para*-Nitrobenzyl bromide (1.2)	10	1	46	40
12	**3**	*para*-Nitrobenzyl bromide (1.2)	10	7	63	56
13	**3**	*para*-Nitrobenzyl bromide (2.4)	10	1	64	47
14	**3**	*para*-Nitrobenzyl bromide (2.4)	2	1	47	43
15	**3**	Allyl bromide (1.2)	10	1	46	22
16	**4**	Allyl bromide (1.2)	2	1	30	17
17	**4**	Allyl bromide (1.2)	2	5	44	17
18	**4**	Allyl bromide (2.4)	2	1	53	15
19	**4**	Allyl bromide (4.8)	2	1	74	18
20	**4**	Allyl bromide (4.8)	10	1	87	20
21	**4**	Allyl bromide (1.2)	10	1	40	31
22	**4**	Allyl bromide (1.2)	25	1	68	27
23	**4**	Allyl bromide (1.2)	50	1	70	19
24	**4**	*para*-Nitrobenzyl bromide (1.2)	10	1	67	34
25	**5**	Allyl bromide (2.4)	2	7	0	
26	**5**	Allyl bromide (2.4)	10	2	0	
27	**5**	Benzyl bromide (2.4)	10	2	0	
28	**6**	Benzyl bromide (1.2)	2	2	69	42
29	**6**	*para*-Nitrobenzyl bromide (1.2)	2	2	45	47
30	**6**	1-Bromobut-2-yne	2	2	46	25

alanine was obtained after 1–5 days. By increasing the concentration of the alkylating agent (entries 18 and 19), it was possible to obtain the product in excellent yield, but the enantiomeric excess of the α-allyl phenylalanine never exceeded 20%. In contrast, use of 10 or 25 mol% of the catalyst (entries 21 and 22) raised the enantiomeric excess of the product to around 30%, though without increasing the chemical yield of the product. A further increase in the amount of catalyst used (to 50%; entry 23) was however severely detrimental to the enantioselectivity. Use of *para*-nitrobenzyl bromide as the alkylating agent under conditions of optimal enantioselectivity (entry 21) gave comparable results (entry 24).

The most hindered naturally occurring α-amino acid is valine, and as such, substrate **5** was felt to represent the most demanding test of the methodology. However, all attempts to alkylate substrate **5** were unsuccessful (Table 1, entries 25–27). Based on these results, there appears to be a relationship between the size of the side chain present in the substrate, and both the enantioselectivity and rate of the alkylation. As the side chain increases in size, and particularly as it becomes branched close to the α-position of the amino acid, the enantioselectivity decreases and the reactions become slower until with valine derived substrate **5**, no reaction occurs.

To test this hypothesis, we investigated the alkylation of allylglycine derivative **6**. In this case, for ease of synthesis of the substrate,[12] an unhalogenated imine was used. Previous results[6] suggest that this will lower the enantioselectivity of the process by up to 10%. Never the less, as the allyl side chain in substrate **6** is unbranched and intermediate in size between those of substrates **2** and **3**, it would be expected that the enantioselectivity of the alkylations would be lower than those observed for compound **2**, but higher than those observed for compound **3**. When benzyl bromide is used as the electrophile, the data in Table 1 show that this trend is indeed followed (compare entries 4, 8, 9, and 28). The enantiomeric excess observed with substrate **3** exceeds that observed for substrate **6** only when the amount of catalyst used is increased from 2 to 10 mol%. Similarly, when *para*-nitrobenzyl bromide was used as the alkylating agent with 2 mol% of the catalyst (entries 6, 14, and 29), the enantioselectivities followed the expected trend.

The absolute configuration of the major enantiomer of the products formed in these reactions has in most cases not been determined, but based on previous work is expected to result from alkylation of the *re*-face of the enolate of the substrate. Consistent with this, two sets of reactions form the methyl ester of α-allyl phenylalanine: entries 16–23 by the alkylation of a phenylalanine derivative with allyl bromide; and entry 28 by the alkylation of an allylglycine derivative using benzyl bromide. These two sets of reactions gave opposite enantiomers of the product as determined by ^{1}H NMR analysis of their (*S*)-1-phenylethyl isocyanate adducts, and the product formed by allylation of phenylalanine derivative **4** was hydrolysed to (+)-α-allyl phenylalanine which is known to correspond to the (*S*)-enantiomer of this compound.[13]

We have previously proposed that the alkylation of amino ester enolates catalysed by complex **1** occurs as shown in Figure 1 (R = H).[4] In this model, the enolate is coordinated to both the copper and sodium ions of a bimetallic complex and is held orthogonal to the plane of the salen ligand. The alkylation is directed by the conformation of the cyclohexane ring, with reaction on the *re*-face of the enolate being less hindered than reaction on the *si*-face. This model works well for glycine and alanine substrates,[4] both of which are alkylated with high enantioselectivity. For other amino acid derived substrates however, an additional factor needs to be considered: rotation around the C_α–C_β bond of the enolate. Thus, the R-group shown in Figure 1 could be located over the *re*- (as shown) or *si*-face of the enolate. The former is most likely since the R-group will be repelled by the same features of the cyclohexane ring that direct alkylation to the *re*-face of the enolate. If the R-group is over the *re*-face of the enolate however, then it will hinder the approach of the electrophile to the *re*-face and this will result in a lower enantioselectivity during the alkylation. The overall rate of reaction will also decrease as the size of the R-group increases. Thus, the model correctly predicts both the absolute configuration of the product, and the relationship between the enantioselectivity and the size of the amino acid side chain.

Another feature of these reactions that requires explanation is the variation of rate of reaction/enantioselectivity with catalyst concentration. Entries 16 and 21–23 of Table 1 show that for the allylation of substrate **4**, there is an optimal concentration of catalyst and higher or lower concentrations give product with lower enantiomeric excess. A similar effect is observed on the rate of reaction during the alkylation of substrate **7** with benzyl bromide (Fig. 2). The most likely explanation of these effects is that the catalytically active, dimeric form of the catalyst (Fig. 1) exists in equilibrium with higher oligomers which are catalytically inactive. Thus, increasing the concentration of the catalyst beyond the

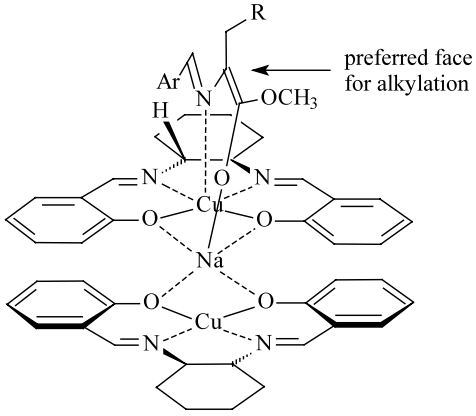


Figure 1.

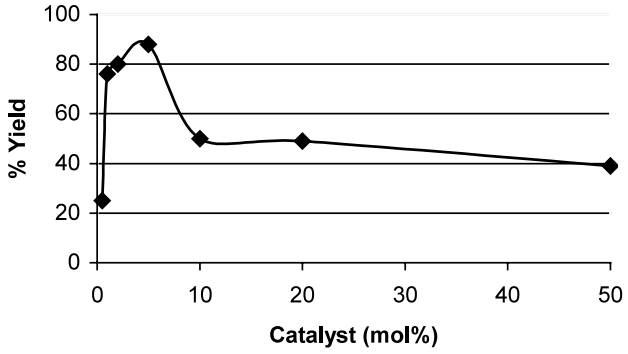


Figure 2.

optimal value favours formation of the higher oligomers and decreases the concentration of the catalytically active form of the catalyst, resulting in a lowering of the rate of reaction. Similarly, reducing the concentration of the catalyst below the optimal value decreases the concentration of the dimeric form due to preferential formation of monomeric species. Control experiments have shown that in the absence of any catalyst, the alkylation of substrates **2**–**7** still proceeds to give racemic product. Thus, any reduction in the rate of the catalysed reaction will result in a decrease in the enantiomeric excess of the product due to an increase in the relative importance of the uncatalysed reaction.

In summary, we have demonstrated that complex **1** will catalyse the alkylation of enolates of a range of amino acids, thus allowing the synthesis of enantiomerically enriched α,α-disubstituted amino acids. There is a clear relationship between the size of the side chain of the amino ester substrate, and the enantioselectivity of the process. This relationship is consistent with the model that we have previously proposed to explain the nature of the catalysis and the origin of the asymmetric induction. Work on the modification of the catalyst structure to enhance the enantioselectivity of the alkylation of amino acids with large side chains is currently in progress.

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