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A practical asymmetric synthesis of α-methyl α-amino acids using a chiral Cu–salen complex as a phase transfer catalyst

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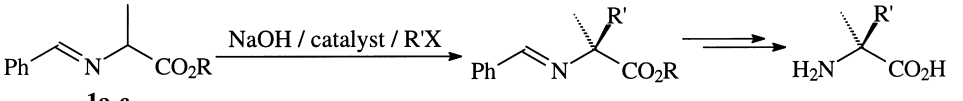
Abstract

The asymmetric *C*-alkylation of *N*-benzylidene alanine methyl ester has been achieved using a copper(II) (salen) complex as an asymmetric phase transfer catalyst and provides a practical synthesis of α-methyl α-amino acids with up to 86% enantiomeric excess.

Keywords: phase transfer; catalysis; copper; asymmetric synthesis; amino acid.

Most asymmetric catalysts are based on transition metal complexes since the coordination geometry of the transition metal can fix the relative positions of the reactants, and the variable oxidation state of transition metals may facilitate the chemical transformation.[1] One notable exception to this trend is asymmetric phase transfer catalysis which until recently has been dominated by derivatives of cinchona alkaloids,[2,3] and more recently by other quaternary ammonium salts.[4] However, even this area has succumbed to metal catalysis. In 1998, Belokon', Kagan and co-workers reported the use of sodium taddolate[5] as a catalyst for the asymmetric alkylation of alanine enolates (Scheme 1), and subsequently reported the use of sodium salts of 2-hydroxy-2′-amino-1,1′-binaphthyl derivatives for the same reaction.[6] Subsequently, we were able to show that nickel(II) or optimally copper(II) complexes of salen (**2a**,**b**) could function as asymmetric phase transfer catalysts, with just 1 mol% of the catalyst being sufficient to produce α,α-disubstituted α-amino acids with >90% enantiomeric excess.[7]



1a-c

a; R = ^{i}Pr: **b**; R = ^{t}Bu: **c**; R = Me

Scheme 1.

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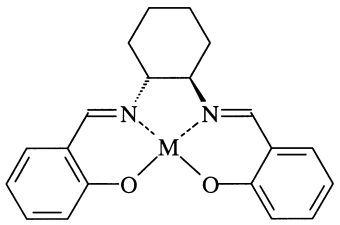
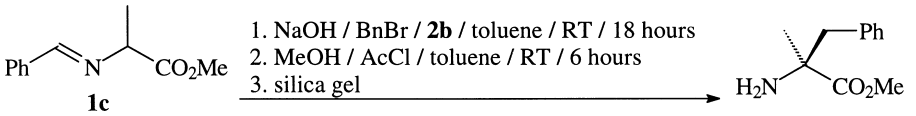
The chemistry shown in Scheme 1 is an attractive test for asymmetric phase transfer catalysis since the products are α-methyl α-amino acids which are components of a wide range of pharmaceutically active compounds.[8] However, to date it has always been necessary to use the *iso*-propyl **1a** or *tert*-butyl esters **1b** of the substrates, the syntheses of which are not trivial and which add considerable cost to any attempt to exploit this chemistry commercially. It would be highly desirable to develop the chemistry shown in Scheme 1 using the methyl ester substrate **1c**. For cinchona alkaloid-catalyzed reactions, it is known that the steric bulk of the ester is important for efficient asymmetric induction;[9] however, this would not necessarily be the case for catalysis involving metal salen complexes. In this manuscript, we report that it is indeed possible to prepare α-methyl α-amino acids using a copper salen catalyst and substrate **1c**.



a; M = Ni
b; M = Cu

2a,b

Our first attempts to alkylate imine **1c** with benzyl bromide using copper complex **2b** (2 mol%) as catalyst gave methyl α-methyl-phenylalaninate with moderate enantiomeric excess[10] (45–50%), but in very poor yield (25%). After considerable experimentation, it was discovered that the low yields were being caused by two factors: (1) hydrolysis of the alkylated imines within the reaction mixture; and (2) the surprisingly high water solubility (even at pH >7) of methyl α-methyl-phenylalaninate. The first of these problems was circumvented by introducing a re-esterification step with methanol and acetyl chloride as part of the reaction, and the second problem was avoided by developing a non-aqueous work-up in which silica gel was used to hydrolyze the imine and absorb metal residues, giving methyl (*S*)-α-methyl-phenylalaninate in 91% isolated yield and with 81% enantiomeric excess[10–12] (Scheme 2). Under these optimized conditions, no unalkylated material was isolated, which implies that the formation of the enolate of **1c** is significantly faster than the hydrolysis of the methyl ester since it is unlikely that sodium hydroxide could form a dienolate under the reaction conditions. The reaction was also found to exhibit an unusual temperature effect: optimal yields and enantiomeric excesses were obtained at room temperature with both higher (64°C; 21% yield, 52% ee) and lower (–78°C; 77% yield, 60% ee) temperatures being detrimental.



Scheme 2.

Having optimized the reaction conditions, the alkylation of **1c** with a range of other electrophiles was investigated, and the results are given in Table 1. Benzylic alkyl halides generally reacted with **1c** in good yields and with moderate to good enantioselectivities. The only exception to this was 4-methoxybenzyl chloride which, under the standard conditions, gave a low chemical yield. This

Table 1

Alkylating agent	Chemical yield (%)	Enantiomeric excess (%)
BnBr	91	81
4-$O_2NC_6H_4CH_2Br$	78*	85
4-$MeOC_6H_4CH_2Cl$	42*	60
4-$MeOC_6H_4CH_2Cl$ / NaH	72*	69
1-bromomethylnaphthalene	85	86
2-bromomethylnaphthalene	82	84
Allyl bromide	75	72
$PhCH=CHCH_2Br$	95	77
Propargyl bromide	70	43
EtI or EtOTf or MeI	0	

* Spectral data for new compounds were consistent with the proposed structures.

problem was caused by a reaction between the particularly reactive alkylating agent and sodium hydroxide, and could be circumvented by changing the base to sodium hydride. Allylic bromides also gave good chemical yields and enantiomeric excesses, but propargyl bromide gave a much lower enantiomeric excess, probably due the small size of the electrophile, and simple alkyl halides or triflates were totally unreactive.

The methyl esters could be hydrolyzed to give the corresponding amino acids simply by refluxing in dilute hydrochloric acid as illustrated for the allyl bromide adduct which was hydrolyzed to (*S*)-α-allyl alanine in 84% yield. Alternatively, it is possible to modify the work-up of the alkylation to give the free amino acid directly. Thus, for a reaction using benzyl bromide, omission of steps 2 and 3 (Scheme 2), filtration and evaporation of the toluene solvent followed by overnight reflux in 2M hydrochloric acid removed both of the protecting groups. Extraction of organic by-products with dichloromethane followed by evaporation of the aqueous solution then gave almost pure α-methyl phenylalanine which could be purified by dissolution in isopropanol, filtration through alumina and evaporation to give (*S*)-α-methyl phenylalanine in 76% overall yield from **1c**.

Our work on the mechanism, optimization, and applications of this novel type of asymmetric phase transfer catalysis is continuing and further results will be reported in due course.

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10. All enantiomeric excesses were determined by a reaction of the amino esters with excess (*S*)-α-methyl-benzyl isocyanate until all of the amino ester had been consumed, followed by analysis of the resulting diastereomers by ^{1}H NMR.
11. The absolute configuration was determined by comparison of the specific rotation with that reported in the literature: Davis, F. A.; Liu, H.; Reddy, G. *Tetrahedron Lett.* **1996**, *37*, 5473.
12. Typical experimental procedure: In oven dried glassware, Schiff base **1c** (0.200 g, 1.05 mmol) was dissolved in dry toluene (2.5 ml), then catalyst **2b** (0.008 g, 0.02 mmol, 0.02 equiv.) was added. Finely ground sodium hydroxide (0.146 g, 3.66 mmol, 3.5 equiv.) was then added to the mixture, followed by the alkylating agent (1.26 mmol, 1.2 equiv.). The reaction was then stirred at room temperature overnight under an argon atmosphere. The resulting suspension was diluted with methanol (3 ml) and acetyl chloride (0.5 ml) was added slowly. The mixture was stirred for a further 6 hours before the solvents were removed in vacuo. The residue was added to a silica gel column and eluted with EtOAc:EtOH to yield the amino-ester.