(*S*)-*o*-*N*-(*N*-Benzylprolyl)aminobenzaldehyde and (*S*)-*o*-*N*-(*N*-Benzylprolyl)aminoacetophenone as Reagents for Asymmetric Synthesis of Threonine

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Chiral aldehydes and ketones, derivatives of proline and piperidine-2-carboxylic acid have been synthesized and their Schiff bases with glycine form copper complexes which were hydroxyethylated with acetaldehyde; decomposition of the complexes obtained gave threonine with an optical purity of up to 97—100% and with threo/allo ratios of up to 19 : 1, and the chiral reagents can be recovered and reused with no loss of optical purity of the threonine.

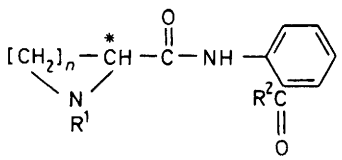
The main disadvantage of chemical methods for the synthesis of (*S*)-amino-acids resides in the necessity to resolve racemic amino-acids and racemise their (*R*)-enantiomers.[1] To eliminate this disadvantage, there has been an intensive search for effective methods for asymmetric synthesis of amino-acids[2] and enantiomeric enrichment of racemic α-amino-acids, obviating the resolution stage.[3–5] Earlier we reported on the use of a chiral aldehyde [enantiomers of 1-(*N*,*N*-dimethylaminomethyl)-2-formylcymanthrene] for asymmetric synthesis of ThrGly from GlyGly with an optical purity of 98%.[5] However, this cymanthrene derivative carries out asymmetric transformations only with dipeptides and cannot be used for direct asymmetric synthesis of amino-acids.

We report here the synthesis of the chiral reagents (**1**)—(**4**), which are derivatives of (*S*)-proline and (*S*)- or (*R*)-piperidine-2-carboxylic acid, and on their use for the asymmetric synthesis of threonine from glycine and acetaldehyde.

Compounds (**2**)—(**4**) were obtained in 30—50% yields by condensation of the hydrochlorides of *N*-benzylprolyl chloride or *N*-benzylpiperidine-2-carbonyl chloride with *o*-aminobenzaldehyde or *o*-aminoacetophenone in the two-phase system CH_2Cl_2–H_2O at 25 °C, with the water layer at pH 8. Compound (**1**) was obtained by condensation of *N*-formylproline with *o*-aminobenzaldehyde, the *N*-formyl group being removed in the subsequent formation of the copper complex of the Schiff base with the amino-acid.

The Schiff bases of compounds (**1**)—(**4**) with amino-acids in MeOH give the complexes with copper(II) in Scheme 1. The structures were assigned by physical and chemical methods. The copper complexes of the Schiff bases of reagents (**1**)—(**4**) with Gly in methanolic sodium methoxide react with acetaldehyde, giving a mixture of intermediate threonine complexes, from which threonine can be isolated with chemical yields of 80—100% and the initial reagents (**1**)—(**4**) with recoveries of 70—90% (Scheme 1). The asymmetric yield of threonine and the threo/allo ratio are presented in Table 1.

In a typical experiment, to a stirred solution of (*S*)-(**3**) (1 mmol) in methanolic NaOMe (0.14 M; 10 ml) at room temperature was added a solution of $CuSO_4.5H_2O$ (1.1 mmol) in water (3 ml), followed by a solution of Gly (1.1 mmol) in methanolic NaOMe (1 M; 1.1 ml), and the solution was then stirred for a further 15 min. The solution was diluted with

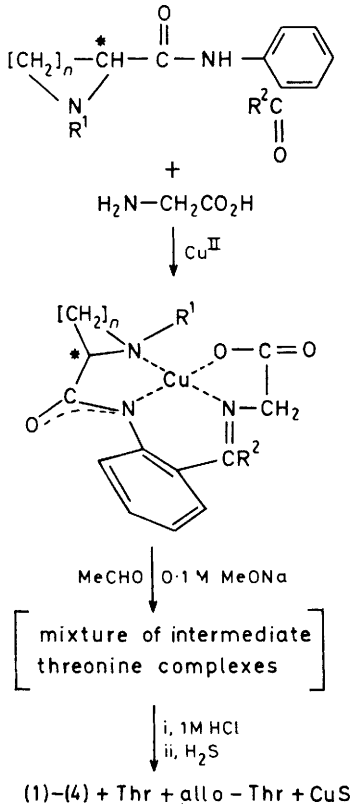


n	R^1	R^2	
3	H	H	(*S*)-(**1**)
3	$PhCH_2$	H	(*S*)-(**2**)
3	$PhCH_2$	Me	(*S*)-(**3**)
4	$PhCH_2$	Me	(*S*)- and (*R*)-(**4**)

Table 1. Enantiomeric composition of threonine obtained in the hydroxyethylation of the copper(II) complexes of (**1**)—(**4**) and Gly.

Reagent	Reaction[a] time/h	Thr/allo-Thr	Enantiomeric purity, %[b] Threonine	Allothreonine
(*S*)-(**1**)	1	2.8	4 (*R*)	6 (*S*)
(*S*)-(**1**)	4	2.5	3 (*R*)	Racemate
(*S*)-(**2**)	0.5	4.9	58 (*R*)	12 (*S*)
(*S*)-(**2**)	1	5.6	56—60 (*R*)[c]	Racemate
(*S*)-(**2**)	4	5.8	61 (*R*)	16 (*R*)
(*S*)-(**2**)	19[d]	9.7	65 (*R*)	30 (*R*)
(*S*)-(**3**)	1	3.8	92 (*R*)	100 (*R*)
(*S*)-(**3**)	4	19	97—100 (*R*)	100 (*R*)
(*R*)-(**4**)	1	10	89 (*S*)	90 (*S*)
(*R*)-(**4**)	3	12	92 (*S*)	100 (*S*)
(*S*)-(**4**)	3	11	92 (*R*)	100 (*R*)

[a] Complex concentration = 0.1 M, MeCHO/complex = 50; in 0.2 M MeONa at 25 °C under Ar. [b] According to g.l.c.[6] [c] The results of four experiments are within this range. [d] Reaction at −5 °C.



Scheme 1

H_2O and extracted with $CHCl_3$. Upon evaporation, (*S*)-(**3**)–Gly–Cu^{II} was obtained in quantitative yield (0.44 g). To a solution of this complex and MeCHO (50 mmol) in anhydrous MeOH (5.2 ml), methanolic NaOMe (1 M; 2 ml) was added under argon, and the mixture was kept at 25 °C for 1 h. HCl (1 M) was then added, and the resulting solution was diluted with H_2O and treated with H_2S. CuS was filtered off, and washed with H_2O and $CHCl_3$. The combined water layers were neutralized and extracted with $CHCl_3$. The combined organic layers were evaporated giving 0.28 g (85% recovery) of (*S*)-(**3**). The amino-acids were isolated from the water solution on a 'Dowex-50' resin in 80—100% yield (g.l.c.).

The retrieved (*S*)-(**3**) can be repeatedly used for the asymmetric synthesis of Thr with no loss of optical purity of the latter.

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