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Synthesis of both enantiomers of β,β-diphenyl-α-alanine (Dip) from glycine using (*S*)- or (*R*)-2-[(*N*-benzylprolyl)amino]benzophenone as a reusable chiral auxiliary

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Abstract: Preparative syntheses of enantiopure (*S*)- and (*R*)-Dip by α-C-alkylation with Ph_2CHX (X=Cl or Br) of the glycine moiety in a Ni(II) Schiff's base complex **1** derived from glycine and (*S*)- or (*R*)-[(*N*-benzylprolyl)amino]benzophenone (**BPB**) is described. The diastereoselectivity of the alkylation with $PhCH_2Br$ in DMF in the presence of NaOH is both kinetically and thermodynamically controlled. © 1997, Elsevier Science Ltd. All rights reserved.

There is an increasing interest in approaches to the synthesis of enantiopure (*S*)- and (*R*)-β,β-diphenyl-α-alanine (Dip), since both compounds find use in the preparation of peptides of biological importance.[1] Recently, the scalemic 4-benzhydryloxazolidine-2-one prepared from Dip was shown to be an effective chiral auxiliary in radical addition reactions.[2] A few synthetically useful methods of preparing the title amino acids have been reported, including: fractional crystallisation of the diastereoisomeric salts of *N*-acyl derivatives with (+)-cinchonidine[1a] and asymmetric syntheses, using the Evans[3] or Oppolzers[4] chiral auxiliaries. The traditional enzymatic methods of enantiomer resolution were found not to be applicable for this unusual amino acid.[5]

We have elaborated (*S*)-2-[(*N*-benzylprolyl)amino]benzophenone [(*S*)-**BPB**] as a chiral auxiliary for the synthesis of a wide range of enantiopure non-proteinogenic amino acids.[6] The synthetic protocols were based on use of Ni(II) complexes of the Schiff's bases derived from (*S*)-**BPB** and simple amino acids (glycine or alanine). The amino acid moiety became a sufficiently strong CH-acid to undergo a set of electrophilic reactions in the presence of such regular bases as NaOH, KOH or K_2CO_3.[6] This approach was also successfully used by other synthetic groups.[7]

In this paper, we report a synthetic protocol for multigram preparations of both enantiomers of Dip *via* (*S*)-**1** and (*R*)-**1**. Thus, *C*-alkylation of (*S*)-**1** with Ph_2CHBr was fast and quantitative in DMF, using NaOH as a base (Scheme 1). The reaction was monitored by TLC on SiO_2 ($CHCl_3$:Me_2CO, 7:1). Almost all (*S*)-**1** was consumed within 5 minutes, with the formation of two diastereoisomeric complexes **2a** [(*S*,*S*)] and **2b** [(*S*,*R*)] as a result of the electrophilic attack on the *si*- and *re*-faces of the intermediate carbanion generated from the glycine moiety of (*S*)-**1**. The diastereoselectivity of the reaction (ratio **2a/2b**) could be visually estimated by comparing the sizes of the coloured spots of the diastereoisomers on a TLC plate and quantitatively established by chiral GLC from the enantiomeric purity of the isolated Dip (see below). The d.e. of the reaction was time dependent and the ratio **2a/2b** was 58:42, 77:23, 87:13 and 95:5 after 5, 10, 30 and 60 minutes respectively. Evidently, the initial ratio of the diastereoisomers reflected the relative rates of the electrophile attack on the diastereotopic faces of the intermediate carbanion of the glycine moiety of **1** (k_1/k_2, Scheme 1). As the complexes **2a** and **2b** were formed in approximately equal amounts, the kinetic diastereoselectivity of the reaction was

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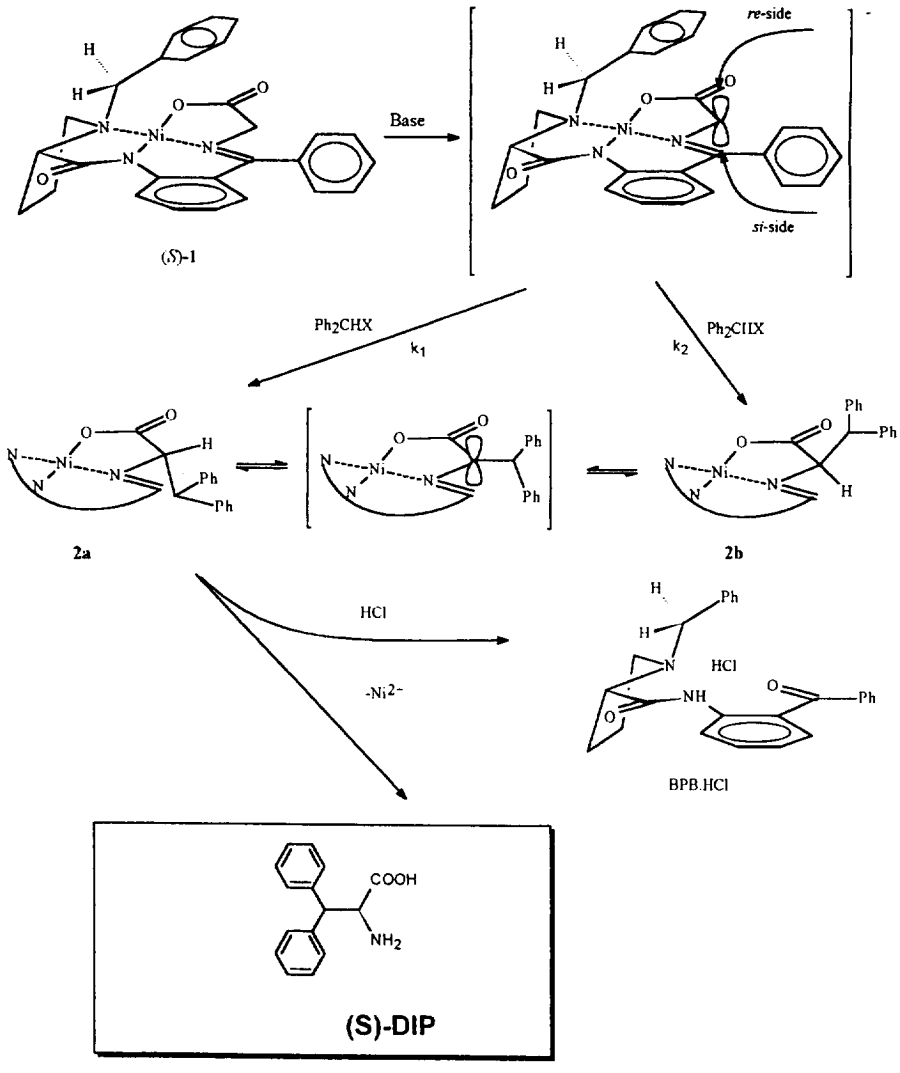

Scheme 1. Synthetic protocol for multigram preparations of both enantiomers of Dip via (*S*)-**1** and (*R*)-**1**.

very low. The diastereoisomeric mixture of **2a** and **2b** could be easily separated (after neutralisation with AcOH 5 minutes after addition of the alkylating agent) by preparative chromatography and each decomposed, giving both enantiomers of Dip from a single alkylation experiment. The base-catalysed epimerisation of the diastereoisomers *via* the reversible α-proton removal from the Dip moieties in **2a** and **2b** followed if the reaction mixture was left without neutralisation (Scheme 1). After the thermodynamic equilibrium had been established (>60 min) the major isomer **2a** was isolated from the neutralised reaction mixture by crystallisation and enantiomerically pure (*S*)-Dip recovered from it, as described below.

The alkylation of (*S*)-**1** with Ph_2CHCl proceeded more slowly than with Ph_2CHBr under similar reaction conditions. The conversion of (*S*)-**1** was nearly complete only after 2h and the formed diastereoisomeric mixture of **2a** and **2b** had already reached the state of equilibrium. The reaction was accompanied by the formation of significant amounts of side products. The yields could be improved

if the reaction was carried out under argon in acetonitrile with NaH as a base. Thermodynamically favoured **2a** [contaminated with traces of starting (*S*)-**1**] was isolated from the neutralised reaction mixture by crystallisation. The yield of **2a** was improved by epimerisation of the filtrate, containing an approximately 1:1 mixture of **2a** and **2b**, in MeONa/MeOH solution and the additional quantity of **2a** isolated.

The complex **2a** was decomposed, using a water–methanol solution of HCl (Scheme 1). For isolation of (*S*)-Dip from the mixture, containing $NiCl_2$, we attempted to use a method elaborated by us especially for aromatic amino acids and based on the poor solubility of their hydrochlorides in conc. HCl. This method had been successfully used by us earlier for a multigram syntheses of α-methyl-β-3,4-dichlorophenyl-α-alanine and *O*-methyl-3-fluorotyrosine.[8] This route was also applicable for the isolation of (*S*)-Dip from the solution. Unfortunately, (*S*)-Dip isolated in this way was contaminated with a substance of unknown structure and several recrystallisations did not result in a pure material. We observed that the impurity disappeared when the isolation of (*S*)-Dip included such procedures as ion-exchange or the transformation of its hydrochloride to the free base but the procedures were not convenient for the isolations of sizeable amounts of the amino acid. Finally, we were able to elaborate a new method suitable for the efficient multigram preparations of (*S*)-Dip which included the separation of Ni(II) ions with EDTA in a neutral water solution. One recrystallization of the amino acid hydrochloride yielded pure (*S*)-Dip.HCl with ee >99%, according to the enantiomeric GLC analysis data.

(*R*)-Dip.HCl was successfully synthesised, using the same synthetic protocol, starting with (*R*)-**1**. The overall yields of the enantiomerically pure amino acids were up to 60% and the chiral auxiliaries, (*S*)-**BPB** and (*R*)-**BPB**, were recovered in 90% yields.

Experimental section

^{1}H NMR spectra were recorded on a Brucker WP-200 instrument. The optical rotations were measured with a Perkin–Elmer M241 polarimeter. Melting points are uncorrected. (*S*)-**BPB** is available from Merck (Cat. No 814473) and Acros (Cat. No 26.919.50). Kieselgel 60 (Merck) was used for column chromatography and silica gel 60F254 precoated plates (Merck) were used for TLC. MeCN was distilled over CaH_2 and, finally, over P_2O_5. (*S*)-**1** and (*R*)-**1** were obtained as previously reported.[6a,9] Ph_2CHCl (Fluka) was used as purchased and Ph_2CHBr was synthesised according to the literature procedure.[10] Enantiomeric GLC analysis of Dip was performed after transformation of the samples into *N*-trifluoroacetyl-*O*-^{i}Pr derivatives on a column packed with ChirasilVal type stationary phase.[11]

Alkylation of (S)-1 with Ph_2CHBr in DMF solution, using NaOH as a base

To a stirred mixture of (*S*)-**1** (1 g, 2 mmol) and finely powdered NaOH (0.24 g, 6 mmol) in DMF (2.4 ml) was added Ph_2CHBr (0.54 g, 2.2 mmol) in one portion under Ar. After 5 minutes, the reaction mixture was neutralised with 0.5 ml AcOH followed by addition of 50 ml water. The red coloured precipitate was filtered, washed with water and air dried, yielding a mixture of **2a** and **2b** (1.3 g, 97.7%) which were separated by column chromatography on SiO_2 (200×18 mm, $CHCl_3$/Me_2CO, 20:1). The diastereoisomers were additionally purified on Sephadex LH-20 (C_6H_6/C_2H_5OH; 3:1), and 0.43 g (32.3%) of **2a** and 0.22 g (16.5%) of **2b** were obtained in this way.

2a. Dark red crystals, m.p. 292–295°C (from MeOH), $[\alpha]_D^{25}$ (c=0.1, MeOH) +2064, (Found, C, 72.5; H, 5.50; N, 6.12. $C_{40}H_{35}N_3NiO_3$ requires C, 72.30; H, 5.31; N, 6.32%). $\delta_H(CDCl_3)$ 1.5–3.0 (m, 6H, Pro); 3.3 (m, 1H, Pro); 3.36 (d, 1H, NCH_2Ph, *J*=13 Hz); 4.22 (d, 1H, NCH_2Ph, *J*=13 Hz); 4.52 (d, 1H, $CHPh_2$, *J*=4 Hz), 4.66 (d, 1H, α-H, *J*=4 Hz), 6.4–8.4 (m, 24H, ArH).

2b. Dark red amorphous solid, m.p. 230°C (decomp.) with a phase transition at 147–150°C, $[\alpha]_D^{25}$ (c=0.1, MeOH) −1160 (Found, C, 74.68; H, 5.84; N, 5.63. $C_{40}H_{35}N_3NiO_3.C_6H_6$ requires C, 74.40; H, 5.57; N, 5.66%). $\delta_H(CDCl_3)$ 1.1–2.5 (m, 5H, Pro), 3.34 (d, 1H, NCH_2Ph, *J*=14 Hz), 3.37–3.5 (m, 1H, Pro), 3.65 (d, 1H, NCH_2Ph, *J*=14 Hz), 3.7–3.9 (m, 1H, Pro), 4.26 (d, 1H, $CHPh_2$, *J*=3 Hz), 4.72

(d, 1H, α-H, *J*=3 Hz), 6.7–8.5 (m, 30H, ArH+C_6H_6 (complex **2b** cocrystallises with a molecule of benzene)).

The time dependence of the diastereoselectivity of the reaction was investigated in a similar experiment. Aliquots (0.3 ml) were withdrawn from the reaction mixture after 5, 10, 30 and 60 min and each was immediately neutralised with 0.1 ml AcOH, diluted with 10 ml MeOH and 10 ml 6N HCl and refluxed for 20 min. After evaporation of the mixture, the residue was diluted with 20 ml of water, and the pH of the solution was brought to 5 by addition of conc. NH_3. The chiral auxiliary, **BPB**, was extracted with $CHCl_3$; Dip was isolated from the water solution by the ion exchange technique.[6,9] The enantiomeric purity of Dip was determined by GLC. The results were presented in the text.

Multigram synthesis of (S)-Dip

a) Alkylation of (S)-1 with Ph_2CHCl in CH_3CN solution, using NaH as a base

A 2-neck round-bottom flask equipped with a mechanical stirrer was charged with (*S*)-**1** (50 g, 0.1 mole) and 100 ml of anhydrous MeCN. The mixture was cooled (dry ice–Me_2CO) and NaH (7.5 g, 0.3 mole, 60% suspension in oil) and Ph_2CHCl (21.5 ml, 0.12 mole) were added without stirring. The air was evacuated with a vacuum pump and the flask was filled with Ar. The cycle was repeated twice, then the stirring was commenced and the reaction mixture allowed to warm to the ambient temperature and the stirring continued for another 2 hours, after which period the reaction mixture was neutralised by slow addition of AcOH under stirring and cooling and, finally, diluted with water to 1 litre. Then the stirring was stopped and after separation of layers, the water layer was withdrawn. The remaining red coloured oil was triturated with 400 ml of ether and the thus formed crystalline material was filtered, washed with ether and air-dried to afford almost pure **2a** (44.9 g, 67.6%). An additional 13.3 g (20%) of **2a** were obtained after evaporation of the filtrate and epimerisation of the **2a+2b** mixture in a MeONa solution in MeOH. Some contamination of **2a** with (*S*)-**1** did not cause any difficulties during the isolation of the chemically pure amino acid.

b) Recovery of (S)-Dip from 2a

A mixture of **2a** (44.9 g, 0.068 mole), 150 ml MeOH and 6N HCl (100 ml) was refluxed for 20 min, and then evaporated to dryness. Water (100 ml) was added to the residue and the insoluble material was filtered, washed with water (3×100 ml) and dried to afford 25.5 g (89%) of (*S*)-**BPB**.HCl. To the water solution, conc. NH_3 was added to bring the pH of the solution to 9–10, followed by ETD (22.9 g, 0.068 mole) and 100 ml of benzene. The mixture was stirred for 1 hour and then the water layer was separated, concentrated, and cooled. The precipitate was filtered and washed successively with 50 ml of cooled aq. ETD solution and 50 ml of cooled water and finally recrystallised from 130 ml of 1N HCl. 11.3 g (yield 60% based on **2a**) of (*S*)-Dip.HCl was obtained as a colourless, crystalline solid with ee >99% (GLC). M.p. 232–6 (dec.) {lit.[3], m.p. 247–50 (dec.)}. $[\alpha]_D^{25}$ +63.3 (c=1, MeOH) {lit.[3], $[\alpha]_D^{25}$ +63.7 (c=1, MeOH)}. (Found: C, 64.10; H, 6.31; N, 5.02; Cl, 12.57. $C_{15}H_{15}NO_2$.HCl requires C, 64.86; H, 5.81; N, 5.04; Cl, 12.76.) $\delta_H(CD_3OD)$ 4.36 (d, 1H, $CHPh_2$, *J*=11 Hz), 4.8 (d, 1H, α-H, *J*=11 Hz), 7.1–7.6 (m, 10H, ArH).

Preparative synthesis of (R)-Dip

The synthesis was conducted as above starting with (*R*)-**1**. (*R*)-Dip.HCl had ee >99%.(GLC). M.p. 230–6 (dec.), $[\alpha]_D^{25}$ (c=1, MeOH) −63.7 {lit.[3], m.p. 248–53 (dec.), $[\alpha]_D^{25}$ (c=1, MeOH) −63.7}. Found: C, 65.03; H, 5.88; N, 4.94; Cl, 12.74. $C_{15}H_{15}NO_2$.HCl requires C, 64.86; H, 5.81; N, 5.04; Cl, 12.76. $\delta_H(CD_3OD)$ 4.36 (d, 1H, $CHPh_2$, *J*=11 Hz), 4.8 (d, 1H, α-H, *J*=11 Hz), 7.1–7.6 (m, 10H, ArH).

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