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# Optimisation of the retroracemisation procedure for α-amino acids using (*S*)-2-[(*N*-alkylprolyl)amino]benzophenones, recyclable chiral auxiliaries

Binod B. De and Neil R. Thomas *

Department of Chemistry, University of Nottingham, University Park, Nottingham, NG7 2RD, UK

***Abstract:*** The retroracemisation procedure developed by Belokon and coworkers has been re-examined using a variety of new (*S*)-2-[(*N*-alkylprolyl)amino]benzophenones chiral auxiliaries. It has been found that (*S*)-2-[(*N*-benzylprolyl)amino] and (*S*)-2-[(*N*-1-(naphthalenyl-1-methyl)prolyl)amino] benzophenones ((*S*)-BPB and (*S*)-NPB) when used in conjunction with $Ni(NO_3)_2 \cdot 6H_2O$ and a racemic α-amino acid preferentially form a single diastereoisomer in the presence of a mild base such as sodium methoxide. Decomposition of this complex under acidic conditions leads to the isolation of the (*S*)-amino acid in good yield, and in 55 to 99% *e.e.* The retroracemisation abilities of a polymer supported form of the (*S*)-BPB ligand have also been investigated and preliminary results for this are presented here. © 1997 Elsevier Science Ltd

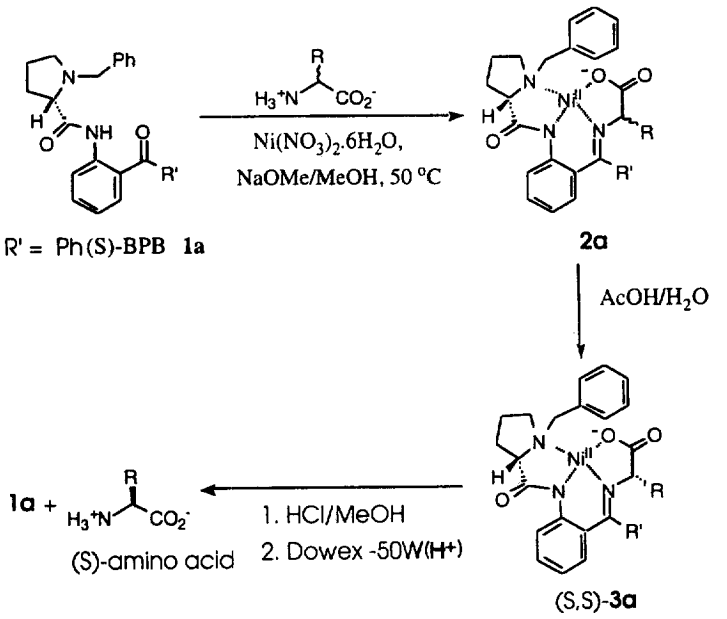
## Introduction

The asymmetric synthesis of amino acids has been an area of intense interest over the the past few decades.[1] A number of elegant approaches have established themselves for use in laboratory or industrial scale syntheses. However many industrial processes still involve classical resolutions which generate considerable amounts of chemical waste in the form of amino acids of the wrong stereochemistry.[2] In 1983 Belokon first reported a procedure he termed "retroracemisation"[3] in which a racemic α-amino acid mixture could be enriched in one of its enantiomeric forms by protonation of a prochiral amino acid enolate generated in an asymmetric environment forming a complex with copper(II), (*S*)-2-[(*N*-benzylprolyl)amino] benzaldehyde or acetophenone and the amino acid (Scheme 1). As can be seen from Table 1 the enrichment resulting from this procedure was significant, but not sufficient for the process to be useful synthetically. Belokon then focused on using both copper(II) or nickel(II) complexes of (*S*)-2-[(*N*-benzylprolyl)amino] benzophenone ((*S*)-BPB) **1a**[4] to produce chiral glycine α-anion equivalents which could then be alkylated to produce new amino acids. We felt that further modification of Belokon's system could result in better enantiomeric enrichment of racemic α-amino acids to the extent that one enantiomer could be converted into its antipode by a simple one-pot procedure. The results of our investigation are presented below.

## Results and discussion

From Belokon's studies it was apparent that the chemical stability of the Ni(II)-complexes was significantly greater than the identical Cu(II)-complex.[2] In almost all cases the (*S*)-2-[(*N*-benzylprolyl)amino] benzophenone ((*S*)-BPB) ligand exhibited the highest diastereoselectivity. Hence we studied the retroracemisation of a series of α-amino acids using this system.[5] Thus a nickel–Schiff's base complex was formed by warming (50°C) the racemic amino acid in the presence of 1 eq. of (*S*)-BPB[6] and nickel(II) nitrate hexahydrate in anhydrous methanol, in the presence of sodium methoxide (10 eq.) for 2 h. The red complex formed was then cooled to room temperature and poured into aqueous acetic acid. The complex was then decomposed by first extracting it into dichloromethane,

* Corresponding author. Email: neil.thomas@nottingham.ac.uk




**Scheme 1.**

**Table 1.** Retroracemisation data. The ligands contains (*S*)-proline, and an enantiomeric excess of the (*S*)-amino acid was observed in all cases. [a]Literature data.[3] [b]Retroracemisation conditions: Ligand/aa/$Cu(OAc)_2$ all at 0.1 M, 0.1 g 3 Å mol. sieves, 7 eq. NaOMe in MeOH (5.0 ml) at RT. [c]Amino acids isolated in 75–100% yield. [d]Retroracemisation conditions: Ligand/aa/$Ni(NO_3)_2.6H_2O$ all at 0.1 M, 10 eq. NaOMe in MeOH (5.0 ml) at 50°C for 2 h. Quenched by pouring into AcOH/water at RT. [e]Enantiomeric excess determined by GLC. [f]Enantiomeric excess determined by chiral HPLC using a CROWNPAK CR(+)® column. [g]Yields for isolated amino acids. [h]Recycled polymer supported ligand.

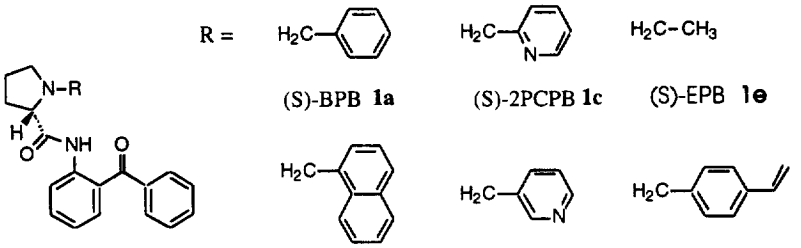
| Amino Acid | BPAB/ Cu(II)[a,b] | BPB/ Ni(II)[d] | | NPB/ Ni(II)[d] | | 2PCPB/ Ni(II)[d] | | 3PCPB/ Ni(II)[d] | | Polymer bound BPB/Ni(II)[d] | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *e.e.* %[c,e] | *e.e.* % | Yield[f] %[g] | *e.e.* % | Yield[f] %[g] | *e.e.* % | Yield[f] %[g] | *e.e.* % | Yield[f] %[g] | *e.e.* % | Yield[f] %[g] |
| (R,S)-Ala | 0 | - | 80 | - | 76 | - | - | - | - | - | - |
| (R,S)-Nva | 12 | 55 | 80 | 72 | 68 | 99 | 70 | 90 | 65 | - | - |
| (R,S)-Val | 54 | - | - | - | - | - | - | - | | - | - |
| (R,S)-Leu | 22 | 58 | 85 | 71 | 70 | 53 | 65 | 75 | 61 | - | |
| (R,S)-Met | - | 91 | 65 | 83 | 64 | 41 | 72 | 59 | 71 | - | - |
| (R,S)-PheGly | 35 | 62 | 87 | 69 | 72 | 51 | 70 | 60 | 66 | - | - |
| (R,S)-Phe | 42 | 96 | 91 | 95 | 75 | 40 | 90 | 69 | 89 | 61 (43)[h] | 83 (76)[h] |
| (R,S)-Tyr | - | 90 | 93 | 99 | 83 | 74 | 81 | 80 | 76 | - | |

removal of solvent *in vacuo* and then treatment with 2 M HCl. The amino acid was purified from the ligand and nickel salts by ion-exchange chromatography using Dowex 50W ($H^+$) resin and then its enantiomeric ratio determined using a CROWNPAK (CR+)® chiral column.[7]

As can be seen from Table 1 the enantiomeric enrichment observed with the (*S*)-BPB:Ni(II):aa system is significantly higher than that observed with Belokon's original system, with several examples

giving *e.e.* values and yields of >90% for the isolated amino acids. To try and improve the enantiomeric enrichment further we examined a number of other (*S*)-2-[(*N*-alkylprolyl)amino]benzophenones ligands[8] to determine their ability in the retroracemisation procedure. Substitution of the prolyl *N*-benzyl substituent by larger groups such as 1-methylnaphthalene, diphenylmethyl and trityl was investigated. (*S*)-2-[(*N*-1-(Naphthalen-1-ylmethyl)prolyl)amino]benzophenone ((*S*)-NPB) **1b** produced complexes that underwent retroracemisation to give a larger diastereomeric ratio of product complexes, but lower yield of isolated amino acid than the (*S*)-BPB ligand.

However, it was not possible to form the Schiff's base complexes with either (*S*)-2-[(*N*-1-diphenylmethylprolyl)amino] or (*S*)-2-[(*N*-1-tritylprolyl)amino] benzophenone and either racemic phenylalanine or glycine.




As we were unable to improve the diastereoselectivity of the reaction by increasing the steric bulk of the prolyl substituent we investigated an alternative approach in which the prolyl nitrogen substituent would be capable of coordinating with the metal of the Schiff's base such that one face of the prochiral amino acid α-carbanion was made permanently inaccessible. There was some precedent for this in the work of Ohno and coworkers[9] who had observed that the copper complex of pyruvyl Gly--D-Phe reacts with imidazole-4-carboxaldehyde to give a square pyramidal intermediate. By replacing the *N*-benzyl group by 2-picolyl or 3-picolyl groups it was hoped that the nickel (or copper) centre would be converted from a square planar to a square pyramidal or octahedral geometry. However crystal structures of the (*S*)-2-PCPB (**1c**) and (*S*)-3-PCPB (**1d**):Ni(II):(*S*)-phenylalanine complexes indicate that the nitrogen of the picolyl group was too far away from the metal to form a bond.[10] As a control system we also examined the retroracemisation abilities of **1e** and found this to be a less effective ligand than either (*S*)-BPB or (*S*)-NPB.

Given the promising results with the (*S*)-BPB:Ni(II):aa system we explored the possibility of producing a polymer supported form of the (*S*)-BPB ligand which would be easier to separate from the amino acid and metallic reaction products. (*S*)-2-[*N*-1-(4-vinyl)benzylprolyl)amino]benzophenone ((*S*)-VBPB) **1f** was synthesised using the standard route,[4] and was then used to form a Schiff's base complex with nickel nitrate and glycine. A macroporous polymer was then produced by mixing together the Schiff's base (10 mol%) with ethylene glycol dimethacrylate (90 mol%) and AIBN in dry toluene. The mixture was heated to 70°C for 24 h and the resulting polymer was filtered off and ground to a fine powder using a mortar and pestle. The powder was then washed with hot methanol to remove unreacted monomer. The polymer supported complex was decomposed using acetic acid in methanol. The polymer was then dried *in vacuo* before being used to conduct a retroracemisation experiment with racemic phenylalanine using the standard conditions (NaOMe/MeOH 50°C then quenched with water at RT). The phenylalanine was released by warming the polymer to 60°C in methanol containing 1 M HCl. The polymer was filtered off and the filtrate concentrated to dryness. The phenylalanine in the filtrate was purified by ion-exchange chromatography (Dowex 50WX8-100 ($H^+$)) and the enantiomeric excess of the product determined by chiral chromatrography as above. Retroracemisation with the polymer supported ligand was less efficient than with (*S*)-BPB, but the optical purity of the phenylalanine produced is sufficiently high to suggest that with optimisation of the linkage between the ligand and the polymer backbone this approach could be viable for use in

the recycling of expensive amino acids. The polymer supported ligand was recycled several times, the enantiomeric excess of the isolated amino acid from the second and subsequent batches being lower (approx. 45%) than those of the initial batch.

Overall we have demonstrated that the BPB:Ni(II):aa system is a viable method of converting racemic amino acids into single enantiomers without the need for a resolution step. Further modification of the polymer supported version of this ligand offers the possibility of creating a simple single-pot automatable method for producing enantiomerically pure amino acids from mixtures.

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2. For examples see *Chirality in Industry*, Collins, A. N.; Sheldrake, G. N.; Crosby, J., Eds; Wiley, Chichester, **1992** (vol. 1), **1997** (vol. 2).
3. Belokon, Y. N.; Zeltzer, I. E.; Bakhmutov, V. I. Saporovskaya, M. B.; Ryzhov, M. G.; Yanovsky, A. I.; Struchkov, Y. T.; Belikov, V. M. *J. Am. Chem. Soc.*, **1983**, *105*, 2010.
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5. **General method for retroracemisation**: (*S*)-2-[(*N*-1-(naphthalenyl-1-methyl)prolyl)amino]-benzophenone (0.37 g, 0.85 mmol), nickel(II) nitrate hexahydrate (0.49 g, 1.15 mmol) and racemic phenylalanine (0.14 g, 0.85 mmol) were taken up in dry methanol (5 ml) and 10 ml of a 1.0 M soln of sodium methoxide in methanol was added. The reaction was warmed to 50°C and maintained at this temperature for 2 h. The reaction was cooled to room temperature and then quenched by addition of water (2 ml). The reaction mixture was extracted with dichloromethane (3×20 ml). The combined organic extracts were dried over magnesium sulphate and the solvent removed *in vacuo*. The residual red Ni(II) complex was dissolved in methanol (10 ml) and decomposed by addition of acetic acid (1.0 ml). The reaction was refluxed for 1 h turning from reddish brown to pale green. The solution was adjusted to pH 8.5 by dropwise addition of 5% aqueous ammonia. Water (10 ml) was added, and the (*S*)-2-[(*N*-(naphthalenyl-1-methyl)prolyl)amino]benzophenone ligand was removed by extracting it into dichloromethane (3×10 ml). The aqueous phase was concentrated *in vacuo* and the residue was taken up in water which was adjusted to pH 7.0 using 2 M HCl. The phenylalanine was purified by ion exchange chromatography using Dowex 50WX8-100, the amino acid being eluted with 5% aqueous ammonia. The optical purity of the isolated amino acid was then determined by chiral chromatography using a CROWNPAK (CR+)® chiral HPLC column under the conditions described in the application guide (aqueous perchloric acid pH 1.5 or 2.0).[7]
6. Available from Merck and Acros Chimica.
7. Available from Daicel Chemical Industries Ltd, Japan.
8. All new compounds gave satisfactory analytical data. **(*S*)-2-[(*N*-1-(Naphthalen-1-ylmethyl) prolyl)amino]benzophenone** $[\alpha]_D = -33.6$ (c=0.5, $CH_3OH$); $^1$H-NMR ($CDCl_3$) δ: 1.90–1.98 (3H, m, β, 2γ Pro-H), 2.10 (1H, m, β Pro-H), 2.39 (1H, m, δ Pro-H), 3.34 (1H, m, α Pro-H), 3.44 (1H, m, δ Pro-H), 3.72, 4.05 (2H, AB, *J*=13 Hz, $CH_2Ph$), 7.20–8.72 (16H, m, ArH), 9.12 (1H, s, NH). **(*S*)-2-[(*N*-1-(2-Picolyl)prolyl)amino]benzophenone** $[\alpha]_D = -78.3$ (c 0.5, $CH_3OH$); $^1$H-NMR ($CDCl_3$) δ: 1.78–1.97 (3H, m, β, 2 Pro-H), 2.28 (1H, m, β Pro-H), 2.51 (1H, m, δ Pro-H), 3.23 (1H, m, α Pro-H), 3.46 (1H, m, δ Pro-H), 3.80, 4.06 (2H, AB, *J*=13 Hz, $CH_2Ph$), 7.02–8.57

(13H, m, ArH, PyrH), 9.01 (1H, s, NH). **(*S*)-2-[(*N*-1-(3- Picolyl)prolyl)amino]benzophenone** $[\alpha]_D=-16.0$ (c 0.5, $CH_3OH$); $^1$H-NMR ($CDCl_3$) δ: 1.79–2.04 (3H, m, β, 2γ Pro-H), 2.29 (1H, m, β Pro-H), 2.43 (1H, m, δ Pro-H), 3.20 (1H, m, α Pro-H), 3.35 (1H, m, δ Pro-H), 3.64, 4.02 (2H, AB, *J*=13 Hz, $CH_2$Pyr), 7.18–8.63 (13H, m, ArH, PyrH), 8.88 (1H, s, NH). **(*S*)-2-[(*N*-1-(4-Vinylbenzyl)prolyl)amino]benzophenone** $[\alpha]_D=-87.2$ (c=0.5, $CH_3OH$); $^1$H-NMR ($CDCl_3$) δ: 1.81–1.94 (3H, m, β, 2γ Pro-H), 2.28 (1H, m, β Pro-H), 2.45 (1H, m, δ Pro-H), 3.20 (1H, m, α Pro-H), 3.35 (1H, m, δ Pro-H), 3.60, 3.90 (2H, AB, *J*=13 Hz, $CH_2$Ar), 5.18, 5.64, 6.69 (3H, m, $-CH=CH_2$), 7.05–8.55 (13H, s, Ar), 9.06 (1H br s, NH).

9. Owa, T.; Otusuka, M.; Ohno, M. *Chem. Lett.*, **1988**, 83.
10. Crystals of (*S*)-2-PCBP:Ni(II):(*S*)-Phe and (*S*)-3-PCBP:Ni(II):(*S*)-Phe were grown up in chloroform. Full crystallographic data for these two compounds have been deposited at the Cambridge Crystallographic Data Centre and are available from the principal author.

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