Preparation of Optically Pure α-Methyl-α-amino Acids *via* Alkylation of the Nickel(II) Schiff Base of (*R,S*)-Alanine with (*S*)-2-*N*-(*N'*-Benzylprolyl)aminobenzaldehyde†

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Chiral nickel(II) complexes of Ala with (*S*)-2-*N*-(*N'*-benzylprolyl)aminobenzaldehyde [(*S*)-bba] were alkylated with alkyl halides and the diastereoisomeric complexes formed were separated on SiO_2; their decomposition led to the isolation of enantiomerically pure (*R*)- and (*S*)-α-alkyl-α-amino acids with recovery of the initial (*S*)-bba.

Some α-substituted α-amino acids find application as drugs because of their ability to serve as specific inhibitors of enzymes which use parent α-amino acids as the substrate.[1] The ability to inhibit enzyme activity is usually associated with one enantiomeric form of the α-amino acid. An efficient and convenient general method for the preparation of optically pure enantiomers of α-substituted α-amino acids would be of general interest.

There are several methods for the diastereoselective asymmetric synthesis of these compounds with high optical purity and high chemical yields,[2] the most convenient being based on the alkylation of chiral amino acid Schiff bases because of the ease of recovery of the auxiliary chiral reagent.[2d–f] However, all these methods allow only a single partially enriched (*R*)- or (*S*)-enantiomer to be obtained with the use of one chiral auxiliary compound.

Earlier we reported on the synthesis of (*S*)-2-*N*-(*N'*-benzylprolyl)aminobenzaldehyde [(*S*)-bba], a reusable reagent for the retroracemization of α-amino acids and the asymmetric synthesis of threonine.[3] Here we describe the use of (*S*)-bba for the preparation of optically pure (*S*)- and (*R*)-α-methyl-α-amino acids *via* alkyl halide alkylation of the nickel(II) complex of (*S*)-bba Schiff base with (*R,S*)-Ala as shown in Scheme 1.

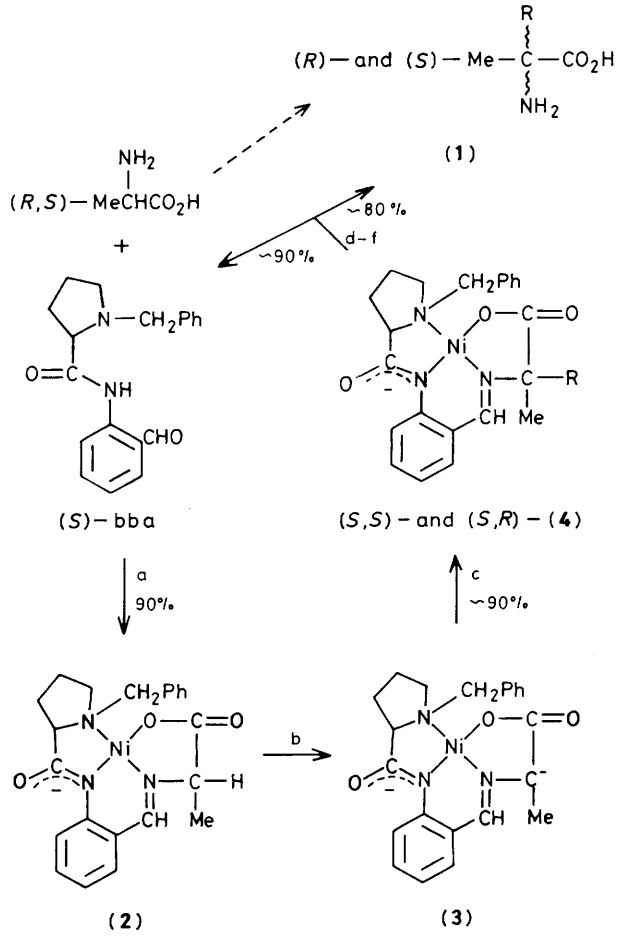
The chiral complex (**2**), obtained by the reaction of (*R,S*)-Ala, NiX_2, and (*S*)-bba as a mixture of diastereoisomers, was deprotonated either by use of BuLi or under phase-transfer conditions (P.T.C.)[4] to give (**3**), which was alkylated with the appropriate alkyl halide. The resulting mixture of alkylated diastereoisomers (**4**) [some excess of

† (*S*)-2-{*o*-[(*N*-Benzylprolyl)amino]phenyl}methyleneiminopropionato(2−)-*N,N',N''*-nickel(II).

Table 1. Preparation of optically pure α-methyl-α-amino acids by alkylation of (*R,S*)-Ala in its Schiff base nickel(II) complex with (*S*)-bba.

	% Yield of (**4**)[a]					
	BuLi		P.T.C.[b]		% Yield of amino	
RX	(*S,S*)	(*S,R*)	(*S,S*)	(*S,R*)	acid	$[\alpha]_D^{25}$ [c]
MeI	92				77	—
$PhCH_2Br$	51	40	63	31	45	−4.4° (*S*) [d]
					30	+4.2° (*R*)
$CH_2{=}CHCH_2Br$	56	33	62	22	49	−14.4° (*S*)
					27	+14.2° (*R*)

[a] Based on initial (**2**). [b] TBA was removed by chromatography on silica or Dowex 50 (Na^+ form) with H_2O–MeOH as eluant. [c] Hydrochloride in D_2O, c = 1.3. [d] Lit.[5] $[\alpha]_D^{20}$ −4.7° (c = 1.025, 1 M HCl).



Scheme 1. *Reagents and conditions*: a, MeOH, $Ni(NO_3)_2$, MeONa, 40 °C, 10 h; b, BuLi, THF, −78 °C, or (P.T.C.) 10% aq. NaOH, CH_2Cl_2, TBA, 20 °C; c, RX at −78 to 20 °C or (P.T.C.) 20 °C; d, chromatography on SiO_2, with $CHCl_3$–acetone as eluant; e, 10% HCl, 100 °C; f, aq. NH_3, $CHCl_3$ extraction, chromatography on Dowex-50.

(*S,S*)-(**4**) over (*S,R*)-(**4**) (see Table 1)] was easily separated on SiO_2 giving diastereoisomerically pure (*S,S*)-(**4**) or (*S,R*)-(**4**) (according to 200 MHz ^1H n.m.r. data). The complex (**4**) was readily hydrolysed with 0.6 M HCl[3c] giving 90% recovery of (*S*)-bba and (*S*)- or (*R*)-α-alkyl-α-amino acids (see Table 1).

The alkylation conditions were as follows (i) BuLi (1 equiv.; 1 M solution in hexane) was added to (**2**) (1 equiv.) in tetrahydrofuran (THF) at −78 °C under argon. After 10 min a THF solution of the alkyl halide (1.5 equiv.) was added, and the temperature was allowed to rise to 20 °C; stirring was continued for another hour. Quenching with dilute HCl and extraction with $CHCl_3$ gave the diastereoisomeric (*S,R*)- and (*S,S*)-(**4**) (90% overall yield). On column chromatography on SiO_2 (*S,S*)-(**4**) was eluted first, followed by (*S,R*)-(**4**).

(ii) P.T.C. experiments were conducted under normal ion-pair extraction conditions[4] which uses a full equivalent of the phase-transfer reagent and dilute aqueous sodium hydroxide. A solution of (**2**) (1 equiv.) and the alkyl halide RX (1.5 equiv.) in CH_2Cl_2 was stirred under argon with 10% aqueous NaOH to which 1 equiv. of tetrabutylammonium iodide (TBA) had been added. The stirring was continued for 5—7 h at 20 °C until (**2**) had been consumed (as monitored by t.l.c.). The mixture was treated as just described, and the overall yield of the diastereoisomers was 90%. (*S,S*)-(**4**) and (*S,R*)-(**4**) had different c.d. spectra, which allowed the absolute configuration of the α-methyl-α-amino acid fragment to be assigned unequivocally.

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