Synthesis of a Chiral Nickel(II) Complex of an Electrophilic Glycinate, and its Use for Asymmetric Preparation of α-Amino Acids

Yuri N. Belokon',* Aleksander N. Popkov, Nina I. Chernoglazova, Marina B. Saporovskaya, Vladimir I. Bakhmutov, and Vasili M. Belikov

A. N. Nesmeyanov Institute of Organoelement Compounds, U.S.S.R. Academy of Sciences, Moscow, U.S.S.R.

A chiral Ni^{II} complex of a Schiff's base derived from (*S*)-*o*-[(benzylpropyl)amino]benzophenone and α-bromoglycine has been obtained and its stereoselective reaction with nucleophiles studied; the synthesis of aspartic acid with 80% optical purity is described.

Chiral derivatives of glycine are often used for asymmetric synthesis of α-amino acids.[1,2] The most popular synthetic route consists of the conversion of a suitable derivative into a carbanion, followed by reaction with an electrophile. The function of the chiral surroundings of the glycine fragment is to stabilize the incipient carbanion and create a stereochemical bias for electrophilic attack.[1]

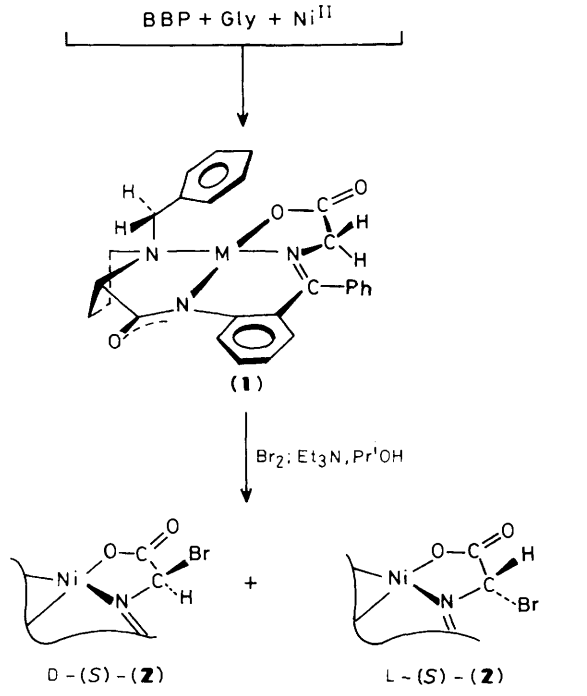
Electrophilic derivatives of glycine have received less attention.[2,3] Until recently,[3] chiral synthons of electrophilic glycine were unknown.

Several recent developments in our laboratory have made it possible to elaborate a general method for preparing optically pure α-amino acids, starting from a Ni^{II} complex (**1**) of a Schiff's base derived from (*S*)-*o*-[(benzylprolyl)amino]benzophenone (BBP) and glycine.[4] The approach is based on converting the glycine fragment of (**1**) into a carbanion. It seemed attractive to attempt to broaden the scope of application of the complex to include electrophilic derivatives of glycine in the synthetic sequence.

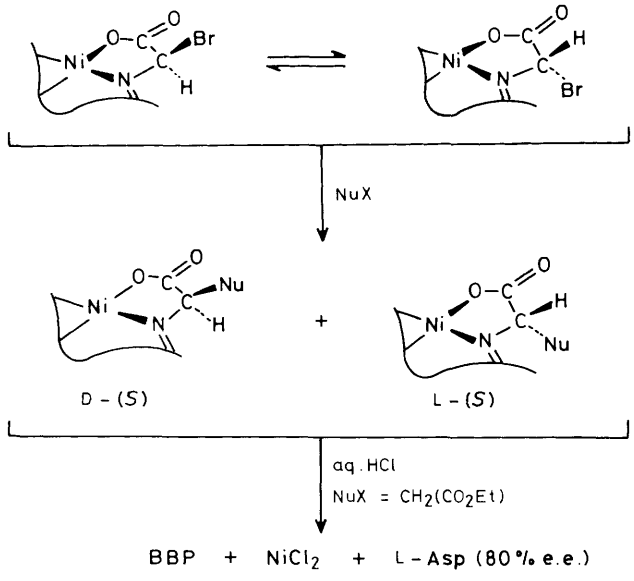
We describe here the synthesis of a Ni^{II} complex (**2**) of a Schiff's base derived from BBP and α-bromoglycine, and preliminary studies of its reactivity.

The complex (**2**) was synthesized by base-catalysed bromination of (**1**) (Scheme 1). To a mixture of (**1**) (3.0 g, 6.0 mmol) and Et_3N (8.2 ml, 60 mmol) in Pr^i OH (100 ml) was added a solution of Br_2 (1.3 ml, 60 mmol) in Pr^iOH (50 ml) with stirring at +5 °C. The mixture was then allowed to warm to ambient temperature, and the reaction was continued until almost all the initial (**1**) was consumed (t.l.c.). The mixture was evaporated, and the residue was partitioned between H_2O and $CHCl_3$; the organic layer was washed with H_2O and evaporated. Flash chromatography (SiO_2; $CHCl_3/Me_2CO$, 5 : 1) of the residue gave a mixture (2.86 g, 4.94 mmol, 82%) of diastereoisomers of (**2**) [L-(*S*):D-(*S*) 2 : 1]. The mixture† was

† The structures of the diastereoisomers were supported by elemental analysis, ^1H n.m.r., electronic spectra, and o.r.d. curves. The separation of isomers could be achieved chromatographically on SiO_2.



Scheme 1



Scheme 2

further purified on Sephadex LH-20 (benzene/EtOH) to obtain analytically pure samples.

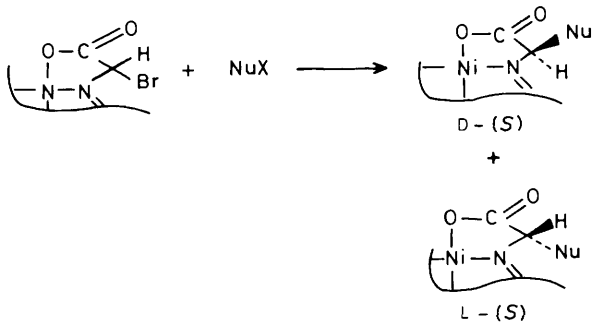
Scheme 2 and Table 1 summarize the results of the reactions of (2) with various nucleophiles. Phenolate and methoxide anions, dimethylamine, and malonic ester in the presence of potassium t-butoxide substitute the bromine anion in (2) to give L-(*S*)-diastereoisomeric complexes [diastereoisomeric excess (d.e.) 80—98%] in high chemical yields.

Only the products of side reactions [mainly reduction of (2) to (1)] were detected when (2) was treated with benzylmagnesium chloride or butyl-lithium. A low-yield substitution reaction was detected when an organozinc compound was used.

Table 1. Reactions of the complex (2) with nucleophiles.

Nucleophile	Conditions	L-(*S*) : D-(*S*)	Chemical yield (%)[c]
MeONa	MeOH, 25 °C	98 : 2[a,d]	>90
PhONa	MeCN	91 : 9[a,d]	60
Me_2NH	MeCN, 25 °C	99 : 1[a,e] (92 : 8)[a,d]	>90
$CH_2(CO_2Et)_2$	MeCN, Bu^{t}OK, 25 °C	90 : 10[a,b,d]	>90
BuLi	THF, −70 °C		
BuZnCl	THF, −70 °C	80 : 20[b,e]	12.7

[a] ^{1}H N.m.r. method; ratio of diastereoisomeric complexes. [b] Enantiomeric purity of α-amino acid according to g.l.c. data[6]. [c] Yield of diastereoisomeric complexes after chromatography on SiO_2. [d] Equilibrium ratio of isomers. [e] Kinetically controlled ratio of isomers.



Diastereoisomerically pure complexes in which bromine was replaced by α-dimethylamino-, α-phenoxy- and α-methoxy-glycine were obtained by flash chromatography (SiO_2; $CHCl_3/Me_2CO$, 5 : 1) of the corresponding diastereoisomeric mixtures.

Absolute configurations of the amino acid moieties were assigned according to the shapes of the o.r.d. curves and (or) the c.d. spectra of the complexes.[4,5]

The origin of the diastereoselective effects in the reactions of this type of complex was discussed earlier.[4a,b] These effects can be either thermodynamic[4a] or kinetic in nature.[4b] The following procedure for the synthesis of L-aspartic acid from (2) and malonic ester is an illustration of the former.

To a stirred solution of (2) (0.106 g, 0.184 mmol) (2 : 1 mixture of isomers) in MeCN (5 ml) at −50 °C under argon was added malonic ester (0.1 ml, 0.6 mmol), followed by potassium t-butoxide (0.056 g, 0.5 mmol). The temperature of the mixture was allowed to rise to *ca* 25 °C, and after the starting material (2) had been consumed (t.l.c.) the mixture was quenched with aqueous acetic acid and evaporated. The residue was purified on SiO_2; the diastereoisomeric mixture of complexes was decomposed with aq. HCl and BBP was recovered in 92% yield, as described earlier.[4] Concentrated hydrochloric acid was then added to the aqueous solution, and the mixture was boiled for 1 h. L-Aspartic acid [enantiomeric excess (e.e.) 80%] was recovered by the usual ion-exchange technique in 50% yield.

The enantiomeric purity of the amino acid closely reflects the thermodynamic stereoselective effects in the initial mixture of alkylated complexes because, under the reaction conditions, equilibration of the complexes is taking place, and the thermodynamically more stable L(*S*)-isomers are always formed under such conditions.[5]

The reaction of (2) with Me_2NH provides an example of a kinetically controlled stereochemical outcome of the substitution reaction.

The reaction was conducted in CD_3CN at 25 °C and monitored by ^{1}H n.m.r.; the concentration of (2) [D-(*S*): L-(*S*)

1.3:1] was 0.07 M and that of Me_2NH 0.28 M. Only epimerization of the initial mixture of the isomers of (**2**) was observed during the first 60 min [final ratio L-(*S*) : D-(*S*) 2 : 1]. After the induction period a slow accumulation of the substitution product was detected; the reaction was complete within 24 h, and the almost pure L-(*S*)-isomer of the α-dimethylaminoglycine complex was formed (d.e. > 90%). Epimerization of the final product proceeds more slowly (period for half reaction > 90 h). Thus, the stereochemical outcome of the substitution reaction is kinetically controlled. Unexpectedly, reaction in a 25% solution of Me_2NH in MeCN gave 56% of the L-(*S*)- and 44% of the D-(*S*)-isomer, although the equilibrium ratio of the isomers was 92% L-(*S*) and 8% D-(*S*). Many nucleophiles are potentially capable of substituting bromine in (**2**), and work in this direction is under way.

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