# Stereoselective Radical Addition of Carbon-centred Radicals to the Dehydroalanine Moiety of the Chiral Nickel(II) Complex of the Schiff's Base Derived from (*S*)-2-[*N*-(*N'*-Benzylprolyl)amino]benzophenone and Dehydroalanine

**Rashid G. Gasanov, Lubov V. Il'inskaya, Michail A. Misharin, Victor I. Maleev, Nicolai I. Raevski, Nicolai S. Ikonnikov, Svetlana A. Orlova, Nadezhda A. Kuzmina and Yuri N. Belokon'** *

*Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 117813, Moscow, Vavilov 28, Russia*

A new approach to the asymmetric synthesis of β-substituted α-aminopropanoic acids by 2,2'-azoisobutyronitrile (AIBN) and $Bu_3SnH$-initiated radical addition of EtI, $Pr^iBr$, $Bu^tBr$, and $PhCH_2Br$ to the dehydroalanine moiety of the $Ni^{II}$ complex **1** of a Schiff's base derived from (*S*)-*o*-[*N*-(*N'*-benzylprolyl)amino]benzophenone (BPB) and dehydroalanine is described. The radical addition produced a mixture of diastereoisomeric complexes **4a–d** with a 40–90% excess of (*S,S*)-diastereoisomers over the (*S,R*)-ones, giving the reaction products in almost quantitative yields. The diastereoselectivity of the reaction depended on the size of the entering radicals, the most effective asymmetric induction being achieved for the $Bu^t$ radical addition. Enantiomerically pure '(*S*)-2-amino-3-(*tert*-butyl)propanoic acid' [(*S*)-γ-methylleucine] and the chiral auxiliary BPB were recovered from compound **4d** after its decomposition with HCl. The reactivities of the carbon-centred radicals towards the carbon–carbon double bond in the amino acid moiety of the complex **1** was quantitatively established by using ESR spectroscopy in the spin-trap technique.

It is widely known that organic reactions, proceeding *via* the key intermediate formation of carbon-centred free radicals, may serve as useful methods for C–C bond formation in organic synthesis.[1] Recently, it was realized that radical reactions might be carried out diastereoselectively[2] and there were cases when the stereoselectivities of the radical reaction and the ionic reaction, leading to the same final compound from similar starting substrates, either did not differ[3] or were giving opposite stereochemical results.[4] This was rationalized by postulating stereodetermining attack of the reagents on the diastereotopic faces of the intermediate ionic and radical particles controlled by either similar or different initial distribution of the rotamers of the intermediates.[3,4] The rotamer distribution, in turn, was suggested to be controlled, apart from the steric non-bonding interactions, either by chelation (ionic enolate reactions) or by intermolecular dipole–dipole repulsion (radical reactions).[3,4] Stereoelectronic effects (partial $sp^3$ character of the intermediate radicals) were invoked as a possible source of the unusual 1,2-asymmetric induction in reactions of nonconjugated acyclic radicals.[2b]

We believed that use of rigid chiral substrates in which all the groups were fixed in space might allow us to discern subtle differences in the stereochemical behaviour of ionic and radical particles in the reactions of C–C bond formation.

Earlier we showed that the asymmetric synthesis of β-substituted α-amino acids might be carried out by employing 1,4-addition of nucleophiles to the dehydroalanine moiety of the chiral $Ni^{II}$ complex **1** of a Schiff's base derived from (*S*)-*o*-[*N*-(*N'*-benzylprolyl)amino]benzophenone (BPB)† and dehydroalanine.[5] Two types of diastereoselectivity were observed in the addition. The first had its origin in the relative rates of the *re*- and *si*-face protonation of the intermediate α-carbanion (kinetic diastereoselectivity) and the other was thermodynamically controlled, as soon as the equilibrium between the resulting diastereoisomers facilitated by the presence of bases in the solution was finally established (Scheme 1).[5] We believed that, in analogy with other types of chiral dehydroalanine substrates,[6] the radical addition of carbon-centred radicals to substrate **1** might also be successfully carried out as outlined in Scheme 1, and kinetic diastereoselectivities of radical and ionic addition to the rigid substrate **1** might be compared and a new route to enantiomerically pure non-proteinogenic α-amino acids opened.

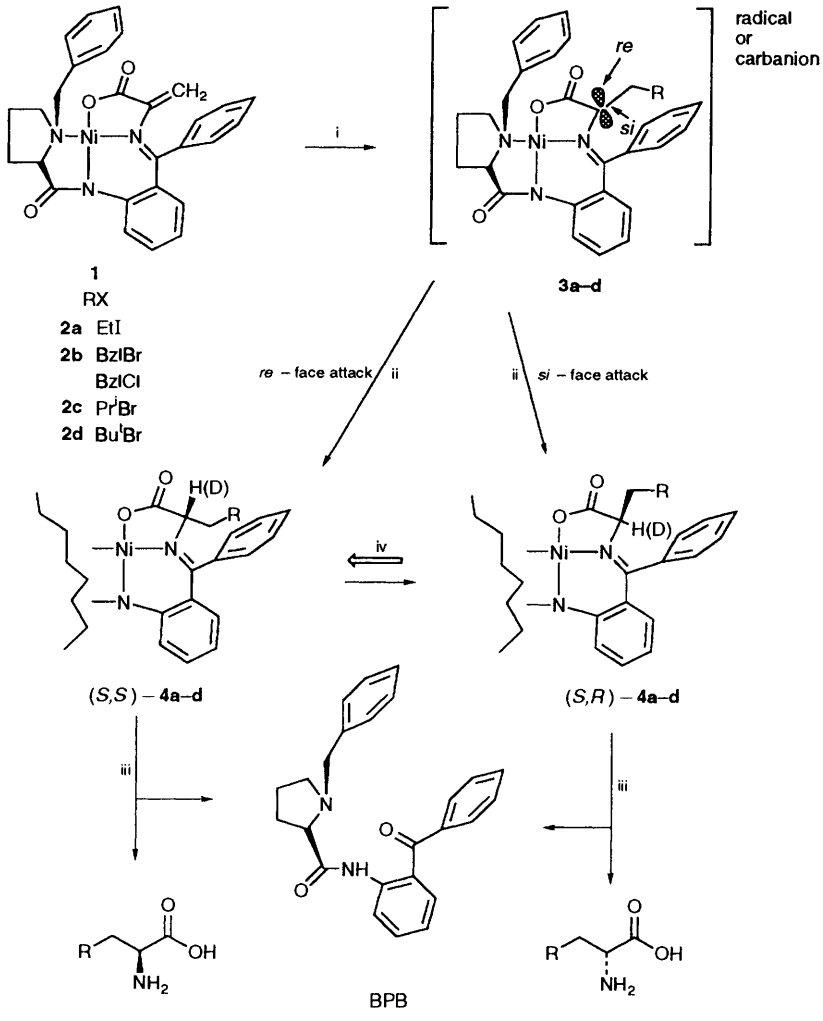
† Available from Merck (cat. no. 814473) and Janssen (cat. no. 2691950).

## Results and Discussion

Alkyl halides EtI **2a**, BzlBr or BzlCl **2b**, $Pr^iBr$ **2c** and $Bu^tBr$ **2d** were chosen as suitable starting materials for the generation of the corresponding free radicals, Et', $^{\cdot}Pr^i$, $^{\cdot}Bu^t$, and $PhCH_2^{\cdot}$ (see Scheme 1). According to the mechanism of free-radical addition reactions,[1] radicals R', generated in the initial step, add to the C=C bond of the dehydroalanine moiety of substrate **1** to give intermediate α-radicals **3a–d**. Then follows the stereodetermining attack by $HSnBu_3$ on the *si*- and *re*-side of the intermediate adduct-radicals **3a–d** (see Scheme 1). The set of the initial carbon-centred radicals generated from alkyl halides **2a–d** provides a sufficiently diverse series to allow definite conclusions to be made as to the importance of the newly formed side-chain size and its conformation in adduct-radicals **3a–d** for the final stereodetermining step of a hydrogen-atom transfer to the intermediate α-radicals (see Scheme 1) in the chain-transfer step, leading to the formation of the complexes **4a–d**.

In order to establish the reactivities of the above mentioned free radicals R towards the C=C bond of the dehydroalanine moiety in the complex **1** we have determined the corresponding rate constants using the spin-trapping method.[7]

*Kinetic Data.*—For the ESR experiments the radicals Et' and $PhCH_2^{\cdot}$ were generated by halogen abstraction from the corresponding alkyl halides by the radical $^{\cdot}Re(CO)_5$, formed photochemically from $Re_2(CO)_{10}$ (Scheme 2).[8] The Et' and $PhCH_2^{\cdot}$ radicals and adduct-radicals **3a** and **3b** were identified




**Scheme 1** *Reagents:* i, RX (**2**), $Bu_3SnH$, AIBN or BzlMgX; ii, $Bu_3SnH$, or water ($D_2O$); iii, aq. HCl; iv, MeONa in MeOH

as their spin-adducts **6a**, **6b** and **7a**, **7b**, correspondingly formed as the result of the interaction of the radicals and the adduct-radicals with tri(*tert*-butyl)nitrosobenzene **5**. The experimental ESR spectra of the spin-adducts **6a**, **6b**, **7a** and **7b** have been simulated with the hyperfine coupling constants $a_N$ 13.42 G, $a_{b\text{-}H}$ 18.00 G, $a_{m\text{-}H}$ 0.8 G for **6a**; $a_N$ 13.62 G, $a_N$ 14.75 G, $a_{m\text{-}H}$ 0.83 G for **6b**; and $a_N$ 10.00 G, $a_{m\text{-}H}$ 2.06 G for **7a** and **7b**. The splitting constants are similar to the same constants for the corresponding Et$^\bullet$ and $PhCH_2^\bullet$ radicals[9] in the case of adducts **6a** and **6b**, and for the tertiary alkyl radicals[9] in the case of adducts **7a** and **7b**. Identification of the signals from adducts **6a** and **7a** or **6b** and **7b** simultaneously in the ESR spectra of their admixture allowed us to determine the rate constants $k_1$ for the addition of the radicals Et$^\bullet$ and $PhCH_2^\bullet$ to the C=C bond of the complex **1**, according to eqn. (1).[7]

$$\frac{d([\mathbf{6a}] \text{ or } [\mathbf{6b}])/dt}{d([\mathbf{7a}] \text{ or } [\mathbf{7b}])/dt} = \frac{k_2[\mathbf{5}]_0}{k_1[\mathbf{1}]_0} \qquad (1)$$

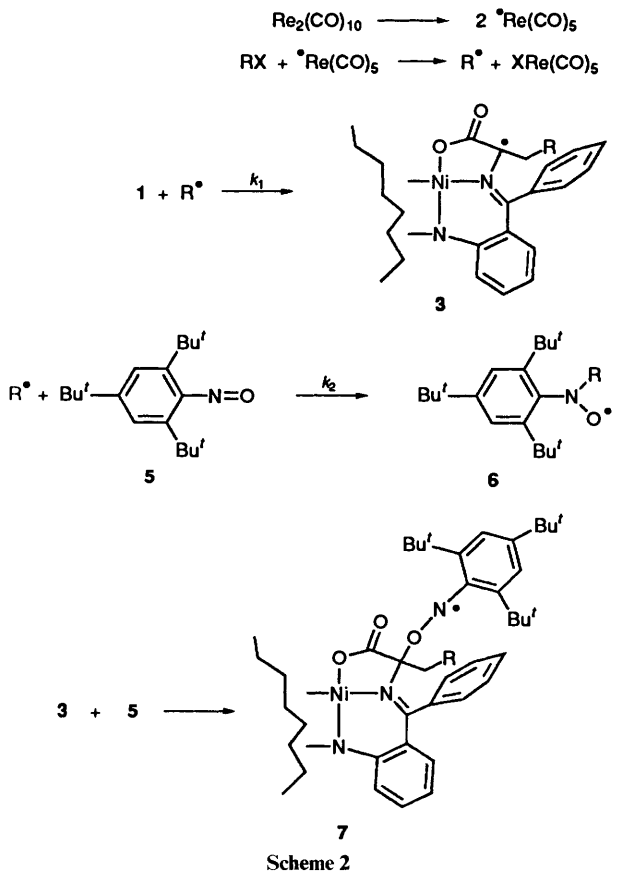
The values of the second-order rate constant $k_1$ were calculated on the basis of the simulated ESR spectral data and known[9] values of $k_2$ ($2 \times 10^5$ dm$^3$ mol$^{-1}$ s$^{-1}$ for Et$^\bullet$, and $1 \times 10^4$ dm$^3$ mol$^{-1}$ s$^{-1}$ for $PhCH_2^\bullet$). The addition rate constant $k_1$ calculated in this manner from eqn. (1) was $1.97 \times 10^5$ dm$^3$ mol$^{-1}$ s$^{-1}$ for Et$^\bullet$ and $1 \times 10^3$ dm$^3$ mol$^{-1}$ s$^{-1}$ for $PhCH_2^\bullet$. It should be noted that the values of $k_1$ have similar magnitudes to the rate constants of the addition of the same radicals to methyl acrylate ($2.5 \times 10^5$ dm$^3$ mol$^{-1}$ s$^{-1}$ for Et$^\bullet$ and $5.5 \times 10^3$ dm$^3$ mol$^{-1}$ s$^{-1}$ for $PhCH_2^\bullet$) and to acryloylpyrrolidine ($9.9 \times 10^5$ dm$^3$ mol$^{-1}$ s$^{-1}$ for Et$^\bullet$, and $3 \times 10^3$ dm$^3$ mol$^{-1}$ s$^{-1}$ for $PhCH_2^\bullet$).[10]

In addition, on the basis of the kinetic data[11] we suggest that the approximate value of $k_1$ for the *tert*-butyl radical addition to substrate **1** may be estimated as $10^5$ dm$^3$ mol$^{-1}$ s$^{-1}$.

The salient feature of the kinetic results was that the $Ni^{II}$ ion complexation had the same effect on the carboxyl group as did its esterification, which was revealed by the similarity of the kinetic parameters of the radical addition to the C=C bond of the dehydroalanine moiety of complex **1** and that of methyl acrylate.

Summing up the kinetic results obtained for the radicals Et$^\bullet$, $^\bullet$Bu$^t$, and $PhCH_2^\bullet$, and reactivity data[12a] for the radical $^\bullet SnBu_3$ towards both the C=C bond in unsaturated compounds and the C=O bond in carbonyl groups, and the rate data for hydrogen transfer from $HSnBu_3$ to various free radicals,[12b,c] suitable experimental conditions for the synthesis of the complexes **4a–d** (see Scheme 1) were chosen.

*Synthetic Procedure.*—The mixture of substrate **1**, an alkyl halide, $HSnBu_3$, and AIBN in benzene solution was kept at 80 °C for 4 h in a sealed ampoule under Ar (method A) or in an open vessel (method B). The complexes **4a–d** were obtained as an assortment of diastereoisomers of (*S*,*S*)- and (*S*,*R*)-configuration in good chemical yields (77–94%) after their purification on $SiO_2$. We were unable to separate the diastereoisomers chromatographically.




Scheme 2

The ratios of the former isomers were estimated by integrating the areas of the H resonances in the $^1$H NMR spectra of the mixtures of the corresponding diastereoisomeric (*S*,*R*)- and (*S*,*S*)-complexes, usually employing the resonances of the diastereotopic ($NCH_2$) protons or some resonances of the protons of the phenyl groups. For complex **4d** the signals for Bu$^t$ (0.65 and 0.73 ppm) might be used. The proportions of diastereoisomers found in the reaction mixture were sometimes corroborated by enantiomeric GLC analysis of the amino acids recovered from the complexes after their decomposition. The use of both methods resulted in similar ratios of the isomers.

*The absolute configuration of the predominant diastereoisomer.* This was established by comparing either the $^1$H NMR spectra of the diastereoisomeric mixtures and that of the pure (*S*,*S*)-diastereoisomer (obtained as usual from the corresponding amino acid and BPB under the thermodynamic control conditions, followed by crystallization)[13] or by analysing their optical rotatory dispersion (ORD) curves. Chiral GLC analysis data of the amino acids recovered from the complexes, according to Scheme 1, might also be used for the purpose.

The synthetic results are summarized in Table 1.

*The ratio of the diastereoisomers.* This evidently reflects the kinetic preference of the hydrogen-atom transfer from $HSnBu_3$ to the intermediate adduct-radicals. Had equilibration of the isomers taken place in the reaction mixture, the proportion of the (*S*,*S*)-isomers would have been much greater (at least 90%),[5,13] as the results of equilibration experiments with some of the complexes indicate (see Table 1, runs 1 and 2). As can be seen, it was always the *re*-attack of $Bu_3SnH$ on the intermediate radicals **3a–d**, leading to the (*S*,*S*)-diastereoisomers, which predominated over the *si*-face attack, giving the (*S*,*R*)-diastereoisomer. The relative rates of the *re*- and *si*-attack of the hydrogen-atom transfer, occurring at the second stage of the radical addition (see Scheme 1), depended on the size of the

**Table 1** Radical addition of alkyl halides (RX) **2a–d** to complex **1**

| Run | RX | Method[a] | Product | Yield (%) | d.e. (*S*,*S*)[b] (%) |
|---|---|---|---|---|---|
| 1 | EtI | A | **4a** | 90 | 54 (92)[c] |
| 2 | $PhCH_2Cl$ | B | **4b** | 94 | 40 (98)[c] |
| 3 | $PhCH_2Br$ | A | **4b** | 77 | 40 |
| 4 | Pr$^i$Br | A | **4c** | 90 | 60 |
| 5 | Bu$^t$Br | A | **4d** | 80 | 90 |
| 6 | Bu$^t$Br | B | **4d** | 90 | 92 |

[a] Method A: the reactions were carried out in sealed glass tubes. Method B: the reaction was carried out in an open vessel. [b] The diastereoselectivities of the reaction were determined by $^1$H NMR spectroscopy corroborated *via* GLC analysis of the amino acids recovered from the complexes. [c] Diastereoselectivity after MeONa-catalysed epimerization of the mixture of the diastereoisomers **4**.

side-chain of the intermediate α-radicals. For example, in the case of •Bu$^t$ radical addition to substrate **1** the best diastereoisomeric excess (d.e.) (up to 92%) of all the reactions was obtained (Table 1, run 5). At the same time the ethyl and benzyl radical additions to substrate **1** gave only 54 and 40% d.e., respectively, of the product (Table 1, runs 1, 2 and 3). The d.e. ratio may be improved by epimerization of the diastereoisomeric mixture with MeONa in MeOH at ambient temperature (Table 1, run 1).

*The stereochemical model of the intermediate radicals.* This, as revealed by molecular mechanics calculations, seems to provide some rationale for the observed stereochemistry of the hydrogen-atom transfer. Fig. 1 shows the calculated structure of adduct-radical **3d**. The chiral proline moiety causes chiral distortion of the system of the interconnected chelate rings. The metallocycle O(1)C(1)C(2)N(1)Ni has a chiral conformation and the bond C(2)–C(22) is tilted downwards. The chiral puckering of the metallocycle formed by C(3)C(4)C(9)-N(2)NiN(1), in turn, causes the phenyl substituent at the C=N bond to turn clockwise. The torsional angle N(1)C(3)C(27)C(32) is 60° and the phenyl substituent shields the *re*-face of the radical centre at the α-atom of the compound. The same type of shielding in the case of a carbanion centre was responsible for the predominant *si*-attack of electrophiles on the alanine moiety in the corresponding Schiff's base complexes of $Ni^{II}$.[13] On the other hand in the case of amino acids with larger side-chains the *si*-side of the radical (or carbanion) is effectively screened by the bulky side-substituent of the amino acid moiety. The chain may adopt several conformations as a result of the C(22)–C(2) rotation but the conformation depicted in Fig. 1 was found to be at least 3 kcal per mole* more favourable than the nearest one in order of its energy. Evidently, the conformation avoids unfavourable interaction between the side-chain and the phenyl substituent at the C=N bond. On the other hand, it is energetically 'cheap' to move the phenyl substituent in an anticlockwise manner to open the *re*-side of the radical to the hydrogen-atom attack. Thus, a 10° rotation would require less than 3 kcal energy. As a result the predominant product of the reaction of Bu$^t$Br with substrate **1** was found to be (*S*,*S*)-**4d**, the product of the *re*-attack of $Bu_3SnH$ on the intermediate α-radical. As the size of the alkyl halide became smaller, the difference in the energies of the transition states of the *si*- and *re*-attack on the intermediate radical **3** decreased and the d.e. of the reactions fell in the sequence Pr$^i$Br > EtI > BzlBr.

The diastereoselectivity of deuteriation experiments, conducted with the carbanion derived from (*S*,*S*)-**4a** with BuLi in tetrahydrofuran (THF), followed by quenching with DCl in $D_2O$, indicated that the d.e. of the heterolytic deuteriation

* 1 cal = 4.184 J.

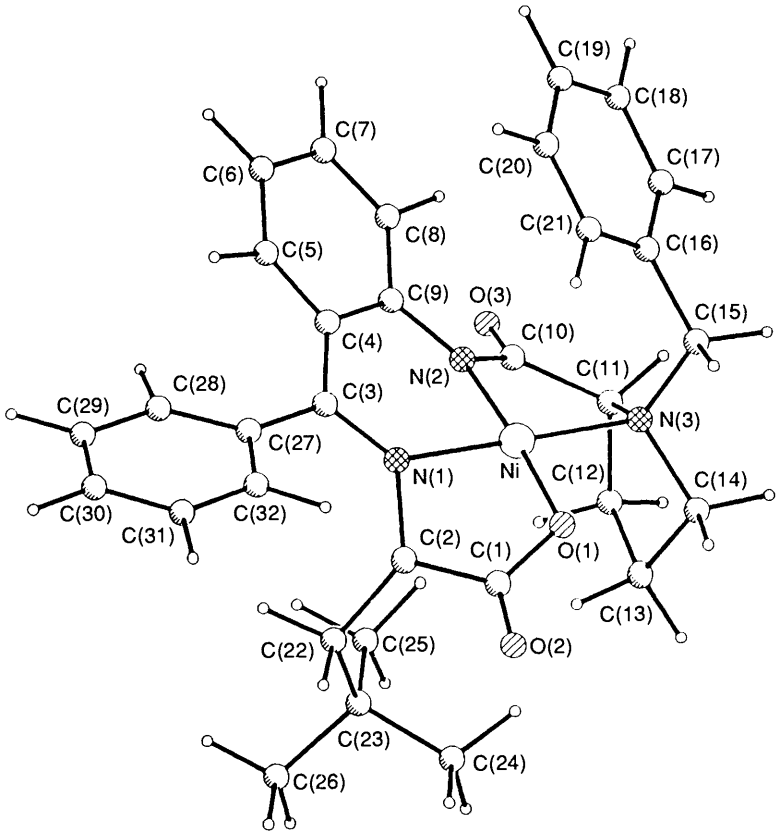



**Fig. 1** The computer-generated (MMX-calculated) structure of the $Ni^{II}$ complex of the carbon α-centred radical of 2-amino-4,4-dimethylpentanoic acid

was similar to the d.e. of the homolytic hydrogen-atom transfer, leading to product **4a**. Similar diastereoselectivities were found in the BzlMgCl addition to substrate **1**.[5] For example, under kinetically controlled conditions the addition gave 50% d.e. in favour of (*S*,*S*)-**4b** whereas the radical addition gave 40% d.e. (see Table 1, runs 2 and 3). Evidently, identical steric factors were responsible for the diastereoselectivities of both homolytic and heterolytic reactions and there are no grounds to invoke any type of specific stereoelectronic effects such as $sp^3$ hybridization of the intermediate radical to account for the observed stereoselectivity of the reactions.

*Conclusions.*—The method elaborated in this work is suitable for the production of new types of α-amino acids with bulky aliphatic side-chains. Although the kinetic stereoselectivity of the addition of smaller alkyl halides to substrate **1** was mostly insignificant, thermodynamic equilibration of the final diastereoisomers with MeONa may bring the quotient of the (*S*,*S*)/(*S*,*R*)-isomers up to 99/1 and thus a viable asymmetric synthesis of a range of α-amino acids might be achieved.

## Experimental

*General.*—Reagents and solvents were purified in the usual way.

*Molecular Mechanics Calculations.*—The calculations were performed as previously described.[14]

Spectra were recorded with the following instruments: ESR, Radiopan SE/X-2547; $^1H$ NMR, Bruker BM-500 (500 MHz) and Bruker WP-200 (200 MHz); *J* values are in Hz; ORD, JASCO ORD/UV-5 (specific rotations, in units of $10^{-1}$ deg $cm^2$ $g^{-1}$, measured with a Perkin-Elmer 241 polarimeter).

Enantiomeric analyses of the α-amino acids were carried out by GLC. The amino acids were analysed as the *N*-trifluoroacetyl derivatives of their isopropyl esters by using a capillary glass column (40 m × 0.23 mm) coated with chiral diamide phase of a Chirasil-Val type (the phase was synthesized and columns produced in our laboratory). Chromatography conditions: column temperature 140 °C, He $1.2 \times 10^5$ Pa.

*Rate Measurements.*—ESR experiments were carried out in the glass-soldered tubes in the spectometer resonator. First, the reaction mixtures put into the tubes were deoxygenated by the freeze–pump–thaw (FPT) method. In each tube the solution (0.2 $cm^3$), containing $Re_2(CO)_{10}$ ($4.2 \times 10^{-3}$ g, $6.5 \times 10^{-6}$ mol), complex **1** ($1.1 \times 10^{-2}$ g, $2.1 \times 10^{-5}$ mol), EtI (0.18 g, $1.18 \times 10^{-3}$ mol) or $PhCH_2Br$ (0.13 g, $7.5 \times 10^{-4}$ mol), and spin trap **5** ($2.6 \times 10^{-3}$ g, $1.0 \times 10^{-5}$ mol) in $CH_2Cl_2$ (0.9 $cm^3$) were mixed. The mixture was irradiated with UV light in the spectrometer resonator (λ 366 nm).

The initial complex **1** was synthesized as described in ref. 5.

*Epimerization of the Mixture of Diastereoisomers.*—A solution of MeONa in MeOH (0.1 mol $dm^{-3}$; 0.1 $cm^3$) was added to a solution of complex **4b** (0.1 g, $4.9 \times 10^{-4}$ mol) in MeOH ($3 \times 10^{-3}$ $dm^3$) under Ar. The mixture has been kept at 20 °C for 24 h, then was neutralized with aq. HCl; the complex was extracted by $CHCl_3$ and the organic layers were combined and evaporated. The resulting complex was obtained as almost pure (*S*,*S*)-diastereoisomer according to its $^1H$ NMR data.

*Deuterium Exchange.*—To a solution of complex **4a** (0.54 g, $1.0 \times 10^{-3}$ mol) in THF (10 $cm^3$) in a glass tube, deoxygenated by FPT and cooled to −70 °C, was added a solution of 0.62 mol $dm^{-3}$ BuLi (4.03 $cm^3$, $2.5 \times 10^{-3}$ mol) in hexane under Ar. The mixture was kept for 15 min at that temperature, allowed to warm up, and then was quenched with DCl (0.35 $cm^3$,

$3.5 \times 10^{-3}$ mol) in $D_2O$ (3 $cm^3$). Water (10 $cm^3$) was added to the mixture and then the resulting complex was extracted by $CHCl_3$, and the organic layers were combined, dried with $MgSO_4$ and evaporated. The product was purified on a silica gel column [45 × 5 cm; $CHCl_3$–acetone (7:1)].

*General Procedure for Syntheses of the* $Ni^{II}$ *Complexes* **4a–d** (*Method A*).—A solution of the complex **1** (0.23 g, $4.5 \times 10^{-4}$ mol), the corresponding alkyl halide ($6.0 \times 10^{-3}$ mol), $HSnBu_3$ (0.43 g, $1.46 \times 10^{-3}$ mol) and AIBN (0.04 g, $2.6 \times 10^{-4}$ mol) in benzene (5 $cm^3$) was placed in a glass tube. The mixture was deoxygenated by FVD and afterwards the tube was sealed under Ar. The tube was kept in a thermostat at 80 °C for 4 h. According to TLC [$SiO_2$; $CHCl_3$–acetone (7:1)], in all cases, $PhCH_2Br$ being the only exception, the final reaction mixture contained none of the initial complex **1**. The reaction mixture was evaporated, and purified on a silica gel column. The first fraction, in the order of its emergence from the chromatographic column (as a red band), was the corresponding addition product **4a–d** as a mixture of (*S,S*)- and (*S,R*)-diastereoisomers in the d.e.s presented in Table 1. The *complex* **4a** had (Found: C, 67.1; H, 5.8; N, 7.5. $C_{30}H_{31}N_3O_3Ni$ requires C, 66.69; H, 5.78; N, 7.78%); $\delta_H(CDCl_3)$ for (*S,S*)-isomer 8.15–6.50 (14 H, m, ArH), 4.38 and 3.52 (2 H, AB, *J* 12.50, $CH_2Ph$), 3.86 (1 H, m, amino acid α-H), 3.50 (1 H, m, Pro α-H), 3.48 and 3.45 (2 H, m, Pro δ-$H_2$), 2.9–1.0 (4 H, m, Pro β-, γ-$H_2$) and 0.8 (3 H, t, Me); and for the (*S,R*)-isomer 8.60–6.60 (14 H, m, ArH), 4.42 and 3.54 (2 H, AB, *J* 12.50, $CH_2Ph$), 4.18 (1 H, m, Pro α-H), 3.78 (1 H, m, amino acid α-H), 3.62 and 3.48 (2 H, m, Pro δ-$H_2$), 2.9–1.0 (4 H, m, Pro β-, γ-$H_2$) and 0.95 (3 H, t, Me).

The *complex* **4c** had (Found: C, 67.3; H, 5.9; N, 7.4. $C_{31}H_{33}N_3O_3Ni$ requires C, 67.17; H, 6.00; N, 7.58%); $\delta_H(CDCl_3)$ for (*S,S*)-isomer 8.20–6.50 (14 H, m, ArH), 4.40 and 3.50 (2 H, AB, *J* 12.50, $CH_2Ph$), 3.85 (1 H, m, amino acid α-H), 3.48 (1 H, m, Pro α-H), 3.69 and 3.52 (2 H, m, Pro δ-$H_2$), 2.67–2.08 (4 H, m, Pro β-, γ-$H_2$), 1.4 (2 H, m, amino acid β-, γ-H) and 1.9 and 0.17 (6 H, d, Me); and for (*S,R*)-isomer $\delta_H(CDCl_3)$ signals were not identified with the exception of 1.95 and 0.13 (6 H, d, Me).

*Synthesis of the Complex* **4d** (*Method B*).—To a solution of complex **1** (3.2 g, $6.3 \times 10^{-3}$ mol) and Bu$^t$Br (11.7 g, $8.5 \times 10^{-2}$ mol) in benzene (70 $cm^3$) under Ar was added a solution of AIBN (0.61 g, $4.0 \times 10^{-3}$ mol) and $HSnBu_3$ (6.0 g, $2.4 \times 10^{-2}$ mol) in benzene (50 $cm^3$) at 80 °C during 0.5 h and then the mixture was boiled for 2 h. The reaction was monitored by TLC (see above). After the disappearance of the initial complex the reaction mixture was evaporated, and purified on a silica gel column [45 × 5 cm; $CHCl_3$–acetone (7:1)]. Complex **4d** was obtained as a mixture of two diastereoisomers in the d.e.s represented in Table 1. The *complex* **4d** had (Found: C, 67.3; H, 6.0; N, 7.2. $C_{32}H_{35}N_3O_3Ni$ requires C, 67.63; H, 6.21; N, 7.38%); $\delta_H(CDCl_3)$ for (*S,S*)-isomer 8.10–6.50 (14 H, m, ArH), 4.38 and 3.50 (2 H, AB, *J* 12.50, $CH_2Ph$), 3.85 (1 H, ABX, $J_{AX}$ 3.68, $J_{BX}$ 11.03, amino acid α-H), 3.48 (1 H, m, Pro α-H), 3.69 and 3.43 (2 H, m, Pro δ-$H_2$), 2.75 and 2.20 (2 H, m, Pro γ-$H_2$), 2.50 and 2.05 (2 H, m, Pro β-$H_2$), 2.95 and 1.47 (2 H, ABX, $J_{AB}$ 13.27, $J_{AX}$ 3.68, $J_{BX}$ 11.03, amino acid β-H) and 0.72 (9 H, s, $Me_3$); and for (*S,R*)-isomer $\delta_H(CDCl_3)$ 7.97–6.50 (14 H, m, ArH), 4.33 and 3.42 (2 H, AB, *J* 12.50, $CH_2Ph$), 2.75 and 2.25 (2 H, m, Pro γ-$H_2$), 2.60 and 2.03 (2 H, m, Pro β-$H_2$) and 0.64 (9 H, s, $Me_3$).

*Synthesis of the Complex* **4b** (*Method B*).—To a solution of the complex **1** (1.6 g, $3.2 \times 10^{-3}$ mol) and $PhCH_2Cl$ (33 g, 0.26 mol) in benzene (20 $cm^3$) under Ar was added a solution of AIBN (0.3 g, $2.0 \times 10^{-3}$ mol) and $HSnBu_3$ (3.0 g, $1.2 \times 10^{-2}$ mol) in benzene (20 $cm^3$) at 80 °C during 0.5 h and then the mixture was refluxed for 2 h. The reaction was monitored by TLC (conditions are mentioned above). After the disappearance of the initial complex the reaction mixture was evaporated, and purified on a silica gel column [45 × 5 cm; $CHCl_3$–acetone (7:1)]. The complex **4b** was obtained as a mixture of two diastereoisomers in the d.e.s represented in Table 1. The *complex* **4b** had (Found: C, 69.4; H, 5.6; N, 6.2. $C_{35}H_{33}N_3O_3Ni$ requires C, 69.79; H, 5.52; N, 6.98%); $\delta_H(CDCl_3)$ for (*S,S*)-isomer 8.05–6.50 (14 H, m, ArH), 4.48 and 3.59 (2 H, AB, *J* 12.50, $CH_2Ph$), 3.86 (1 H, m, amino acid α-H), 3.56 (1 H, m, Pro α-H), 3.60 and 3.42 (2 H, m, Pro δ-$H_2$), 2.73 and 2.17 (2 H, m, Pro γ-$H_2$), 2.38 and 2.05 (2 H, m, Pro β-$H_2$), 3.20 and 2.50 (2 H, m, amino acid β-$H_2$) and 2.27 and 1.88 (2 H, m, amino acid γ-$H_2$); the proton chemical shifts for the (*S,R*)-isomer were not identified with the exception of $\delta_H$ 8.50–6.65 (14 H, m, ArH), 4.49 and 3.59 (2 H, AB, *J* 12.50, $CH_2Ph$) and 3.77 (1 H, m, amino acid α-H).

*Procedure for the Recovery of BPB and the α-Amino Acids from the* $Ni^{II}$ *Complexes.*—This was carried out as described in refs. 5, 13 and 14. The recoveries of the amino acids and BPB were in the range 80–98%. The structures of the amino acids recovered from complexes **4a** and **4c** were established by TLC and GLC, by comparison of the samples with the standard commercially available amino aicds.

Recovery of (*S*)-2-amino-4,4-dimethylpentanoic acid from complex **4d** (2.0 g, $3.6 \times 10^{-3}$ mol) was made in the usual way; the *amino acid* (0.43 g, mol 77%) was recrystallized from EtOH–water (7:3); m.p. 235 °C (decomp.) (Found: C. 58.0; H, 10.3; N, 9.6. $C_7H_{15}NO_2$ requires C, 57.95; H, 10.34; N, 9.65%); $[\alpha]_D^{25}$ +14.2 (*c* 1.6 mol $dm^{-3}$ HCl). Enantiomeric purity of the amino acid was higher than 99% according to GLC; $\delta_H(D_2O$–DCl 1:1) 4.20 (1 H, ABX, $J_{BX}$ 4.92, $J_{AX}$ 6.89, α-H), 1.93 and 1.64 (2 H, ABX, $J_{AB}$ 14.77, $J_{AX}$ 6.89, $J_{BX}$ 4.92, β-$H_2$) and 0.95 (9 H, s, $Me_3$).

Recovery of 2-amino-4-phenylbutanoic acid from complex **4b** was made in the usual way. According to GLC the ratio of (*S*) and (*R*) isomers was 7:3; $\delta_H$(5 mol $dm^{-3}$ DCl in $D_2O$) 7.22 (5 H, m, Ph), 4.11 (1 H, AB, $J_{AB}$ 6.2, NCH), 2.70 (2 H, m, $CH_2Ph$) and 2.20 (2 H, m, $CCH_2$).

## Acknowledgements

Support has been provided by the Russian Fundamental Research Fund (No. 93-03-4497).

## References

1 B. Giese, *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, New York, Pergamon Press, 1986; D. P. Curran, *Synthesis*, 1988, 489; *Selectivity and Synthetic Applications of Radical Reactions; Tetrahedron Symposia in Print*, ed. B. Giese, *Tetrahedron*, 1985, **41**, 3887; P. P. Jasperse, D. P. Curran and T. L. Flevig, *Chem. Rev.*, 1991, **91**, 1237.

2 (*a*) N. A. Porter, R. Breyer, E. Swann, J. Nally, J. Pradhan, T. Allen and A. T. McPhail, *J. Am. Chem. Soc.*, 1991, **113**, 7002; (*b*) G. Thoma, D. P. Curran, S. Geib, B. Giese, W. Damm and F. Wetterich, *J. Am. Chem. Soc.*, 1993, **115**, 8585 and cited references; (*c*) D. P. Curran and A. C. Abraham, *Tetrahedron*, 1993, **49**, 4821 and cited references.

3 B. H. Kim and D. P. Curran, *Tetrahedron*, 1993, **49**, 293 and cited references.

4 J. G. Stack, D. P. Curran, J. Rebek and P. Ballester, *J. Am. Chem. Soc.*, 1991, **113**, 5918; J. G. Stack, D. P. Curran, S. V. Geib, J. Rebek and P. Ballester, *J. Am. Chem. Soc.*, 1992, **114**, 7007.

5 Yu. Belokon', A. Sagyan, S. Djamgaryan, V. Bachmutov and V. Belikov, *Tetrahedron*, 1988, **44**, 5507.

6 A. Beckwith and Ch. Chai, *J. Chem. Soc., Chem. Commun.*, 1990, 1087.

7 R. Gasanov and R. Freidlina, *Usp. Khim.*, 1987, **56**, 447 (*Russ. Chem. Rev., Engl. Transl.*, 1987, **56**, 264).

8 M. Wrighton and D. Ginley, *J. Am. Chem. Soc.*, 1975, **97**, 2065.
9 S. Terabe and R. Konaka, *J. Chem. Soc., Perkin Trans. 2*, 1973, 369.
10 R. Gasanov, A. Tumanskaya and L. Il'inskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1992, 136 (*Bull. Russ. Acad. Sci., Div. Chem. Sci.*, 1992, **41**, 107).
11 R. Gasanov, T. Churkina, L. Il'inskaya, K. Kochetkov and D. Bodrov, *Dokl. Akad. Nauk SSSR*, 1992, **326**, 126.
12 (*a*) K. Ingold, J. Lusztyk and J. Scaiano, *J. Am. Chem. Soc.*, 1984, **106**, 343; (*b*) C. Chatgilialoglu, J. C. Scaiano and K. Ingold, *Organometallics*, 1982, **1**, 466; (*c*) L. Johnston, J. Lusztyk, D. Wayner, A. Abelwickereyma, A. Beckwith, J. Scaiano and K. Ingold, *J. Am. Chem. Soc.*, 1985, **107**, 4594.
13 Yu. N. Belokon', *Janssen Chim. Acta*, 1992, **10**, 4.
14 V. Soloshonok, V. Kukhar, S. Galushko, N. Svistunova, D. Avilov, N. Kuzmina, N. Raevski, Yu. Struchkov, A. Pysarevsky and Yu. N. Belokon', *J. Chem. Soc., Perkin Trans. 1*, 1993, 3143.

*Paper* 4/02422B
*Received* 25*th April* 1994
*Accepted* 9*th June* 1994