Halo-substituted (*S*)-*N*-(2-benzoylphenyl)-1-benzylpyrolidine-2-carboxamides as new chiral auxiliaries for the asymmetric synthesis of (*S*)-α-amino acids

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The synthesis of new chiral auxiliaries (*S*)-*N*-(2-benzoylphenyl)-1-(3,4-dichlorobenzyl)-pyrrolidine-2-carboxamide (**1a**), (*S*)-*N*-(2-benzoylphenyl)-1-(pentafluorobenzyl)pyrrolidine-2-carboxamide (**1b**), and (*S*)-*N*-(2-benzoylphenyl)-1-(4-isopropoxytetrafluorobenzyl)pyrrolidine-2-carboxamide (**1c**) and their application in the asymmetric synthesis of amino acids using Ni^{II} complexes of their Schiff´s bases with alanine and glycine are described. Compound **1a** is particularly appropriate for highly stereoselective synthesis of α-methyl-α-amino acids with high enatiomeric purity (*ee* >95%).

Key words: asymmetric synthesis, amino acids, chiral auxiliaries, nickel(II) complexes.

The search for new methods of asymmetric synthesis of amino acids is a topical task.[1—14] In particular, methods for asymmetric synthesis suitable for the preparation of ^{11}C-labeled amino acids are currently of interest. These substances are used for the diagnosis of cancer by positron emission tomography (PET).[15] The most important criteria for such syntheses are short reaction time and high optical purity of the final product. Relying on the experience of using a recyclable chiral auxiliary, (*S*)-*N*-(2-benzoylphenyl)-1-benzylpyrrolidine-2-carboxamide (BPB),[16—18] we attempted to design new chiral reagents that would allow fast and efficient asymmetric synthesis of amino acids suitable for PET diagnostics. This approach has several advantages including simplicity of operations, high concentration of reagents, and high reaction rates at room temperature and is used successfully not only in our studies[16—19] but in other researchers´ works,[20—23] in particular, in those dealing with the synthesis of ^{11}C-labeled amino acids.[15,24] In addition, recently, we improved the procedures for the synthesis of BPB and the corresponding Ni^{II} complexes.[18]

Although the enantioselectivity of the synthesis of protein amino acids using BPB is rather high (*ee* 85—95%), α-alkyl-substituted amino acids are produced with *ee* ≤ 80%.[16] In our first steps to improve the method by modifying the reagent, we prepared (*S*)-*N*-(2-benzoylphenyl)-1-(1-naphthylmethyl)pyrrolidine-2-carboxamide.[25] However, this did not provide the expected increase in the stereodifferentiating capacity, and, in addition, the solubility in organic solvents and the reactivity of the corresponding Ni^{II} complexes of both alanine and glycine proved to be very low, which substantially restricted the use of this chiral auxiliary.[25] Based on these results, we assumed that stereodifferentiation in the amino acid synthesis could be increased by introducing substituents into the aromatic ring of the benzyl group. In this paper, we present new chiral reagents, *viz.*, (*S*)-*N*-(2-benzoylphenyl)-1-(3,4-dichlorobenzyl)pyrrolidine-2-carboxamide (**1a**) and its analogs containing F atoms in the benzyl fragment and studied their stereodifferentiating capacity.

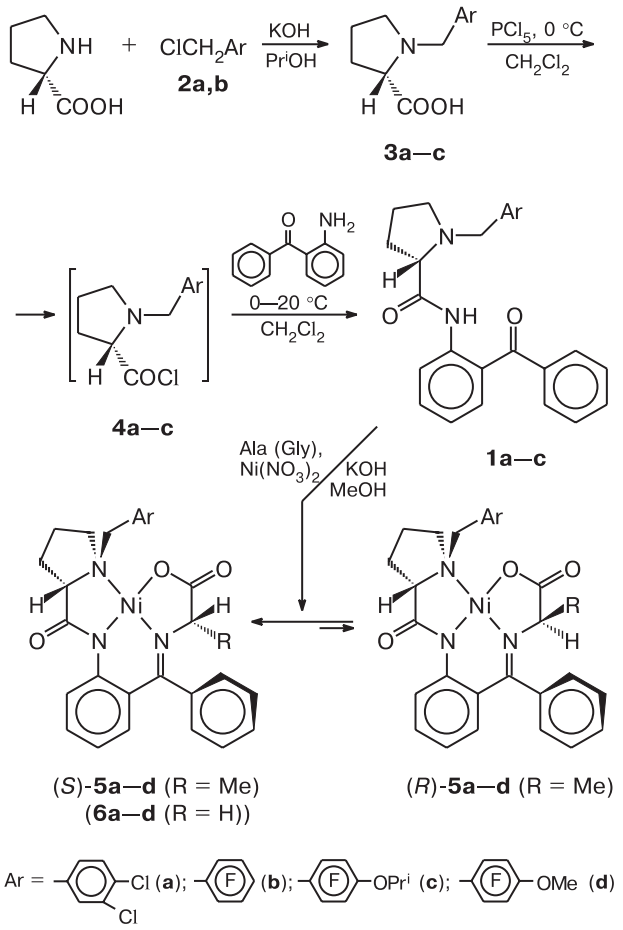
Results and Discussion

The synthesis of reagent **1a**, the attempted preparation of (*S*)-*N*-(2-benzoylphenyl)-1-(pentafluorobenzyl)pyrrolidine-2-carboxamide (**1b**), and the synthesis of Ni^{II} complexes of Schiff´s bases of these reagents with amino acids are presented in Scheme 1. The chiral reagents were synthesized using (*S*)-*N*-(3,4-dichlorobenzyl)- and (*S*)-*N*-(pentafluorobenzyl)prolines **3a,b**, prepared by alkylation of (*S*)-proline with halides **2a,b**.

In the synthesis of compound **3b**, it was found that one F atom of the pentafluorobenzyl fragment is re-

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 8, pp. 1464—1470, August, 2002.

Scheme 1



placed by the OPr^i group under reaction conditions, and, as a consequence, the reaction gives mainly (*S*)-*N*-(4-isopropoxytetrafluorobenzyl)proline (**3c**).* To prepare compound **3b**, we used a smaller amount of the base and a shorter reaction time, but in this case, too, the reaction affords a mixture of **3b** and **3c** in approximately equal amounts. We could not prepare the pure product **3b** but the proline derivative **3c** was isolated from the mixture by crystallization. It was found that the acid chlorides of benzylprolines **4a—c** containing electron-withdrawing substituents are formed with greater difficulty than the chloride of benzylproline. Therefore, instead of the usual reagent $SOCl_2$,[18] we used PCl_5. Chiral auxiliaries **1a—c** were prepared from all the substituted prolines including **3b** and **3c** in CH_2Cl_2 at 0 °C, according to Scheme 1. The Ni^{II} complexes of glycine and alanine Schiff´s bases with the chiral reagents (**5** and **6**, respectively) are formed in MeOH in >80% yields (see Scheme 1). The preparation of the Ni^{II} complexes of alanine and glycine Schiff´s bases with **1b** resulted in complexes **5d** and **6d**, derived from (*S*)-*N*-(2-benzoylphenyl)-1-(4-methoxytetrafluorobenzyl)pyrrolidine-2-carboxamide (**1d**), as a product of nucleophilic replacement of one F atom located in the *para*-position relative to the methylene group (by analogy with the replacement of the F atom during the synthesis of substituted benzylproline). The complexes **5b** and **6b** containing the unsubstituted reagent were isolated in a low yield (20 and 4%, respectively) when the synthesis was carried out in Pr^iOH.

Figure 1 shows the structure of complex (*S*)-**5a** determined by X-ray diffraction analysis. Some significant peculiarities of this structure deserve attention. The dichlorobenzyl group shields the coordination plane of the complex more efficiently, the Ni—N(15)—C(26)—C(27) torsion angle being −50° and the Ni—N(15)—C(26) angle being 108°, whereas in complexes with the unsubstituted benzyl group, these values are normally −57 and 110°, respectively.[26—29] In addition, the Ni—C(27) distance in (*S*)-**5a** is 2.992(5) Å (this is smaller than the sum of the van der Waals radii), whereas this distance in BPB complexes amounts to 3.2 Å. Apparently, the weak interaction existing between the Ni atom and the dichlorobenzyl group stabilizes additionally the *endo*-conformation of the complex in which the dichlorobenzyl group is fixed above the central Ni atom and decreases the Ni—C(27) distance in complexes **5a** and **6a**.

The synthesis of the Ni^{II} complexes of alanine Schiff´s bases gave a mixture of diastereomers. Since the com-

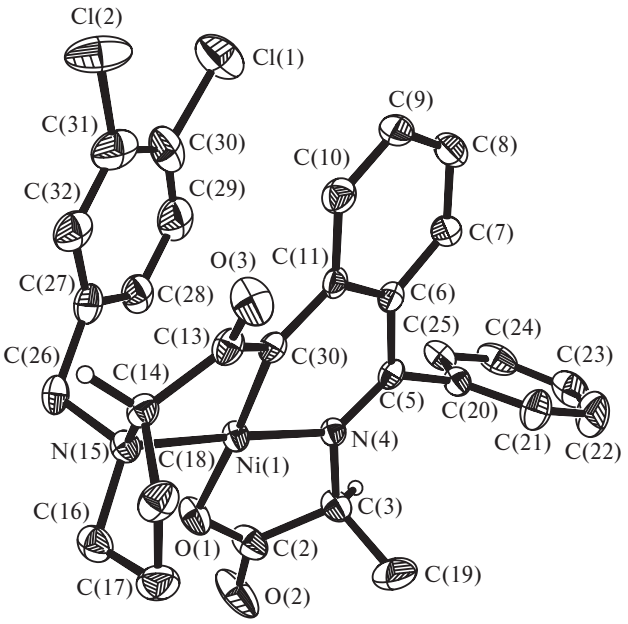


Fig. 1. Molecular structure of complex (*S*)-**5a** with 50% probability ellipsoids of anisotropioc displacements.

* The fact that the OPr^i group replaces the F atom in the *para*-position of the pentafluorophenyl fragment was established based on the analysis of the ^{19}F NMR spectrum of the chiral reagent **1c** prepared subsequently (the spectrum is given in the Experimental).

Table 1. Alkylation of complexes **5** and **6**

Run	Initial complex	Alkylating reagent	Amino acid	Yield (%)	*ee* (%)[a]
1	**6a**	BnBr	(*S*)-Phenylalanine	71	97
2	**6b**	BnBr	2,2-Dibenzylglycine	45	—
3	**6c**	BnBr	2,2-Dibenzylglycine[b]	68	—
4	**6d**	BnBr	(*S*)-Phenylalanine	20[c]	74
5	**6a**	MeI	(*S*)-Alanine	69	95
6	Ni—BPB—Ala[d]	BnBr	(*S*)-α-Methylphenylalanine	81	80
7	Ni—BPB—Ala[d]	EtBr	(*S*)-Isovaline	76	81
8	**5a**	BnBr	(*S*)-α-Methylphenylalanine	85	>99
9	**5a**	EtBr or EtI	—	—	—
10	**5c**	BnBr	(*S*)-α-Methylphenylalanine	80	95
11	**5c**	EtBr	(*S*)-Isovaline	77	98
12	**5d**	BnBr	(*S*)-α-Methylphenylalanine	79	96
13	**5d**	EtBr	(*S*)-Isovaline	68	97
14	**5d**	AllBr	(*S*)-α-Allylalanine	83	>98[e]

[a] Determined by GLC on a chiral phase.
[b] After decomposition of the reaction mixture, only 2,2-dibenzylglycine was isolated.
[c] Together with phenylalanine, 50% of 2,2-dibenzylglycine was isolated.
[d] The data of Ref. 16.
[e] Determined from the ^{1}H NMR data for the alkylated complex.

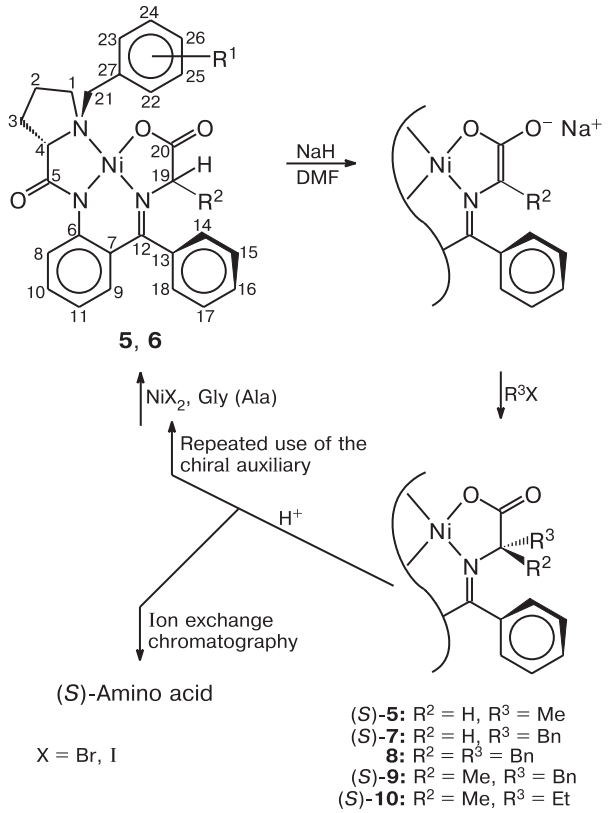
plex is synthesized in highly alkaline media at elevated temperatures (64 °C, KOH, MeOH), epimerization of the amino acid fragment proceeds faster and the ratio of the diastereomeric complexes reflects the thermodynamic equilibrium between them. The (*SS*)/(*SR*) diastereomer ratios for several complexes determined by ^{1}H NMR spectroscopy from the relative intensity of the aromatic-proton signals at about 8—9 ppm are presented below.

Complex	Ni—BPB—Ala	**5a**	**5c**	**5d**
(*SS*)/(*SR*)*	96/4	97/3	>98/2	94/6

To appraise their efficiency to the asymmetric synthesis of amino acids, complexes **5** and **6** based on new chiral auxiliaries were alkylated (Scheme 2).

It was found that complexes **6b—d** are exceptionally reactive, their alkylation with BnBr giving predominantly (>50%) bis-alkylated products **8b—d** (Table 1, runs *2—4*). The alkylation of **6a** with BnBr and MeI under the same conditions yields only monoalkylated products (*S*)-**7a** and (*S*)-**5a** with excellent *ee* (97 and 95%, respectively) (see Table 1, runs *1* and *5*). The alkylation of complexes **5** with BnBr and EtBr gives α-methylphenylalanine complexes **9a,c,d** (see Table 1, runs *6*, *8*, *10*, and *12*) and isovaline (α-methyl-α-aminobutyric acid) complexes **10c,d** (runs *7*, *11*, and *13*), respectively, which contain no α-protons and do not undergo epimerization under the reaction conditions. Thus, the (*SS*)/(*SR*) ratio for complexes **9a,c,d** and **10c,d** and/or the enantiomeric

Scheme 2



purity of α-methyl-α-amino acids isolated from these complexes are dictated by the relative rates of the attack by the alkylating reagent of the *re*- and *si*-sides of the

* The thermodynamic equilibrium was established in the presence of a 0.2 *M* solution of MeONa in MeOH, the equilibrium position being determined by ^{1}H NMR.

carbanion. The data of Table 1 illustrate the kinetic stereoselectivity in the synthesis of amino acids. Comparison of runs *6* and *8*, *10*, *12* (see Table 1) shows an increase in the diastereomer ratio from 11/1 (for the alkylation of Ni—BPB—(*S*)-Ala) to 40/1 (for the alkylation of (*S*)-**5c,d**) and to >99/1 (for the use of (*S*)-**5a**). The optical purity of amino acids isolated from the EtBr- and AllBr-alkylated complexes (*S*)-**5d** (see Table 1, runs *13* and *14*) exceeded 95%.

We were unable to accomplish alkylation of complex **5a** with EtBr or EtI (see Table 1, run *9*), whereas alkylation with BnBr rapidly (in 10 min) proceeded at room temperature with a good yield and a very high stereoselectivity (run *8*).

On decomposition of complexes and isolation of amino acids,[18,25,26] the starting reagent **1a** is easily recovered in >87% yield.

Thus, the amino acid synthesis making use of the Ni^{II} complexes of Schiff´s bases of glycine and chiral reagent **1a** is of interest for the preparation of isotopically labeled amino acids to be used in the PET diagnostics. This complex has already been employed to prepare ^{18}F-labeled amino acids.[30]

Experimental

^1H NMR spectra were measured on Bruker WP-200 and Bruker AMX-400 instruments in $CDCl_3$ (unless indicated otherwise). The C atom numbering for the description of ^{13}C NMR spectra is shown in Scheme 2. Optical rotation was measured on a Perkin—Elmer 241 polarimeter. Freshly distilled solvents were used. The enantiomeric GLC analysis of amino acids (Chromatograph-3700) as the *N*-trifluoroacetyl derivatives of their *n*-propyl esters was performed using a Chirasil Val type chiral phase[31] on quartz capillary columns (40 m × 0.23 mm) with 0.12 μm film thickness at a column temperature of 125 °C using helium as the carrier gas. The following commercial chemicals were used: alanine, glycine, and (*S*)-proline (Reanal); MeI, EtBr, AllBr, BnBr, 3,4-dichlorobenzyl chloride, and 2-aminobenzophenone (Aldrich); and pentafluorobenzyl chloride (Lancaster). The decomposition of complexes, the isolation of amino acids, and ligand extraction were described previously.[18,25,26] The chiral auxiliaries were recovered in 88—90% yields.

(*S*)-*N*-(3,4-Dichlorobenzyl)proline (3a). (*S*)-Proline (10.2 g, 0.09 mol) was added to a solution of KOH (15.12 g, 0.27 mol) in 40 mL of Pr^iOH, and the mixture was stirred at 40—50 °C until the compound completely dissolved. After that, freshly distilled 3,4-dichlorobenzyl chloride (**2a**) (21.1 g, 0.108 mol) was added dropwise over a period of 30 min, and the mixture was stirred for an additional 15 h at ~20 °C. The reaction was monitored by TLC (SiO_2, elution with $CHCl_3$—EtOH, 1 : 1). Then the reaction mixture was neutralized with 6 *M* HCl to pH 5—6, diluted with 25 mL of $CHCl_3$, and allowed to stand for 4 h. The precipitated salts were filtered off and washed with $CHCl_3$, the filtrate was concentrated, and the residue was treated with Me_2CO. The precipitate was filtered off, washed with Pr^iOH, and dried with P_2O_5 to give 17.2 g (70%) of compound **3a**, m.p. 185—186 °C; $[\alpha]_D^{25}$ −18.8, $[\alpha]_{578}^{25}$ −19.6, $[\alpha]_{546}^{25}$ −22.2, $[\alpha]_{436}^{25}$ −36.3, $[\alpha]_{365}^{25}$ −51.1 (*c* 3.0, 0.1 *M* HCl); $[\alpha]_D^{25}$ −5.6, $[\alpha]_{578}^{25}$ −6.2, $[\alpha]_{546}^{25}$ −7.0, $[\alpha]_{365}^{25}$ −14.7 (*c* 1, EtOH). Found (%): C, 50.88; H, 4.91; N, 5.00. $C_{12}H_{13}Cl_2NO_2 \cdot 0.5\,H_2O$. Calculated (%): C, 50.88; H, 4.95; N, 4.95. ^1H NMR (CD_3OD), δ: 2.08—2.80 (m, 4 H, β-H, γ-H Pro); 3.48 (m, 1 H, δ-H Pro); 3.77 (m, 1 H, δ-H Pro); 4.20 (m, 1 H, α-H Pro); 4.67, 4.51 (AB system, 2 H, $NC\underline{H}_2Ph$, $J_{A,B}$ = 13.1 Hz); 7.66—8.00 (m, 3 H, Ar).

(*S*)-*N*-[(4-Isopropoxy)tetrafluorophenylmethyl]proline (3c). (*S*)-Proline (3.4 g, 0.03 mol) was added to a solution of KOH (5.00 g, 0.089 mol) in 20 mL of Pr^iOH, and the mixture was stirred at 40—50 °C until the substance completely dissolved. After that, freshly distilled pentafluorobenzyl chloride (**2b**) was added dropwise over a period of 30 min and the mixture was stirred for an additional 15 h at 20 °C. The reaction was monitored by TLC (SiO_2, elution with $CHCl_3$—EtOH, 1 : 1). Then the reaction mixture was neutralized with 6 *M* HCl to pH 5—6 and diluted with 25 mL of $CHCl_3$. The precipitate was filtered off and washed with 10 mL of $CHCl_3$. The chloroform extracts were concentrated and Me_2CO was added to the dry residue. The precipitate was filtered off, washed with Pr^iOH, and dried over P_2O_5. Yield 5.9 g (59%), m.p. 92—94 °C. Found (%): C, 52.30; H, 5.12; N, 3.98. $C_{15}H_{18}F_4NO_3 \cdot 0.5\,H_2O$. Calculated (%): C, 52.33; H, 5.27; N, 4.07. ^1H NMR, δ: 1.37 (d, 6 H, $\underline{Me}_2CH$, J = 6 Hz); 1.88—2.00 (m, 2 H, β-H, γ-H Pro); 2.01—2.12 (m, 1 H, β-H Pro); 2.13—2.22 (m, 1 H, γ-H Pro); 2.61—2.81 (m, 1 H, δ-H Pro); 3.27—3.44 (m, 1 H, δ-H Pro); 3.51—3.73 (m, 1 H, α-H Pro); 4.10, 4.26 (AB system, 2 H, $NC\underline{H}_2Ph$, $J_{A,B}$ = 13.1 Hz); 10.1 (s, 1 H, OH). ^{19}F NMR, δ: 144.77, 157.50 (AA´XX´ system, J_o = 23.5 Hz, J_p = 8.5 Hz).

(*S*)-*N*-(Pentafluorophenylmethyl)proline (3b) was prepared as described in the above procedure using 1.5—2 equiv. of KOH instead of 3 equiv. The final product containing a 1 : 1 mixture of **3b** and **3c** (^1H NMR data) was used in the subsequent syntheses without separation.

(*S*)-*N*-(2-Benzoylphenyl)-1-(3,4-dichlorobenzyl)pyrrolidine-2-carboxamide (1a) was prepared as a hydrochloride. Phosphorus pentachloride (6.9 g, 0.033 mol) was added at 0 °C to a solution of compound **3a** (9 g, 0.033 mol) in 10 mL of CH_2Cl_2, the mixture was stirred for 10 min, and 2-aminobenzophenone (6.51 g, 0.033 mol) was slowly added. The reaction mixture was stirred at ~20 °C up to complete conversion of 2-aminobenzophenone (TLC monitoring, SiO_2, elution with hexane—Et_2O, 1 : 1). The reaction mixture was concentrated and treated successively with acetone and water. The crystals thus formed were dissolved in 5 mL of 12 *M* HCl and diluted with 15 mL of H_2O. The precipitate of pure hydrochloride **1a** was filtered off, washed with water, and dried in air. Yield 12.2 g (76%), m.p. 203—205 °C, $[\alpha]_D^{25}$ −45 (*c* 1, MeOH). Found (%): C, 61.18; H, 4.68; N, 5.78. $C_{25}H_{23}Cl_3N_2O_2$. Calculated (%): C, 61.30; H, 4.73; N, 5.72. ^1H NMR (CD_3OD), δ: 1.73 (m, 1 H, β-H Pro); 2.04 (m, 1 H, γ-H Pro); 2.33 (m, 1 H, γ-H Pro); 2.57 (m, 1 H, β-H Pro); 3.50 (m, 1 H, δ-H Pro); 3.77 (m, 1 H, δ-H Pro); 4.55 (m, 1 H, α-H Pro); 4.59, 4.53 (AB system, 2 H, $NC\underline{H}_2Ar$, $J_{A,B}$ = 17.0 Hz); 7.50—8.11 (m, 12 H, Ar).

(*S*)-*N*-(2-Benzoylphenyl)-1-(4-isopropoxytetrafluorobenzyl)pyrrolidine-2-carboxamide (1c) was synthesized in a similar way from compound **3c** and 2-aminobenzophenone, but the ligand was isolated as a free base after neutralization of the reaction mixture with an aqueous solution of K_2CO_3 and CH_2Cl_2

extraction. The product was purified by column chromatography (SiO_2, elution with hexane—Et_2O, 1 : 1). Yield 52%. ^{1}H NMR, δ: 1.30 (d, 6 H, $\underline{Me}_2CH$, J = 6.0 Hz); 1.80—2.11 (m, 3 H, 2 β-H, γ-H Pro); 2.10—2.44 (m, 1 H, γ-H Pro); 2.51—2.78 (m, 1 H, δ-H Pro); 3.21—3.50 (m, 2 H, δ-H, α-H Pro); 3.87, 3.98 (AB system, 2 H, NC$\underline{H}_2$Ar, $J_{A,B}$ = 12.0 Hz); 4.29—4.51 (m, 1 H, $Me_2C\underline{H}$); 7.00—8.70 (m, 12 H, Ar); 11.51 (s, 1 H, NH).

(*S*)-*N*-(2-Benzoylphenyl)-1-(pentafluorobenzyl)pyrrolidine-2-carboxamide (1b) was synthesized in a similar way from a mixture of compounds **3b** and **3c**. The resulting mixture of **1b** and **1c** was separated by column chromatography (SiO_2, elution with hexane—Et_2O, 1 : 1). The yield of product **1b** was 67% (based on the real amount of **3b** in the mixture), m.p. 74—76 °C, $[\alpha]_D^{25}$ −108.2 (*c* 1, MeOH). Found (%): C, 62.63; H, 3.81; N, 5.958. $C_{25}H_{19}F_5N_2O_2$. Calculated (%): C, 63.29; H, 4.04; N, 5.91. ^{1}H NMR, δ: 1.58—2.05 (m, 3 H, 2 β-H, γ-H Pro); 2.05—2.41 (m, 1 H, γ-H Pro); 2.41—2.75 (m, 1 H, δ-H Pro); 3.20—3.48 (m, 2 H, δ-H, α-H Pro); 3.86, 4.00 (AB system, 2 H, NC$\underline{H}_2$Ar, $J_{A,B}$ = 13.3 Hz); 7.12 (m, 1 H, Ar); 7.43—7.72 (m, 7 H, Ar); 11.53 (s, 1 H, NH).

(*S*)-{({2-[1-(3,4-Dichlorobenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*S*)-alaninato-*N*,*N*′,*N*″,*O*}nickel(II) ((*S*)-5a). A solution of KOH (4.48 g, 0.08 mol) in 10 mL of MeOH was added to a solution containing reagent **1a** (4.89 g, 0.01 mol), alanine (1.8 g, 0.02 mol), and $Ni(NO_3)_2 \cdot 6\,H_2O$ (5.82 g, 0.02 mol) in 15 mL of MeOH. The mixture was stirred for 2 h at 50—60 °C. The reaction was monitored by TLC (SiO_2, elution with $CHCl_3$—Me_2CO, 1 : 1). After completion of the reaction, the mixture was neutralized with AcOH to pH 5—6 and diluted with water, and the precipitate was filtered off and recrystallized from MeOH. Yield 81%, m.p. 327 °C, $[\alpha]_D^{25}$ +2821 (*c* 0.3, MeOH). Found (%): C, 57.95; H, 4.34; N, 7.09. $C_{28}H_{25}Cl_2N_3NiO_3$. Calculated (%): C, 57.87; H, 4.34; N, 7.23. ^{1}H NMR, δ: 1.61 (d, 3 H, Me, J = 7.0 Hz); 2.09 (m, 1 H, γ-H Pro); 2.29 (m, 1 H, β-H Pro); 2.63 (m, 1 H, γ-H Pro); 2.75 (m, 1 H, β-H Pro); 3.43 (m, 1 H, α-H Pro); 3.59—3.77 (m, 2 H, δ-H Pro); 3.94 (q, 1 H, α-H Ala, J = 7.0 Hz); 4.32, 4.35 (AB system, 2 H, NC$\underline{H}_2$Ar, $J_{A,B}$ = 12.5 Hz); 6.65 (m, 2 H, Ar); 6.92 (m, 1 H, Ar); 7.17 (m, 1 H, Ar); 7.32—7.57 (m, 5 H, Ar); 7.82 (m, 1 H, Ar); 8.00 (m, 1 H, Ar); 8.84 (s, 1 H, Ar).

(*S*)-{({2-[1-(Pentafluorobenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*S*)-alaninato-*N*,*N*′,*N*″,*O*}nickel(II) ((*S*)-5b). Yield 20%. ^{1}H NMR, δ: 1.55 (d, 3 H, Me, J = 6.8 Hz); 1.83—2.14 (m, 1 H, γ-H Pro); 2.41—2.68 (m, 1 H, β-H Pro); 2.62—2.78 (m, 1 H, γ-H Pro); 2.97—3.11 (m, 1 H, β-H Pro); 3.33—3.45 (m, 3 H, δ-H, α-H Pro); 3.58—3.77 (m, 1 H, δ-H Pro); 4.03, 4.44 (AB system, 2 H, NC$\underline{H}_2$Ar, $J_{A,B}$ = 13.2 Hz); 6.65—6.83 (m, 2 H, Ar); 6.96 (m, 1 H, Ar); 7.21—7.96 (m, 5 H, Ar); 8.24 (m, 1 H, Ar).

(*S*)-{({2-[1-(4-Isopropoxytetrafluorobenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*S*)-alaninato-*N*,*N*′,*N*″,*O*}nickel(II) ((*S*)-5c). Yield 82%, $[\alpha]_D^{25}$ +2227 (*c* 0.037, MeOH). Found (%): C, 59.35; H, 5.12; F, 11.00; N, 5.79. $C_{34}H_{31}F_4N_3NiO_4$. Calculated (%): C, 59.94; H, 4.73; F, 11.15; N, 6.17. ^{1}H NMR, δ: 1.32 (m, 6 H, $\underline{Me}_2CHO$); 1.53 (d, 3 H, Me, J = 6.8 Hz); 1.97 (m, 1 H, γ-H Pro); 2.24 (m, 1 H, β-H Pro); 2.64 (m, 1 H, γ-H Pro); 2.96 (m, 1 H, β-H Pro); 3.38 (m, 2 H, δ-H Pro); 3.68 (m, 1 H, α-H Pro); 3.87 (q, 1 H, α-H Ala, J = 6.8 Hz); 4.00, 4.33 (AB system, 2 H, NC$\underline{H}_2$Ar, $J_{A,B}$ = 13.1 Hz); 4.50 (m, 1 H, $Me_2C\underline{H}O$); 6.71 (m, 2 H, Ar); 6.95 (m, 1 H, Ar); 7.15—7.61 (m, 5 H, Ar); 8.25 (m, 1 H, Ar). ^{13}C NMR, δ: 17.8 (Me Ala); 18.5 ($\underline{Me}_2CHO$); 20.2 (C(2)); 26.5 (C(3)); 45.0 (C(21)); 52.7 (C(1)); 62.7 (C(4)); 66.9 (C(19)); 74.5 ($Me_2\underline{C}HO$); 101.2 (C(27)); 117.2 (C(9)); 119.4 (C(10)); 122.7 (C(7)); 123.7 (C(15)); 123.4 (C(17)); 124.2 (C(26)); 124.9 (C(14)); 125.1 (C(18)); 125.8 (C(8)); 128.5 (C(16)); 129.4 (C(13)); 129.7 (C(11)); 136.5 (C(22)); 137.9 (C(6)); 139.1 (C(23)); 141.0 (C(24)); 143.4 (C(25)); 166.7 (C(5)); 175.2 (C(12)); 176.3 (C(20)).

(*S*)-{({2-[1-(4-Methoxytetrafluorobenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*S*)-alaninato-*N*,*N*′,*N*″,*O*}nickel(II) ((*S*)-5d). Yield 81%, m.p. 230—232 °C, $[\alpha]_D^{25}$ +2335 (*c* 0.03, MeOH). Found (%): C, 56.98; H, 4.03; F, 11.51; N, 6.95. $C_{29}H_{25}F_4N_3NiO_4$. Calculated (%): C, 56.70; H, 4.10; F, 11.84; N, 6.84. ^{1}H NMR, δ: 1.52 (d, 3 H, Me, J = 6.8 Hz); 1.96 (m, 1 H, γ-H Pro); 2.23 (m, 1 H, β-H Pro); 2.64 (m, 1 H, γ-H Pro); 2.95 (m, 1 H, β-H Pro); 3.35 (m, 2 H, δ-H Pro); 3.64 (m, 1 H, α-H Pro); 3.87 (q, 1 H, α-H Ala, J = 6.8 Hz); 3.98 (s, 3 H, OMe); 3.92, 4.31 (AB system, 2 H, NC$\underline{H}_2$Ar, $J_{A,B}$ = 13.0 Hz); 6.69 (m, 2 H, Ar); 6.93 (m, 1 H, Ar); 7.15—7.57 (m, 5 H, Ar); 8.20 (m, 1 H, Ar). ^{13}C NMR, δ: 17.8 (Me Ala); 20.1 (C(2)); 26.5 (C(3)); 45.0 (C(21)); 52.7 (C(1)); 58.0 (OMe); 62.7 (C(4)); 67.0 (C(19)); 101.0 (C(27)); 117.3 (C(9)); 119.2 (C(10)); 122.7 (C(7)); 123.3 (C(15)); 123.4 (C(17)); 124.2 (C(26)); 124.9 (C(14)); 125.1 (C(18)); 125.8 (C(8)); 128.4 (C(16)); 129.3 (C(13)); 129.7 (C(11)); 135.4 (C(22)); 137.8 (C(6)); 138.1 (C(23)); 141.0 (C(24)); 143.4 (C(25)); 166.7 (C(5)); 175.1 (C(12)); 176.3 (C(20)).

All complexes **6** were prepared by a procedure similar to that described for compound (*S*)-**5a**. The time of stirring was 1 h and the solvent used for recrystallization was hexane—$CHCl_3$ (1 : 1).

(*S*)-{({2-[1-(3,4-Dichlorobenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)glycinato-*N*,*N*′,*N*″,*O*}-nickel(II) (6a). Yield 78%, m.p. 236—237 °C, $[\alpha]_D^{25}$ +2213 (*c* 0.3, MeOH). Found (%): C, 57.11; H, 4.06; N, 7.21. $C_{27}H_{23}Cl_2N_3NiO_3$. Calculated (%): C, 57.14; H, 4.06; N, 7.41. ^{1}H NMR, δ: 2.00—2.56 (m, 4 H, β-H, γ-H Pro); 3.39 (m, 3 H, α-H, δ-H Pro); 3.67, 3.83 (AB system, 2 H, CH_2 Gly, $J_{A,B}$ = 20.4 Hz); 3.75, 4.36 (AB system, 2 H, NC$\underline{H}_2$Ar, $J_{A,B}$ = 12.5 Hz); 6.60—8.30 (m, 11 H, Ar); 8.79 (s, 1 H, Ar).

(*S*)-{({2-[1-(Pentafluorobenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)glycinato-*N*,*N*′,*N*″,*O*}nickel(II) (6b). Yield 4%. ^{1}H NMR, δ: 1.78—2.24 (m, 2 H, γ-H, β-H Pro); 2.48—2.66 (m, 1 H, β-H Pro); 2.66—2.98 (m, 1 H, γ-H Pro); 3.31—3.55 (m, 3 H, δ-H, α-H Pro); 3.60, 3.77 (AB system, 2 H, CH_2 Gly, $J_{A,B}$ = 18.6 Hz); 4.34, 4.16 (AB system, 2 H, NC$\underline{H}_2$Ar, $J_{A,B}$ = 13.6 Hz); 6.65—7.58 (m, 8 H, Ar); 8.33 (m, 1 H, Ar).

(*S*)-{({2-[1-(4-Isopropooxytetrafluorobenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)glycinato-*N*,*N*′,*N*″,*O*}nickel(II) (6c). Yield 85%. ^{1}H NMR, δ: 1.27 (m, 6 H, $\underline{Me}_2CHO$); 1.83—2.25 (m, 2 H, γ-H, β-H Pro); 2.52 (m, 1 H, γ-H Pro); 2.72 (m, 1 H, β-H Pro); 3.36 (m, 3 H, δ-H, α-H Pro); 3.61, 3.69 (AB system, 2 H, CH_2 Gly, $J_{A,B}$ = 16.3 Hz); 4.08, 4.36 (AB system, 2 H, NC$\underline{H}_2$Ar, $J_{A,B}$ = 13.7 Hz); 4.49 (m, 1 H, $Me_2C\underline{H}O$); 6.61—7.48 (m, 8 H, Ar); 8.34 (m, 1 H, Ar).

(*S*)-{({2-[1-(4-Methoxytetrafluorobenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)glycinato-*N*,*N*′,*N*″,*O*}nickel(II) (6d). Yield 91%. ^{1}H NMR, δ: 1.72—2.20 (m, 2 H, γ-H, β-H Pro); 2.38—2.67 (m, 1 H, γ-H Pro);

2.67—2.92 (m, 1 H, β-H Pro); 3.26—3.48 (m, 3 H, δ-H, α-H Pro); 3.68, 3.75 (AB system, 2 H, CH_2 Gly, $J_{A,B}$ = 19.6 Hz); 4.02 (s, 3 H, OMe); 4.12, 4.41 (AB system, 2 H, NC$\underline{H}_2$Ar, $J_{A,B}$ = 12.3 Hz); 6.61—7.48 (m, 7 H, Ar); 8.38 (m, 1 H, Ar).

Alkylation of complexes 6 with BnBr and MeI (general procedure). Complex **6** (0.53 mmol), DMF (2 mL), and alkylating reagent (0.53 mmol) were placed in an argon-filled flask, the mixture was cooled, the argon was pumped out, the flask was filled again with argon, and NaH (0.053 g, 1.325 mmol) was added. The mixture was stirred under argon for 5—10 min. The reaction was monitored by TLC (SiO_2, elution with AcOEt—$CHCl_3$, 4 : 1). After completion of the reaction, 2 mL of a 3 *M* solution of MeONa in MeOH was added, and the mixture was stirred for an additional 10—15 min, neutralized with AcOH, and diluted with 20 mL of H_2O. The precipitate was washed with water, and in the case of BnBr, additionally with hexane. The (*S*,*S*)-/(*S*,*R*)-isomer ratio was determined by ^{1}H NMR spectroscopy.

(*S*)-{({2-[1-(3,4-Dichlorobenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*S*)-phenylalaninato-*N*,*N*′,*N*″,*O*}nickel(II) ((*S*)-7a). Yield 75%, m.p. 144—145 °C, $[\alpha]_D^{25}$ +2273 (*c* 0.3, MeOH). Found (%): C, 62.03; H, 4.37; N, 6.11. $C_{34}H_{29}Cl_2N_3NiO_3$. Calculated (%): C, 62.10; H, 4.41; N, 6.39. ^{1}H NMR, δ: 1.71 (m, 1 H, β-H Pro); 1.88 (m, 1 H, γ-H Pro); 2.30 (m, 3 H, γ-H, β-H, δ-H Pro); 2.82, 3.08 (AB part of an ABX system, 2 H, CH_2 Phe, $J_{A,B}$ = 13.6 Hz, $J_{A,X}$ = 5.6 Hz, $J_{B,X}$ = 4.0 Hz); 3.00—3.22 (m, 2 H, α-H, δ-H Pro); 3.11, 4.16 (AB system, 2 H, NC$\underline{H}_2$Ph, $J_{A,B}$ = 12.4 Hz); 4.28 (X part of an ABX system, 1 H, α-H Phe); 6.65 (m, 2 H, Ar); 6.80 (m, 1 H, Ar); 7.10—7.68 (m, 12 H, Ar); 8.12 (m, 1 H, Ar); 8.89 (s, 1 H, Ar).

(*S*)-5a. Yield 74%, m.p. 327 °C, $[\alpha]_D^{25}$ +2821 (*c* 0.3, MeOH). Found (%): C, 57.85; H, 4.70; N, 6.89. $C_{28}H_{25}Cl_2N_3NiO_3$. Calculated (%): C, 57.87; H, 4.34; N, 7.23. ^{1}H NMR, δ: 1.61 (d, 3 H, Me Ala, *J* = 7.0 Hz); 2.09 (m, 1 H, γ-H Pro); 2.29 (m, 1 H, β-H Pro); 2.63 (m, 1 H, γ-H Pro); 2.75 (m, 1 H, β-H Pro); 3.43 (m, 1 H, α-H Pro); 3.59 (m, 1 H, δ-H Pro); 3.77 (m, 1 H, δ-H Pro); 3.94 (m, 1 H, α-H Ala); 4.32, 4.35 (AB system, 2 H, NC$\underline{H}_2$Ar, $J_{A,B}$ = 12.5 Hz); 6.65 (m, 2 H, Ar); 6.92 (m, 1 H, Ar); 7.17 (m, 1 H, Ar); 7.32—7.57 (m, 5 H, Ar); 7.82 (m, 1 H, Ar); 8.00 (m, 1 H, Ar); 8.84 (s, 1 H, Ar).

Alkylation of complexes 6b,c with BnBr. These reactions (for reaction conditions, see above) afford bis-alkylated products, *i.e.*, complexes of α-aminoisobutyric acid **8b,c** (with a 15% impurity of the initial glycine complex according to ^{1}H NMR data).

(*S*)-{({2-[1-(Pentafluorobenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-2-benzylphenylalaninato-*N*,*N*′,*N*″,*O*}nickel(II) (8b). Yield 78%. ^{1}H NMR, δ: 1.63—1.84 (m, 1 H, γ-H Pro); 2.03—2.22 (m, 1 H, β-H Pro); 2.23—2.41 (m, 1 H, γ-H Pro); 2.42—2.65 (m, 3 H, β-H, δ-H Pro); 2.62, 3.29 (AB system, 2 H, C$\underline{H}_2$Ph, $J_{A,B}$ = 16.6 Hz); 3.02, 3.12 (AB system, 2 H, C$\underline{H}_2$Ph, $J_{A,B}$ = 10.0 Hz); 3.83, 4.76 (AB system, 2 H, NC$\underline{H}_2$Ar, $J_{A,B}$ = 13.2 Hz); 3.52—3.64 (m, 1 H, α-H Pro); 6.52—7.53 (m, 18 H, Ar); 8.26 (m, 1 H, Ar).

(*S*)-{({2-[1-(4-Isopropoxytetrafluorobenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-2-benzylphenylalaninato-*N*,*N*′,*N*″,*O*}nickel(II) (8c). Yield 74%. ^{1}H NMR, δ: 1.22—1.31 (m, 6 H, CH$\underline{Me}_2$); 1.50—1.64 (m, 1 H, γ-H Pro); 1.64—2.05 (m, 2 H, β-H, γ-H Pro); 2.11—2.46 (m, 3 H, β-H, δ-H Pro); 2.51, 3.61 (AB system, 2 H, C$\underline{H}_2$Ph, $J_{A,B}$ = 17.5 Hz); 3.00, 3.16 (AB system, 2 H, C$\underline{H}_2$Ph, $J_{A,B}$ = 14.6 Hz); 3.61, 4.50 (AB system, 2 H, NC$\underline{H}_2$Ar, $J_{A,B}$ = 13.2 Hz); 4.51 (m, 1 H, $Me_2C\underline{H}O$); 6.49—7.63 (m, 18 H, Ar); 7.96 (m, 1 H, Ar).

2-Benzylphenylalanine was isolated from complexes **8b,c** in 68% yield, m.p. 288—290 °C. Found (%): C, 72.93; H, 6.63; N, 5.11. $C_{16}H_{18}NO_2 \cdot 0.5\ H_2O$. Calculated (%): C, 72.73; H, 6.59; N, 5.30. ^{1}H NMR (D_2O), δ: 2.86, 3.23 (AB system, 4 H, C$\underline{H}_2$Ph, $J_{A,B}$ = 14.4 Hz); 6.94—7.12 (m, 10 H, Ar).

Alkylation of complexes 5 with alkyl halides (general procedure). The reaction was carried out by a procedure similar to that described above for the alkylation of complexes **6**. Complex **5a** (0.34 mmol), DMF (1 mL), alkyl halide (0.68 mmol), and NaH (0.041 g, 1.02 mmol) were used. After completion of the reaction (2 h), the reaction mixture was neutralized with AcOH, diluted with water, and extracted with $CHCl_3$ (3×10 mL). The chloroform extracts were concentrated and the residue was treated with hexane (to remove traces of the alkylating reagent) and Et_2O. The precipitate was filtered off.

(*S*)-{({2-[1-(3,4-Dichlorobenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*S*)-2-benzylalaninato-*N*,*N*′,*N*″,*O*}nickel(II) ((*S*)-9a). Yield 0.17 g (85%) (96% degree of conversion according to ^{1}H NMR spectroscopy), m.p. 191 °C, $[\alpha]_D^{25}$ +1860 (*c* 0.3, MeOH). Found (%): C, 62.76; H, 4.75; N, 6.18. $C_{35}H_{31}Cl_2N_3NiO_3$. Calculated (%): C, 62.59; H, 4.62; N, 6.30. ^{1}H NMR, δ: 1.15 (s, 3 H, Me α-MePhe); 1.55—1.78 (m, 1 H, β-H Pro); 1.80—1.89 (m, 1 H, γ-H Pro); 2.00—2.12 (m, 1 H, β-H Pro); 2.15—2.39 (m, 2 H, γ-H, δ-H Pro); 3.07—3.25 (m, 4 H, α-H, δ-H Pro, CC$\underline{H}_2$Ph); 3.19, 4.16 (AB system, 1 H, NC$\underline{H}_2$Ar, $J_{A,B}$ = 13.0 Hz); 6.57—6.70 (m, 2 H, Ar); 6.79 (m, 1 H, Ar); 7.10—7.65 (m, 12 H, Ar); 8.05 (m, 1 H, Ar); 8.95 (s, 1 H, Ar).

(*S*)-{({2-[1-(4-Isopropoxytetrafluorobenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*S*)-2-benzylalaninato-*N*,*N*′,*N*″,*O*}nickel(II) ((*S*)-9c). Yield 77%. ^{1}H NMR, δ: 1.15 (s, 3 H, Me α-MePhe); 1.32 (m, 6 H, $\underline{Me}_2$CHO); 1.48—1.76 (m, 2 H, β-H, γ-H Pro); 1.77—2.10 (m, 1 H, γ-H Pro); 2.21—2.48 (m, 2 H, β-H, δ-H Pro); 2.91—3.29 (m, 2 H, α-H, δ-H Pro); 3.05 (s, 2 H, C$\underline{H}_2$Ph); 4.04, 4.13 (AB system, 2 H, NC$\underline{H}_2$Ar, $J_{A,B}$ = 13.5 Hz); 4.41—4.68 (m, 1 H, $Me_2C\underline{H}O$); 6.66 (m, 2 H, Ar); 7.05 (m, 1 H, Ar); 7.19—7.61 (m, 10 H, Ar); 8.35 (m, 1 H, Ar).

(*S*)-{({2-[1-(4-Methoxytetrafluorobenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*S*)-2-benzylalaninato-*N*,*N*′,*N*″,*O*}nickel(II) ((*S*)-9d). Yield 81%. ^{1}H NMR, δ: 1.14 (s, 3 H, Me α-MePhe); 1.51—1.74 (m, 2 H, β-H, γ-H Pro); 1.77—2.14 (m, 1 H, γ-H Pro); 2.23—2.45 (m, 2 H, β-H, δ-H Pro); 2.89—3.32 (m, 2 H, α-H, δ-H Pro); 3.08 (s, 2 H, C$\underline{H}_2$Ph); 3.91, 4.19 (AB system, 2 H, NC$\underline{H}_2$Ar, $J_{A,B}$ = 13.2 Hz); 3.98 (s, 3 H, OMe); 6.65 (m, 2 H, Ar); 6.95 (m, 1 H, Ar); 7.17—7.51 (m, 10 H, Ar); 8.29 (m, 1 H, Ar).

(*S*)-{({2-[1-(4-Methoxytetrafluorobenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*S*)-2-ethylalaninato-*N*,*N*′,*N*″,*O*}nickel(II) ((*S*)-10d). Yield 35%. ^{1}H NMR, δ: 1.19 (s, 3 H, α-Me Iva); 1.50 (m, 3 H, $MeCH_2$, Iva); 1.71 (m, 2 H, $MeC\underline{H}_2$, Iva); 1.81—1.94 (m, 1 H, γ-H Pro); 2.07—2.21 (m, 1 H, β-H Pro); 2.55—2.69 (m, 1 H, γ-H Pro); 2.88—3.03 (m, 1 H, β-H Pro); 3.19—3.39 (m, 2 H, α-H, δ-H Pro); 3.40—3.49 (m, 1 H, δ-H Pro); 4.03 (s, 3 H, OMe); 4.13, 4.36 (AB system, 2 H, NC$\underline{H}_2$Ar, $J_{A,B}$ = 13.4 Hz); 6.68 (m, 2 H, Ar); 6.97 (m, 1 H, Ar); 7.15—7.55 (m, 5 H, Ar); 8.17 (m, 1 H, Ar).

X-Ray diffraction study of complex (*S*)-5a. The crystals ($C_{28}H_{25}Cl_2N_3NiO_3$, M = 581.12) are orthorhombic, space group $P2_12_12_1$; at T = 153 K, a = 9.136(3) Å, b = 10.734(3) Å, c = 26.338(7) Å, V = 2583.0(13) Å^3, Z = 4, d_{calc} = 1.494 g cm^{-3}, μ = 0.994 mm^{-1}. The unit cell parameters and the intensities of 3424 reflections were measured on a Syntex $P2_1$ four-circle automated diffractometer (153 K, Mo-Kα radiation, graphite monochromator, θ/2θ scan mode, θ_{max} = 28°). The structure was solved by the direct method and refined by the full-matrix least-squares calculations in the anisotropic approximation for nonhydrogen atoms. The chlorine atom Cl(2) is disordered over two positions with occupancies of 0.8 and 0.2, which implies the presence in the crystal of two rotational conformers with respect to the dichlorophenyl substituent. The positions of H atoms were calculated geometrically and refined in the isotropic approximation with fixed positional (the riding model) and thermal parameters ($U_{iso}(H) = 1.5U_{eq}(C)$ for Me groups and $U_{iso}(H) = 1.2U_{eq}(C)$ for other groups). The absolute configuration was determined objectively by refining the Flack parameter, which is equal to 0.06(2). The final discrepancy factors were R_1 = 0.0428 for 2731 independent reflections with $I > 2\sigma(I)$ and wR_2 = 0.0989 for 3361 independent reflections. All calculations were carried out using the SHELXTL PLUS program package (Version 5.0).[32] The coordinates and anisotropic parameters of atoms, the bond lengths, and the bond and torsion angles for compound (*S*)-**5a** are deposited in the Cambridge Structural Database.

This work was supported by the International Scientific and Technical Center (Grant ISTC A-356), the US Civilian Research and Development Foundation (Grant CRDF RC-1-2205), and the Russian Foundation for Basic Research (Project No. 99-03-32970).

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Received June 21, 2001;
in revised form March 11, 2002