Asymmetric Synthesis of Organoelement Analogues of Natural Products; Part 12: General Method for the Asymmetric Synthesis of Fluorine-Containing Phenylalanines and α-Methyl(phenyl)alanines via Alkylation of the Chiral Nickel(II) Schiff's Base Complexes of Glycine and Alanine

Valeri P. Kukhar',[a] Yuri N. Belokon',[b] Vadim A. Soloshonok,[a] Nataly Yu. Svistunova,*[a] Alexander B. Rozhenko,[a] Nadezhda A. Kuz'mina[b]

[a] Institute of Bioorganic Chemistry and Oil Chemistry of the Ukrainian Academy of Sciences, 253160 Kiev, Ukraine
[b] A.N. Nesmeyanov Institute of Organoelement Compounds, Academy of Sciences, Moscow, Russia

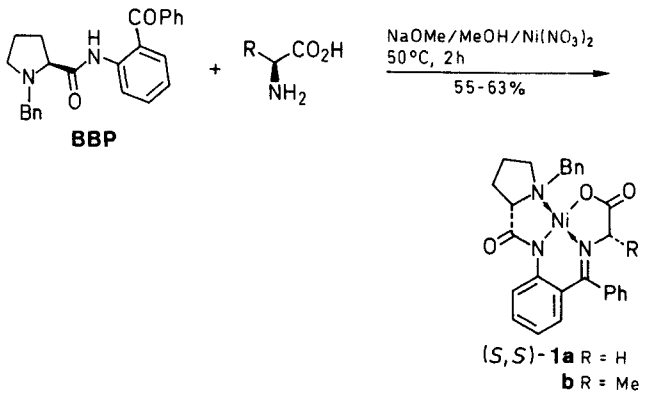
Received 13 January 1992

Nickel(II) complexes of Schiff's bases derived from (*S*)-*o*-[(*N*-benzyl]prolyl)amino]benzophenone [*N*-(2-benzoylphenyl)-1-benzylpyrrolidine-2-carboxamide] **(BBP)** and glycine or alanine have been used for asymmetric synthesis of fluoro (*S*)-phenylalanines and (*S*)-α-methyl(phenyl)alanines. Large selectivity (> 90 %) is observed for the alkylation of both complexes **1a** and **1b**. The optically pure fluoro phenylalanines are obtained after the alkylated diastereoisomeric complexes had been separated on silica gel and hydrolyzed with aqueous hydrogen chloride.

Fluoro phenylalanines and their derivatives have numerous biological uses. They are important because of their pharmaceutical properties and their ability to serve as building blocks for physiologically active peptides.[1] In all these applications enantiomerically pure fluoro phenylalanines are needed. The most significant results for the preparation of fluoro phenylalanines in optically active form were achieved by enzymatic resolution of racemic mixtures.[2] Only a few reports concerning the asymmetric synthesis of these compounds have been reported, among which the achievement of Seebach and his collegues should be mentioned.[3]

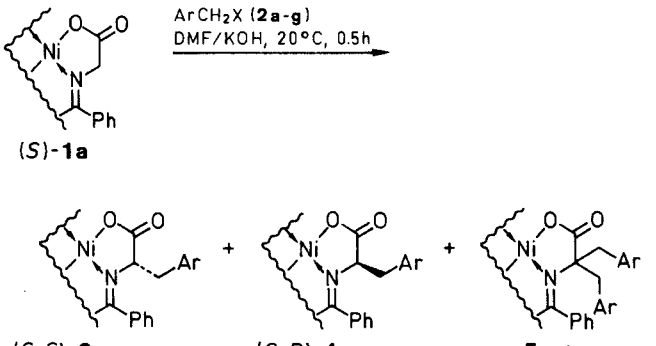
The present work describes a general method for the asymmetric synthesis of fluorine-containing phenylalanines and their α-methyl-substituted analogues via benzyl halide alkylation of glycine and alanine as their chiral Nickel(II) complexes with the Schiff's bases formed from them and a chiral auxiliary **BBP** (see Scheme 1).

The starting complexes **1a,b** were prepared in good yield by the reaction between **BBP**, Nickel(II) ions and glycine or (*S*)-alanine according to the previously reported procedure (Scheme 1).



Scheme 1

The reactions of **1** with benzyl halides **2a–g** was performed in dimethylformamide at 25 °C using solid potassium hydroxide as a catalyst. The reaction course was monitored by TLC plates (silica gel). The carbanion generated from complex **1** by the action of potassium hydroxide reacted with the corresponding benzyl halide **2a–g**, yielding a mixture of the corresponding diastereoisomeric complexes, as shown in Scheme 2.



2–5	Ar	2–5	Ar
a	4-FC_6H_4	**e**	2-F, 4-BrC_6H_3
b	3-FC_6H_4	**f**	C_6F_5
c	2-FC_6H_4	**g**	2-F, 6-ClC_6H_3
d	3-$F_3CC_6H_4$		

Scheme 2

After the starting material **1** had been consumed (30 minutes) the reaction mixture was quenched with aqueous acetic acid and precipitated products were filtered off. In some cases diastereoisomeric complexes **3**, **4** and **5** were obtained in diastereo- and enantiomerically pure form by flash chromatography (silica gel), in other ones the ratio of **3–5** were determinated by fluorine and proton NMR analysis of the mixture **3–5**. The main experimental results are given in Table 1.

According to these data, the chemical yields and the ratio of formed diastereoisomeric complexes **3**, **4** and dialkylated products **5** was not influenced by the nature of the corresponding benzyl halides.

The absolute configuration of the α-amino acid residues in complexes **3** and **4** were established according to the shapes of the ORD curves of compound **3** or **4** (see Figure). The sign of the Cotton effect in the 500–700 nm region was always positive for *S* or L α-amino acids and negative for their enantiomers. This general trend was not influenced by the structure of the α-amino acid side chain.[4]

Table 1. Complexes **3–5** and **7** Prepared

Product	Yield[a] (%)	mp (°C)	Molecular Formula[b]	$[\alpha]_D^{20}$ (*c*, MeOH)	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{19}F NMR ($CDCl_3$/$CFCl_3$) δ, *J* (Hz)
3a	72[c]	260–263	$C_{34}H_{30}FN_3NiO_3$ (606.3)	+2589.9 (0.07)	1.66–3.22 (m, 7H, Pro H's), 2.95, 3.19 (ABX, 2H, ^2J = 13.0, $^3J_{AX}$ = 4.5, $^3J_{BX}$ = 5.5, CH_2), 3.50, 4.29 (AB, 2H, $^2J_{AB}$ = 12.0, CH_2), 4.25 (m, 1H, CH), 6.65–8.29 (m, 18H$_{arom}$)	−114.0 (m, F_{arom})
3b	70[c]	163–168	$C_{34}H_{30}FN_3NiO_3$ (606.3)	+2401.2 (0.08)	1.70–3.33 (m, 7H, Pro H's), 2.85, 3.08 (ABX, 2H, $^2J_{AB}$ = 13.5, $^3J_{AX}$ = 6.0, $^3J_{BX}$ = 4.45, CH_2), 3.50, 4.30 (AB, 2H, $^2J_{AB}$ = 12.0, CH_2), 4.25 (m, 1H, CH), 6.69–8.25 (m, 18H$_{arom}$)	−111.3 (m, F_{arom})
3c	71[c]	214–217	$C_{34}H_{30}FN_3NiO_3$ (606.3)	+2516.3 (0.09)	1.75–3.36 (m, 7H, Pro H's), 2.83, 3.05 (ABX, 2H, $^2J_{AB}$ = 13.2, $^3J_{AX}$ = 5.4, $^3J_{BX}$ = 4.2, CH_2), 3.48, 4.30 (AB, 2H, $^2J_{AB}$ = 12.2), 4.25 (m, 1H, CH), 6.68–8.23 (m, 18H$_{arom}$)	−114.11 (m, F_{arom})
3d	68[d]	65–70	$C_{35}H_{30}F_3N_3NiO_3$ (656.3)	+1952.3 (0.04)	1.71–3.34 (m, 7H, Pro H's), 2.84, 3.05 (ABX, 2H, $^2J_{AB}$ = 13.3, $^3J_{AX}$ = 5.5, $^3J_{BX}$ = 4.2, CH_2), 3.49, 4.31 (AB, 2H, $^2J_{AB}$ = 12.6, CH_2), 4.24 (m, 1H, CH), 6.69–8.22 (m, 18H$_{arom}$)	−63.6 (s, CF_3)
3e	76[d]	60–65	$C_{34}H_{29}BrFN_3NiO_3$ (699.2)	+1904.8 (0.04)	1.76–3.34 (m, 7H, Pro H's), 2.84, 3.09 (ABX, 2H, $^2J_{AB}$ = 13.3, $^3J_{AX}$ = 5.5, $^3J_{BX}$ = 4.1, CH_2), 3.44, 4.35 (AB, 2H, $^2J_{AB}$ = 12.5), 4.23 (m, 1H, CH), 6.69–8.20 (m, 17H$_{arom}$)	−113.6 (m, F_{arom})
3f	84[d]	134–141	$C_{34}H_{26}F_5N_3NiO_3$ (678.3)	+2341.9 (0.08)	1.71–3.31 (m, 7H, Pro H's), 2.88, 3.11 (ABX, 2H, $^2J_{AB}$ = 13.5, $^3J_{AB}$ = 6.1, $^3J_{BX}$ = 4.5, CH_2), 3.51–4.30 (AB, 2H, $^2J_{AB}$ = 12.3, CH_2), 4.27 (m, 1H, CH), 6.68–8.26 (m, 14H$_{arom}$)	−141.6 (m, 2F_{arom}), −155.9 (m, 1F_{arom}), −163.8 (m, 2F_{arom})
3g	69[d]	85–90	$C_{34}H_{29}ClFN_3NiO_3$ (640.7)	+1786.9 (0.05)	1.67–3.35 (m, 7H, Pro H's), 2.83, 3.14 (ABX, 2H, $^2J_{AB}$ = 13.6, $^3J_{AX}$ = 6.0, $^3J_{BX}$ = 4.4, CH_2), 3.51–4.40 (AB, 2H, $^2J_{AB}$ = 12.6, CH_2), 4.25 (m, 1H, CH), 6.69–8.30 (m, 17H$_{arom}$)	−112.5 (m, F_{arom})
4c	3[d]	224–228	$C_{34}H_{30}FN_3NiO_3$ (606.3)	−1297.3 (0.11)	1.60–3.85 (m, 7H, Pro H's), 2.88, 3.21 (ABX, 2H, $^2J_{AB}$ = 13.5, $^3J_{AX}$ = 3.0, $^3J_{BX}$ = 6.0, CH_2), 3.45, 3.92 (AB, 2H, $^2J_{AB}$ = 13.5, CH_2), 4.26 (dd, 1H, $^3J_{HH}$ = 3.0, $^3J_{HH}$ = 6.0, CH), 6.80–8.52 (m, 18H$_{arom}$)	−113.6 (m, F_{arom})
5a	3[d]	204–210	$C_{41}H_{35}F_2N_3NiO_3$ (714.4)	+1880.0 (0.1)	2.02–3.20 (m, 7H, Pro H's), 2.75, 3.26 (AB, 2H, $^2J_{AB}$ = 16.5, CH_2), 2.98–3.13 (AB, 2H, $^2J_{AB}$ = 14.0, CH_2), 3.26, 4.26 (AB, 2H, $^2J_{AB}$ = 12.0, CH_2), 6.55–8.07 (m, 22H$_{arom}$)	−113.9 (m, 1F_{arom}), −115.1 (m, 1F_{arom})
5b	4[d]	125–129	$C_{41}H_{35}F_2N_3NiO_3$ (714.4)	+1937.0 (0.07)	2.25–3.23 (m, 7H, Pro H's), 2.78, 3.30 (AB, 2H, $^2J_{AB}$ = 16.5, CH_2), 3.02, 3.13 (AB, 2H, $^2J_{AB}$ = 14.0, CH_2), 3.32, 4.33 (AB, 2H, $^2J_{AB}$ = 12.0, CH_2), 6.56–8.08 (m, 22H$_{arom}$)	−110.8 (m, 1F_{arom}), −111.4 (m, 1F_{arom})
7a	63[d]	95–100	$C_{35}H_{32}FN_3NiO_3$ (620.4)	+1976.9 (0.15)	1.15 (s, 3H, Me), 1.68–3.25 (m, 7H, Pro H's), 3.10 (m, 2H, CH_2), 3.55, 4.30 (AB, 2H, $^2J_{AB}$ = 12.0, CH_2), 6.60–8.13 (m, 18H$_{arom}$)	−114.0 (m, F_{arom})
7b	70[d]	130–133	$C_{35}H_{32}FN_3NiO_3$ (620.4)	+1925.7 (0.09)	1.18 (s, 3H, Me), 1.65–3.20 (m, 7H, Pro H's), 3.11 (m, 2H, CH_2), 3.60, 4.31 (AB, 2H, $^2J_{AB}$ = 12.0, CH_2), 6.60–8.20 (m, 18H$_{arom}$)	−111.1 (m, F_{arom})
7c	72[d]	143–147	$C_{35}H_{32}FN_3NiO_3$ (620.4)	+1939.8 (0.13)	1.10 (s, 3H, Me), 1.63–3.30 (m, 7H, Pro H's), 3.03, 3.50 (AB, 2H, $^2J_{AB}$ = 13.5, CH_2), 3.60, 4.30 (AB, 2H, $^2J_{AB}$ = 12.5, CH_2), 6.51–8.23 (m, 18H$_{arom}$)	−112.5 (m, F_{arom})

[a] Yield and physical properties of crude products. Products have been shown to be pure by TLC (eluent: $CHCl_3$/acetone, 4 : 1) and ^{1}H NMR spectra.

[b] Satisfactory microanalysis obtained: C, H, F, N ± 0.4.

[c] Obtained by recrystallization of a mixture of **3–5** from H_2O/acetone (5 : 1).

[d] Obtained by chromatographic separation of the mixture **3–5** on a silica gel column using as eluent $CHCl_3$/acetone (5 : 1).

As expected[4] a large excess (90% de) (*S,S*)-**3** isomers over the (*S,R*)-**4** and bisalkylation products **5** was obtained.

To make the reaction synthetically useful two problems had to be solved: firstly, bisalkylation had to be eliminated or minimized; secondly, optically pure phenylalanines should be the final products of the synthesis.

Thus, if the ratio of the benzyl halide **2**/complex **1a** was not greater than 1.2 : 1.0, yield of bisalkylation products was almost 5%. Decrease of the ratio **2**/**1a** to 1.0 resulted in the disappearance of products **5** by NMR analysis as well as incomplete conversion of starting complex **1**. Optimum results were achieved with the ratio of **2**/**1a** as 1.15 : 1.0. In this case the yield of bisalkylation products **5**

Table 2. Amino Acids **6** and **9** Prepared

Product	Yield[a] (%)	mp (°C)	$[\alpha]_D^{25}$ (*c*, H_2O)	Molecular Formula[b] or Lit. $[\alpha]_D$ (*c*, H_2O)	^1H NMR (D_2O/TMS) δ, *J* (Hz)	^{19}F NMR (D_2O/$CFCl_3$) δ
6a	83	252–255	−26.9 (0.3)	−23.0 (2)[2]	3.18, 3.29 (ABX, 2H, $^2J_{AB}$ = 14.5, $^3J_{AX}$ = 7.8, $^3J_{BX}$ = 5.6, CH_2), 3.24 (dd, 1H, *J* = 7.8, 5.6, CH), 7.50–7.68 (m, $4H_{arom}$)	−113.9 (m, F_{arom})
6b	95	240–245	−27.0 (0.2)	−24.0 (2)[2]	3.20, 3.30 (ABX, 2H, $^2J_{AB}$ = 14.3, $^3J_{AX}$ = 7.7, $^3J_{BX}$ = 6.0, CH_2), 3.26 (dd, 1H, *J* = 7.7, *J* = 5.9, CH), 7.54–7.60 (m, $4H_{arom}$)	−111.6 (m, F_{arom})
6c	94	208–210	−14.3 (0.2)	−15.0 (2)[2]	3.24, 3.30 (ABX, 2H, $^2J_{AB}$ = 13.9, $^3J_{AX}$ = 8.0, $^3J_{BX}$ = 6.1, CH_2), 3.25 (dd, 1H, *J* = 8.0, 6.0, CH), 7.55–7.66 (m, $4H_{arom}$)	−114.5 (m, F_{arom})
6d	87	243–245	+21.5 (0.2)	+21.3 (0.3)[3] +22.4 (1.0)[2]	3.15,[c] 3.33 (ABXY$_2$, 2H, $^2J_{HH}$ = 14.0, $^3J_{HH}$ = 9.2, $^3J_{HH}$ = 5.4, $^4J_{HF}$ = 1.2, CH_2), 4.16 (dd, 1H, *J* = 9.2, 5.4, CH)	−143.0 (m, $2F_{arom}$) −159.3 (m, $1F_{arom}$), −162.2 (m, $2F_{arom}$)
9a	91	289–292	−14.8 (0.3)	$C_{10}H_{12}FNO_2$ (197.2)	1.25 (s, 3H, Me), 3.0 (m, 2H, CH_2), 7.0–7.1 (m, $4H_{arom}$)	−114.5 (m, F_{arom})
9b	80	298–300	−21.7 (0.3)	$C_{10}H_{12}FNO_2$ (197.2)	1.55 (s, 3H, Me), 3.05, 3.31 (AB, 2H, *J* = 13.5, CH_2), 7.0–7.3 (m, $4H_{arom}$)	−111.7 (m, F_{arom})
9c	85	300–303	−17.3 (0.1)	$C_{10}H_{12}FNO_2$	1.31 (s, 3H, Me), 2.85, 3.08 (AB, 2H, *J* = 12.0, CH_2), 6.9–7.1 (m, $4H_{arom}$)	−113.8 (m, F_{arom})

[a] Yield of isolated product **6** or **9** based on the corresponding complexes **3** or **7**.

[b] Satisfactory microanalyses obtained: C, H, F, N ± 0.3.

[c] HCl salt.

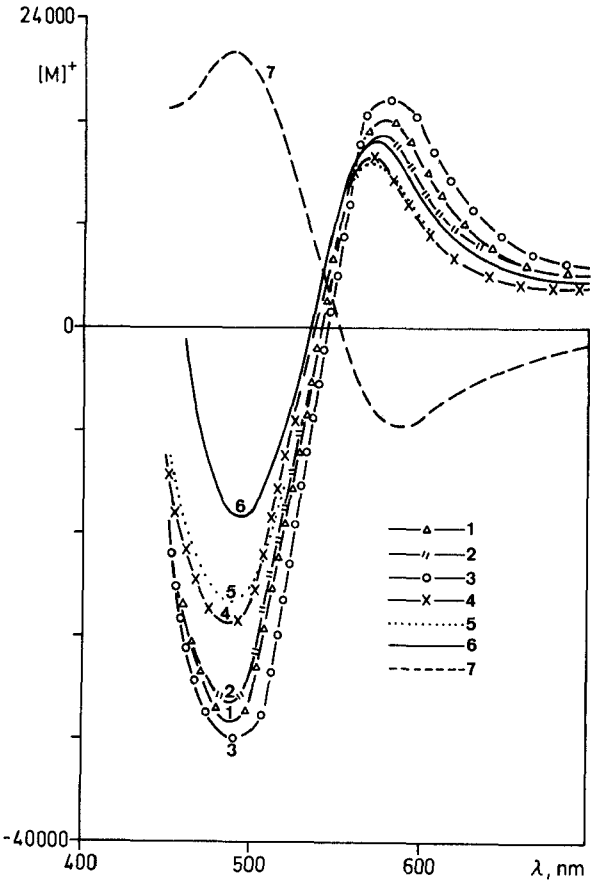
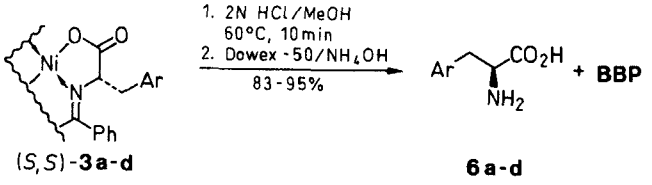


Figure. ORD curves (25°C; MeCN) of some Ni(II) complexes: 1 (*S*)-2-fluorophenylalanine (**3c**); 2 (*S*)-3-fluorophenylalanine (**3b**); 3 (*S*)-4-fluorophenylalanine (**3a**); 4 (*S*)-α-methyl-(4-fluorophenyl)alanine (**7c**); 5 (*S*)-α-methyl-(3-fluorophenyl)alanine (**7b**); 6 (*S*)-α-methyl-(2-fluorophenyl)alanine (**7a**); 7 (*R*)-(2-fluorophenyl)alanine (**4c**).

was not greater than 1–2% (within the limits of NMR analysis) and conversion of complex **1a** was not less than 95%.

The preparation of fluorine-containing phenylalanines in optically pure form using two different procedures was examined. Additional chromatographic separation of the diastereoisomeric complexes (*S,S*)-**3**, (*S,R*)-**4** and bisalkylation products **5** allowed us to obtain the desired enantio- and diastereoisomerically pure complexes (*S*)-**3**. Optically pure (fluorophenyl)alanines can be easily obtained from the optically pure complexes (*S,S*)-**3**, after decomposition of the latter with aqueous hydrogen chloride (Scheme 3), while the chiral auxiliary **BBP** was recovered; this is illustrated by the (*S*)-(2-, (*S*)-(3- and (*S*)-(4-fluorophenyl)alanine synthesis.

Enantiomerically pure amino acids **6** can also be obtained by recrystallization of a mixture of amino acids, prepared from the mixture of the complexes **3**–**5**, this is illustrated by the (*S*)-(pentafluorophenyl)alanine synthesis.



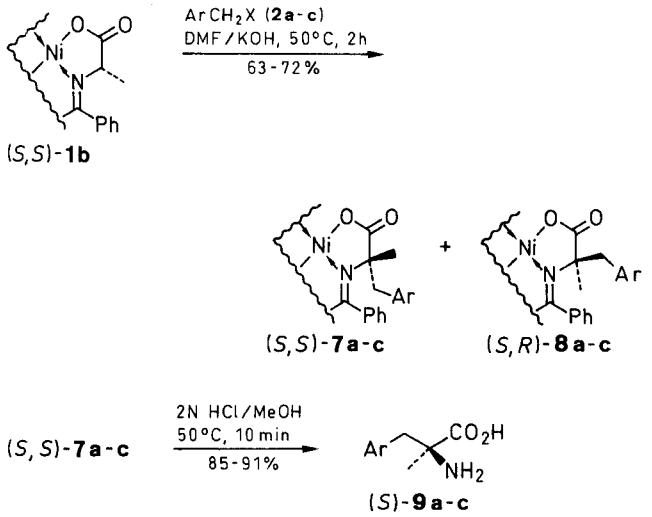
3, 6	a	b	c	d
Ar	2-FC_6H_4	3-FC_6H_4	4-FC_6H_4	C_6F_5

Scheme 3

Alkylation of complexes (*S,S*)-**1b** with corresponding benzyl halides was carried out under the conditions which were employed for the alkylation of complex (*S*)-**1a**. But, in this case, the reaction was sluggish and for a successful result a greater excess of the alkylating agent was needed (Scheme 4). The ratio of diastereoisomers **7**, **8** formed was

not sensitive to the diastereoisomeric purity of the starting material **1b** and was greatly in favor of an corresponding (*S*)-phenylalanine containing isomer; diastereoisomeric excess was $\geqslant 90\%$ (Table 1). Optically pure α-methyl(fluorophenyl)alanines **9** could be obtained after the separation of the alkylated isomers on silica gel. The absolute configuration of the amino acids was established on the basis of the ORD curves of the corresponding complexes (see Figure).

Optically pure fluorinated α-methyl(phenyl)alanines **9a–c** can be easily obtained from the corresponding pure complexes **7a–c** by treatment of the latter with aqueous hydrogen chloride in methanol (Scheme 4).



7–9	a	b	c
Ar	2-FC_6H_4	3-FC_6H_4	4-FC_6H_4

Scheme 4

In summary, a simple, reliable high yield method for the synthesis of fluorinated phenylalanines, as well as α-methyl(phenyl)alanines has been developed. Additional purification of diastereoisomeric complexes by preparative flash chromatography ensures more than 99% optical purity of the amino acids prepared. The procedures described provide a means for obtaining a variety of relatively large quantities of optically pure fluorinated phenylalanines from readily synthesized or commercially available starting materials.

Reagents were purchased from Reakhim (Russia), with the exception of silica gel F_{254} purchased from Merck, Sephadex LH-20 from Pharmacia and silica gel L 40/100 obtained from Chemapol. Reagents and solvents were purified in the usual way. Initial complexes **1a,b** were available from previous work.[5]

Melting points were taken in open capillaries and are uncorrected. ^1H NMR and ^{19}F NMR spectra were recorded on a Bruker WP-200 und Varian VXR-300 instruments using TMS and $CFCl_3$ as internal references in $CDCl_3$ solutions and HMDS and TFA sealed in a glass capillary for D_2O solutions. Assignments of protons in the complexes under study were made by decoupling each, separatively observable proton multiplet and observing the collapse of the splitting produced. ORD curves were recorded on Jasco ORD/UV-5 instrument, specific rotations were measured on a Perkin-Elmer 241 polarimeter.

Reaction of Complex 1a with Fluorinated Benzyl Halides 2; General Procedure:

Corresponding benzyl halide **2a–g** (16 mmol, 1.1 equiv) was added to complex **1a** (6.972 g, 14 mmol) in DMF (10 mL) followed by addition of finely ground KOH (1.960 g, 35 mmol, 2.5 equiv) with vigorous stirring under N_2. Stirring was continued for 30 min after which the mixture was added slowly, with stirring, to a solution of AcOH (0.1 mol) in H_2O (200 mL). The precipitated thick, red suspension of diastereoisomeric complexes was filtered off, washed with H_2O several times and dried in vacuo (filtration could be substituted with $CHCl_3$ extraction followed by evaporation of the solvent) (Table 1).

Reaction of Complex 1b with Fluorinated Benzyl Halides 2; General Procedure:

Corresponding benzyl halide **2a–c** (3.5 mmol, 3.5 equiv) was added to complex **1b** (0.510 g, 1 mmol) in DMF (3 mL) followed by addition of finely ground KOH (0.280 g, 5 mmol, 5 equiv) with vigorous stirring under N_2. Stirring was continued for 2 h after which the mixture was added to a solution of AcOH (10 mmol) in H_2O (200 mL). Diastereoisomeric complexes were extracted with $CHCl_3$ followed by evaporation of the solvent. The residue was subjected to chromatography on silica gel (3.5 × 30 cm, $CHCl_3$/acetone, 5:1). Two major fractions were obtained. The second fraction containing (*S*)-**7** was further purified on Sephadex LH-20 (benzene/EtOH, 3:1) (Table 1).

Isolation of Amino Acids from the Complexes (*S*)-3a–d, (*S*)-7a–c and Recovery of Chiral Auxiliary (BBP); General Procedure:

2 N aq HCl (50 mL) was added to a solution of the corresponding complex (7 mmol) in MeOH (50 mL) and the mixture was stirred and refluxed until the red color had disappeared (5–10 min). The solution was then evaporated almost to dryness under reduced pressure when H_2O (20 mL) was added with stirring to the residue. The mixture was then filtered and the precipitate (**BBP** · HCl) washed with H_2O. Amino acids **6a–d**, **9a–c** were isolated from the aqueous layer with Dowex-50 (H^+-form). The optical purity of the amino acids was determined by ligand exchange HPLC on L-proline and L-hydroxyproline sorbents[6] and polarimetry.

(1) Imperiali, B. *Adv. Biotechnol. Proc.* **1988**, *10*, 97.
(2) Bosshard, H.R.; Berger, A. *Helv. Chim. Acta.* **1973**, *56*, 1838.
Bennett, E.L.; Niemann, C.J. *J. Am. Chem. Soc.* **1950**, *72*, 1800.
Tong, I.H.; Petitclerc, C.; D'Iorio, A.; Benoiton, N.L. *Can. J. Biochem.* **1971**, *49*, 877.
Fauchere, J.L.; Schwyzer, R. *Helv. Chim. Acta.* **1971**, *54*, 2078.
(3) Fitzi, R.; Seebach, D. *Tetrahedron* **1988**, *44*, 5277.
(4) Belokon', Yu.N.; Bulychev, A.G.; Vitt, S.V.; Struchkov, Yu.T.; Batsanov, A.S.; Timofeeva, T.V.; Tsyryapkin, V.A.; Ryzhov, M.G.; Lysova, L.A.; Bakhmutov, V.I.; Belikov, V.M. *J. Am. Chem. Soc.* **1985**, *107*, 4252.
(5) Belokon', Yu.N.; Bakhmutov, V.I.; Chernoglazova, N.I.; Kochetkov, K.A.; Vitt, S.V.; Garbalinskaya, N.S.; Belikov, V.M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 305.
(6) Galushko, S.V.; Shishkina, I.P.; Soloshonok, V.A.; Kukhar' V.P. *J. Chromatogr.* **1990**, *511*, 115.