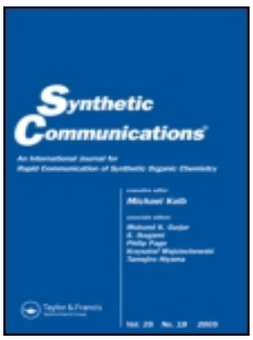

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Diastereoselective Synthesis of Anti-β-Substituted α-Aminobutanoic Acids via Michael Addition Reactions of Nucleophiles to New Chiral Ni(II) Complexes of Dehydroaminobutanoic Acid

A. S. Saghiyan, H. H. Hambardzumyan, L. L. Manasyan, and A. A. Petrosyan
Yerevan State University, Chemistry Department, Faculty of Pharmaceutical Chemistry, Yerevan, Republic of Armenia

V. I. Maleev and A. S. Peregudov
A.N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Moscow, Russia

Abstract: New chiral Ni^{II} complex of the dehydroaminobutanoic acid Schiff base with (*S*)-N-(2-benzoylphenyl)-1-(3,4-dichlorbenzyl)pyrrolidyl-2-carboxamide (CPB) was synthesized and tested as electrophile component in the asymmetric Michael addition reactions with nucleophiles (imidazole, benzylamine, methoxy ion, ethoxy ion). The method of the asymmetric synthesis of β-substituted (*S*)-α-amino acids with high d.e $> 80\%$ was developed.

Keywords: Diastereoselective synthesis, chiral Ni^{II} complex, β-substituted (*S*)-α-amino acids

The synthesis of chiral compounds in optically pure form is one of the basic requirements of modern organic chemistry. This requirement is imposed by

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Address correspondence to A. S. Saghiyan, Yerevan State University, Chemistry Department, Faculty of Pharmaceutical Chemistry, 1 Manukyan, 375025, Yerevan, Republic of Armenia. E-mail: sagysu@netsys.am

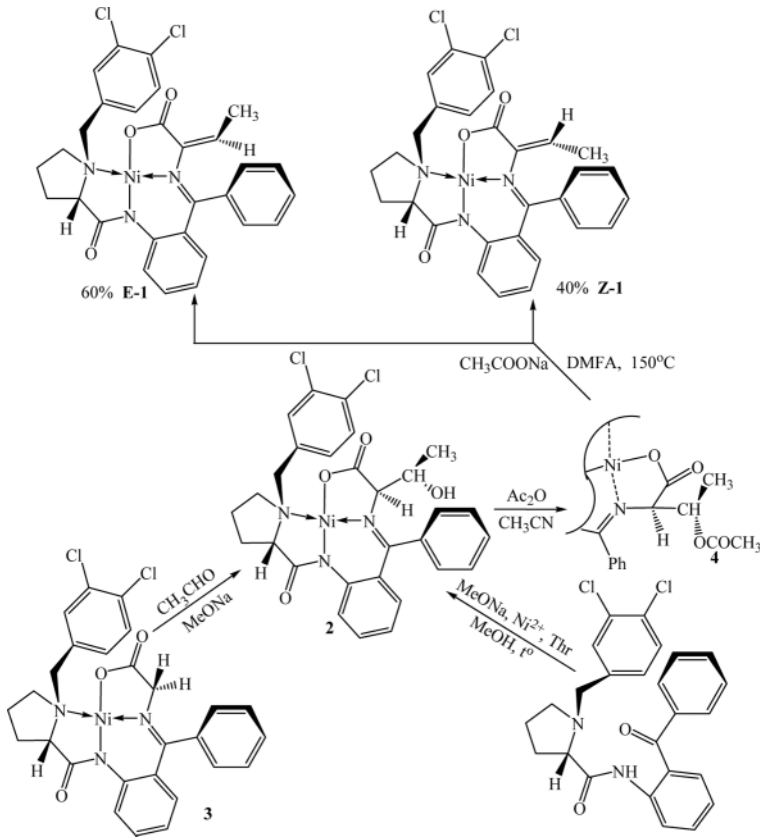
economic and environmental considerations. A major objective of the current research is to obtain enantiomerically pure compounds by asymmetric synthesis, thus avoiding expensive and labor-intensive resolutions of racemic products.[1,2] Among the most useful methods reported up to now are the chiral organic base catalyzed asymmetric C–C bond forming reactions. The asymmetric conjugate addition of organometallic compounds to activated olefins and the asymmetric Michael reactions are among the most important C–C bond-forming synthetic procedures.[3–8] Several diastereoselective Michael additions of organometallic reagents to chiral unsaturated esters,[9] oxazolines,[10] amides,[11] and imides[12] have been successfully reported in the literature.

In the previous work we used a Ni^{II} complex of (*S*)-BPB[13] Schiff's base with dehydroaminobutyric acid as a Michaels acceptor. The stereoselectivity of the addition varied from moderate to good. To improve the protocol we elaborated a new chiral auxiliary (*S*)-N-(2-benzoylphenyl)-1-(3,4-dichlorbenzyl)pyrrolidyl-2-carboxamide (CPB). The Ni^{II} complexes of the Schiff's bases of CPB with glycine and alanine (*Ni^{II}-(S)-CPB-Gly* and *Ni^{II}-(S)-CPB-(S)-Ala* respectively) were synthesized[14] and tested in alkylation's reactions. The enantiomeric excesses of the α-alkylated α-amino acids prepared, using the new chiral auxiliary (*S*)-CPB, exceeded those obtained with (*S*)-BPB.[15]

In this work we present our results on the asymmetric synthesis of β-substituted α-aminobutanoic acids via the chiral Ni^{II} complex, obtained from the Schiff base of (*S*)-N-(2-benzoylphenyl)-1-(3,4-dichlorbenzyl)pyrrolidyl-2-carboxamide (CPB) and *E* and *Z* isomers of dehydroaminobutanoic acid. In this system, the double bond of dehydroaminobutanoic moiety possesses high electrophilicity and reacts with nucleophiles (Michael addition) with the formation of α-aminobutanoic acids with different substituents at β-position.

Complexes of the dehydroaminobutanoic acid Schiff base with chiral auxiliaries and (*S*)-N-(2-benzoylphenyl)-1-(3,4-dichlorbenzyl)pyrrolidyl-2-carboxamide (***E*-1** and ***Z*-1**) were obtained by the dehydratation of (*R*)-threonine moiety in the initial threonine complex **2**, which was prepared from (*S,R*)-Thr, (*S*)-CPB and $Ni(NO_3)_2 \times 6H_2O$ in 0.1N CH_3ONa (CH_3OH) or from the complex **3** by the condensation with CH_3CHO catalyzed by CH_3ONa (see Scheme 1).

Attempts at a direct dehydration of the complex **2** were unsuccessful because of retroaldol fragmentation of the threonine moiety. The threonine moiety in **2** was easily acetylated by acetic anhydride in acetonitrile and as a result *O*-acetylated complex **4** was formed (Scheme 1). Deacylation of the (*R*)-threonine moiety of **4** was promoted with CH_3COONa in dimethylformamide (DMF) at 138°C[13] leading to **1** in a yield of 60% and a ratio of *E*/*Z* isomers–3/2 (Scheme 1). Ratio of ***E***- and ***Z***- isomers was determined by ^{1}H-NMR. The deacetylation of the threonine fragment of complex **4** could

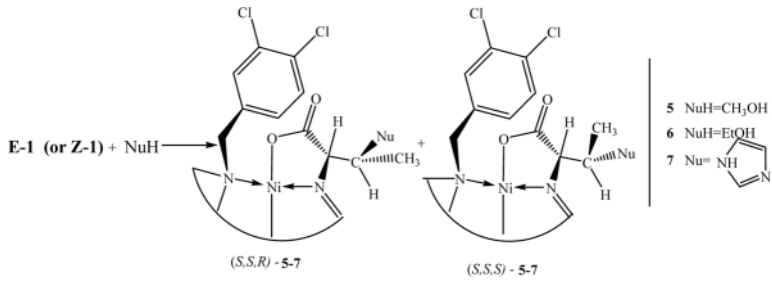


Scheme 1.

be monitored by the ^{1}H-NMR also upon the disappearance of the singlet of acetoxy group at 1.84 ppm and appearance of a doulet of the methylene hydrogen resonances of dehydroaminobutanoic fragment of ***E*-1** and ***Z*-1** at 1.73 ppm and 0.83 ppm, respectively. It is remarkable that no dehydroaminobutanoic acid complexes were formed from the corresponding (*S*)-*O*-acetylthreonine isomer of **4** under the experimental conditions.

All the complexes were isolated and ***E***- and ***Z***-isomers of **1** chromatographically separated on SiO_2. The structures and absolute configurations of all the compounds were established by analogy with the corresponding Ni^{II} complexes of the Schiff bases of BPB and amino acids, including dehydroaminobutanoic acid.

The addition of nucleophiles to the dehydroaminobutanoic acid moiety of ***E*-1** and ***Z*-1** was carried out according to Scheme 2. The resulting mixture of the diastereoisomers was separated by TLC.

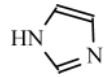
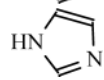


Scheme 2.

The configuration of the α-carbon atom of the amino acid moieties was determined using the sign of specific optical rotation of the complexes at 589 nm (sodium D-line). The complexes of (*S*)-amino acids had positive specific optical rotation values, whereas the complexes of (*R*)-amino acids had negative ones, as was found in previous works.[16,17] The ^{1}H NMR signals of the methyl groups of the *anti*-isomers [(*S,S,S*)-configuration of the complexes] were located at stronger fields than those of the *syn*-isomers [(*S,S,R*)-configuration], as earlier described.[13]

Data presented in Table 1 (runs 1–4) showed that addition of MeOH and EtOH to ***E*-1** led to the corresponding complexes of (*S*)-*anti*-amino acids as the main final products (yield >91%) of the addition reaction after two hours.

Table 1. The addition of nucleophiles to ***E*-1** and ***Z*-1**[a]

Run	Initial complex	NuH	Time, (h)	Product	Yield, (%)	(*S,S,S*)/(*S,S,R*)
1	***E*-1**	MeOH[b]	2	**5**	92	92/0.9[c]
2	***Z*-1**	MeOH[b]	30	**5**	58	61/20[d]
3	***E*-1**	EtOH[b]	2	**6**	88	94/1[c]
4	***Z*-1**	EtOH[b]	40	**6**	47	62/23[d]
5[e]	***E*-1**		32	**7**	80	50/39.9[d]
6[e]	***Z*-1**		52	**7**	90	41/30.5[d]

[a]All reactions were carried out at 50–60°C under argon.

[b]0.2N MeONa in MeOH (run 1, 2) and 0.04N EtONa in EtOH (run 3, 4) were used.

[c]In addition to the major product a minor amount (<8%) of by-products were obtained, containing most likely (*S,R,S*) and (*S,R,R*) diastereomers, but the structures of these compounds were not established unequivocally.

[d]Up to 25% of other isomers were formed.

[e]CH_3CN was used as a solvent.

Other diastereoisomers, containing (*R*)-*anti*, (*R*)-*syn* -amino acids and (*S*)-*syn*-amino acids were detected as by-products in amounts of less than 8%. The addition reaction was much faster than the corresponding addition to the analogues complexes of BPB.

***Z*-1** proved to be much slower substrate with the yield of the products of ROH addition about 60% after 30 h. In addition, the ratio of (*S*)-*anti*-isomers [(*S,S,S*)-configuration of the complexes] and (*S*)-*syn*-isomers [(*S,S,R*)-configuration] was disappointingly low and equal to 3/1.

Molecular mechanics calculations indicated very significant steric interaction of the Me-group of the dehydroaminobutanoic moiety with the neighboring phenyl ring, leading to an additional significant puckering of the amino acid chelate ring and twisting of the C═C bond of the moiety (see Fig. 1). For example, the Ph substituent at the C═N bond has a rotation angle relative to the plane of C═N bond of 31° for ***E*-1** and 28° for ***Z***-isomer. The torsion angles for >C═N-C═$CHCH_3$ are 33° and 39° correspondingly, and for N-C═CH-CH_3 are 0° and 6°.

The net result is significant loss of the electrophilicity of the C═C bond in ***Z***-isomer relative to ***E***-isomer due to the electronic effects, accompanying some loss of conjugation and simultaneous additional steric hindrance to the electrophile approach from the *re*-side, as the trajectory of the attack come closer to the β- and γ-protons of the proline moiety. Thus both the neighboring Ph-group and the protons of the proline moiety unfavorably interfere with its trajectory (see Fig. 1). As compared to ***E*-1** isomer, the additional hindrance in ***Z*-1** created by the proline moiety led to slowing the reaction rate and because of the additional hindrance of the *re*-attack significantly decreased stereoselectivity of the addition.

The step of protonation of the intermediate carbanion occurred fast and then followed by the epimerization of the amino acid moiety under the reaction conditions, leading to formation of the thermodynamically

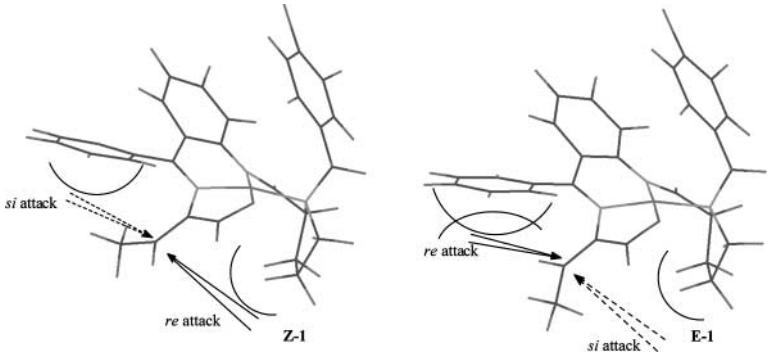


Figure 1. MM2-optimized geometries of the diastereomers ***E*-1** and ***Z*-1.**

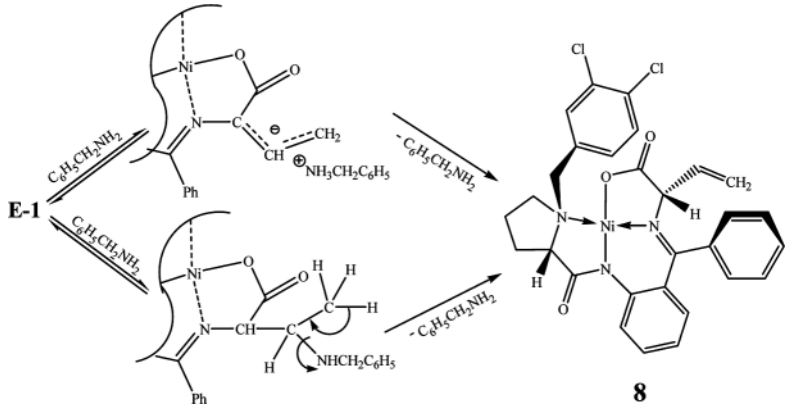
favorable (*S*)-amino acid moiety for both initial isomers ***E*-1** and ***Z*-1**, as observed in the corresponding complexes of (*S*)-BPB.[13]

Thus the addition of the alcohols reflected both kinetic stereoselectivity of the irreversible addition to the *re*-face of β-carbon atom of the dehydroaminobutanoic acid and the thermodynamic effects connected with the relative stability of the final (*S,S,S*)-diastereoisomers.

The addition of imidazole was another case of increased reactivity of **1**, as compared to the corresponding complex of BPB, where such addition was not observed. As the addition was reversible, the data of Table 1 (runs 5, 6) reflected the thermodynamic ratio of syn- and anti-isomers at equilibrium. Most likely, under the experimental conditions ***Z*-1** and ***E*-1** undergo epimerization and the addition of imidazole occurred via ***E*-1** isomer.

The addition of the nucleophiles was accompanied by a side reaction of vinylglycine formation in some amounts. An attempt at the addition of benzylamine to ***E*-1** resulted in formation of vinylglycine complex as the main product. Probably, the underlying mechanism included benzylamine acting as a base inducing the allyl rearrangement of **1**, or the reversible addition of benzylamine with its elimination, leading to the vinylglycine complex, according to Scheme 3.

Addition of alcohols to the C═C double bond of the dehydroaminobutanoic acid moiety in ***E*-1** occurred smoothly achieving high de and high chemical yields. As the cases of imidazole and benzylamine addition indicated, other nucleophiles can enter the reaction with some limitations connected with the stability of the final compounds. The number of the nucleophiles that could be used for the synthesis of the amino acids with unusual structure was not limited by their list in the present paper, as preliminary experiments with thiols and other strong nucleophiles indicated. Amino



Scheme 3.

acids can be easy recovered from complexes with using the earlier described procedure.[13]

EXPERIMENTAL

^{1}H NMR spectra were recorded on Bruker WP-200 and AP-400 instruments (200 and 400 MHz). NMR data were reported in δ units. The optical rotation measurements were obtained on Perkin-Elmer 241 polarimeter. All reagents were available from Aldrich and were used without additional purification. All used solvents were freshly distilled. Molecular mechanic calculations were made with HyperChem software in MM2 force field.

Synthesis of the initial complex 3 was carried out as described in Ref.[14].

Synthesis of 2 by condensation of 3 with acetaldehyde. To a solution of 6.2 g (11 mmol) of **3** in 30 mL of 0.2 N MeONa under argon was added 10 mL of 40% acetaldehyde. The mixture was stirred at room temperature. The reaction was monitored by TLC [SiO_2, $CHCl_3$-CH_3COOEt (1 : 3)] with the initial neutralization of an aliquot. After the ratio of the isomers ceased changing (less than 4 h), the reaction mixture was neutralized with 0.5 mL concentrated AcOH and evaporated to dryness. $CHCl_3$ and H_2O (ratio of 1 : 5) were added to the stirred residue; the organic layer was separated, washed several times with water, and evaporated. Pure complex **2** was obtained after purification by column chromatography [SiO_2, 3 × 30 cm, $CHCl_3/CH_3COOEt$ (1 : 3)] and recrystallization from $CH_3COOC_2H_5$.

Yield: 5 g (8.2 mmol), 75%. Found, %: C 57.01; H 4.41; N 6.84. $C_{29}H_{27}O_4N_3NiCl_2$. Calculated, %: C 57.01; H 4.41; N 6.84. mp 174–176°C. $[\alpha]_D^{25}$ −660.7 (*c* 0.056, $CHCl_3$); ^{1}H NMR spectrum ($CDCl_3$):1.64 (d, 3H, CH_3, $J = 6$ Hz), 1.92 (m, 1H, β-H Pro), 2.15 (m, 1H, γ-H Pro), 2.29 (m, 1H, β-H Pro), 2.54 (m, 1H, γ-H Pro), 2.70 (m, 1H, δ-H Pro), 3.53 (m, 1H, α-H Pro), 3.71 and 4.55 (AB, 2H, $NCH_2C_6H_3Cl_2$, $J = 13.12$ Hz), 3.79 (m, 1H, CH-CH_3), 4.07 (m, 1H, N-CH), 4.08 (m, 1H, δ-H Pro), 6.74–6.89 (m, 2H, Ar), 7.17 (m, 1H, OH), 7.27–7.78 (m, 8H, Ar), 8.05 (s, 1H, Ar), 8.42 (d, 1H, Ar).

Synthesis of 4 by acetylation of 2. To a solution of 1.9 g (3.1 mmol) of **2** in mixture of 12 mL of anhydrous CH_3CN and 5 mL of $CHCl_3$ was added 5 mL (46.5 mmol) of acetic anhydride. The reaction mixture was stirring under argon atmosphere at 70°C. The reaction was monitored by TLC [SiO_2, $CHCl_3$-CH_3COOEt (1 : 3)]. When the initial complex was disappeared (approx. 5 h) 20 mL of C_2H_5OH was added into the reaction mixture and steamed to dryness. Residue was dissolved in the $CHCl_3$ and washed with 10 mL of 0.2 N HCl, 30 mL of 1 M Na_2CO_3 solution (3 × 10 mL) and 10 mL H_2O, consecutively. Complex **4** was purified by column chromatography [SiO_2, 3 × 30 cm, $CHCl_3/CH_3COOEt$ (1 : 3)]. Yield: 1.81 g

(2.79 mmol), 90%. Found, %: C 53.45; H 4.04; N 5.73. $C_{31}H_{29}O_5N_3NiCl_2 \times 0.33\ CCl_4$. Calculated, %: C 53.42; H 4.15; N 5.96. mp 115–117°C. $[\alpha]_D^{25}$ −1078.57 (*c* 0.056, $CHCl_3$); ^{1}H NMR spectrum ($CDCl_3$): 1.45 (d, 3H, CH_3, $J = 6$ Hz), 1.71 (m, 1H, β-H Pro), 1.84 (s, 3H, $COCH_3$), 1.95 (m, 1H, γ-H Pro), 2,23 (m, 1H, β-H Pro), 2.49 (m, 1H, γ-H Pro), 2.57 (m, 1H, δ-H Pro), 3.59 (m, 1H, α-H Pro), 3.85 (m, 1H, N-CH), 3.88 and 4.78 (AB, 2H, $NCH_2C_6H_3Cl_2$, $J = 13.2$ Hz), 4.03 (m, 1H, δ-H Pro), 5.52 (m, 1H, CH-CH_3), 6.74–6.86 (m, 2H, Ar), 7.19–7.85 (m, 9H, Ar), 8.52 (d, 1H, Ar).

Synthesis of complexes *E*-1 and *Z*-1. To a solution of 0.6 g (0.92 mmol) of **4** in 2 mL of DMF 0.5 g (6.1 mmol) of anhydrous CH_3COONa were added. After several evacuations and purges with Ar, the reaction was heated to 138°C for 1.5 h under argon. The course of the reaction was monitored by TLC [SiO_2, $CHCl_3/CH_3COOEt$ (1 : 3)]. Afterward it was poured into stirred, cooled solution of 0.1% aq. acetic acid. The precipitate was separated and dissolved in $CHCl_3$. The organic layer was washed with water and evaporated. Product was formed as a mixture of ***E*** and ***Z*** isomers (ratio of ***E***/***Z*** 3 : 2). ***E*** and ***Z*** isomers were separated in the column with silicagel [3 × 30 cm, $CHCl_3/CH_3COOEt$ (1 : 3)] and additionally were purified with LH-20 in C_6H_6/EtOH (3 : 1). Complex ***E*-1** was obtained as the first fraction 0.19 g (0.32 mmol) 60%, complex ***Z*-1** was obtained as the second fraction 0.13 g (0.22 mmol) 40%.

***E*-1.** Found, %: C 55.39; H 4.00; N 6.21. $C_{29}H_{25}O_3N_3NiCl_2 \times 0.25\ CCl_4$. Calculated, %: C 55.63; H 3.99, N 6.65. mp 248–250°C. $[\alpha]_D^{25}$ +2146.2 (*c* 0.052, $CHCl_3$); ^{1}H NMR spectrum ($CDCl_3$): 1.72 (d, 3H, CH_3, $J = 7.4$ Hz), 2.03 (m, 1H, β-H Pro), 2.21 (m, 1H, γ-H Pro), 2.57 (m, 1H, β-H Pro), 2.67 (m, 1H, γ-H Pro), 3.13 and 4.23 (AB, 2H, $NCH_2C_6H_3Cl_2$, $J = 12.64$ Hz), 3.39 (m, 1H, α-H Pro), 3.55 (m, 1H, δ-H Pro), 3.72 (m, 1H, δ-H Pro), 5.09 (q, 1H, = CH-CH_3, $J = 7{,}4$ Hz), 6.69–6.86 (d, 2H, Ar), 7.16–7.41 (m, 7H, Ar), 7.81–8.04 (m, 2H, Ar), 8.83 (s, 1H, Ar).

***Z*-1.** Found, %: C 58.68; H 4.02; N 6.97. $C_{29}H_{25}O_3N_3NiCl_2$. Calculated, %: C 58.73; H 4.25; N 7.08. mp 235–236°C. $[\alpha]_D^{25}$ +712.5 (*c* 0.048, $CHCl_3$); ^{1}H NMR spectrum ($CDCl_3$): 0.82 (d, 3H, CH_3, $J = 7{,}44$ Hz), 2.07 (m, 1H, β-H Pro), 2.25 (m, 1H, γ-H Pro), 2.61 (m, 1H, γ-H Pro), 2.74 (m, 1H, β-H Pro), 3.11 and 4.14 (AB, 2H, $NCH_2C_6H_3Cl_2$, $J = 12.64$ Hz), 3.42 (m, 2H, α-, δ-H Pro), 3.87 (m, 1H, δ-H Pro), 5.83 (q, 1H, = CH-CH_3, $J = 7.44$ Hz), 6.72–6.98 (d, 2H, Ar), 7.16–7.41 (m, 7H, Ar), 7.85–8.08 (m, 2H, Ar), 8.79 (s, 1H, Ar).

Addition of alcohols to *E*-1 and *Z*-1 complexes. The 0.1 g (0.17 mmol) of complex **1** was dissolved in 2.8 mL (0.51 mmol) of 0.2 N CH_3ONa in CH_3OH [or in 13 mL of 0.04 N EtONa (0.51 mmol) in EtOH] and the reaction mixture was stirred in Ar atmosphere at 50–60°C. The course of reaction was monitored by TLC [SiO_2, $CHCl_3/CH_3COOEt$ (1 : 3)]. Reaction was stirred to the disappearance of initial substance on chromatogram. After

the end of reaction into the reaction mixture 2 mL of $CHCl_3$ and 10 mL of H_2O were added, then the organic layer was separated, washed with water, and evaporated to dryness. The product was separated by preparative TLC [SiO_2, 25 × 25 cm, $CHCl_3/CH_3COCH_3$ (5 : 1)] and additionally purified on the column with LH-20 [C_6H_6/EtOH (3 : 1)]. Benzylamine and imidazole were added to CH_3CN (2 mL) using 3 eq. of the nucleophiles.

The complex 5. Found, %: C 56.18; H 4.51; N 6.41. $C_{30}H_{29}O_4N_3NiCl_2$ - H_2O. Calculated, %: C 56.02; H 4.86; N 6.53. mp 262–264°C. $[\alpha]_D^{25}$ +2208.0 (*c* 0.05, $CHCl_3$); ^{1}H NMR spectrum ($CDCl_3$): 1.13 (d, 3H, CH_3, $J = 6$ Hz), 2.01 (m, 1H, β-H Pro), 2.14 (m, 1H, γ-H Pro), 2.62 (m, 1H, β-H Pro), 2.79 (m, 1H, γ-H Pro), 3.21 and 4.30 (AB, 2H, $NCH_2C_6H_3Cl_2$, $J = 12.2$ Hz), 3.34 (m, 2H, δ-H Pro, N-CH-), 3.55 (m, 1H, α-H Pro), 3.56 (s, 3H, OCH_3), 3.90 (m, 2H, δ-H Pro, CH-CH_3), 6.65–6.89 (m, 3H, Ar), 7.17–7.51 (m, 6H, Ar), 7.77–8.07 (m, 2H, Ar), 8.90 (s, 1H, Ar).

The complex 6. Found, %: C 58.35; H 4.96; N 6.5. $C_{31}H_{31}O_4N_3NiCl_2$. Calculated, %: C 58.24; H 4.85; N 6.57. mp 215–217°C. $[\alpha]_D^{25}$ +2530.0 (*c* 0.05, $CHCl_3$); ^{1}H NMR spectrum ($CDCl_3$): 1.21 (d, 3H, CH_3-CH, $J = 6.8$ Hz), 1.43 (t, 3H, CH_3-CH_2), 1.85 (m, 1H, β-H Pro), 2.22 (m, 1H, γ-H Pro), 2.78 (m, 1H, β-H Pro), 3.28 (m, 1H, γ-H Pro), 3.45 (m, 1H, CH_3-CH), 3.47 and 4.01 (AB, 2H, $NCH_2C_6H_3Cl_2$, $J = 12.6$ Hz), 3.38 (m, 1H, δ-H Pro), 3.75 (m, 1H, α-H Pro), 3.72 (m, 2H, CH_3-CH_2), 3.85 (m, 2H, δ-H Pro, CH-CH_3), 6.68–6.82 (m, 3H, Ar), 7.23–7.4 (m, 6H, Ar), 7.75–7.9 (m, 2H, Ar), 8.75 (s, 1H, Ar).

The complex 7. Found, %: C 57.63; H 4.66; N 9.49. $C_{32}H_{29}O_3N_5NiCl_2$ - $1.25C_2H_5OH$. Calculated, %: C 57.65; H 5.12, N 9.74. mp 169–171°C. $[\alpha]_D^{25}$ +1900.0 (*c* 0.016, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$): 1.25 (m, 1H, β-H Pro), 1.35 (d, 3H, CH_3, $J = 7.44$ Hz), 1.80 (m, 1H, γ-H Pro), 2.06 (m, 1H, β-H Pro), 2.41 (m, 2H, γ-, δ-H Pro), 2.65 (m, 1H, α-H Pro), 3.14 and 4.15 (AB, 2H, $NCH_2C_6H_3Cl_2$, $J = 13.0$ Hz), 3.13 (m, 1H, CH-CH_3), 3.24 (m, 1H, δ-H Pro), 4.32 (m, 1H, N-CH), 6.70–7.00 (m, 3H, Ar), 7.19–8.29 (m, 11H, Ar), 8.99 (s, 1H, Ar).

The complex 8. Yield: 0.05 g. (0.0085 mmol) 50%; Found, %: C 57.58; H 4.24; N 6.86. $C_{29}H_{25}O_3N_3NiCl_2 \times 0.5H_2O$. Calculated, %: C 57.85; H 4.35; N 6.98. mp 252–254°C. $[\alpha]_D^{25}$ +1475 (*c* 0.05, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$): 2.21 (m, 2H, β-H Pro), 2.60 (m, 1H, δ-H Pro), 2.69 (m, 2H, γ-H Pro), 3.26 and 4.29 (AB, 2H, $NCH_2C_6H_3Cl_2$, $J = 12.64$ Hz), 3.39 (m, 1H, α-H Pro), 3.47 (m, 1H, δ-H Pro), 5.39–5.56 (AB part of ABX system, 2H, $J_{AB} = 0.2$ Hz, $J_{AX} = 7.8$ Hz, $J_{BX} = 16.72$ Hz), 6.04 (X part of ABX system, 1H, $CH = CH_2$), 6.71–6.79 (m, 3H, Ar), 7.27–7.49 (m, 6H, Ar), 7.82–8.05 (m, 2H, Ar), 8.83 (s, 1H, Ar).

Amino acids have been recovered from the corresponding complexes using earlier described procedure.[13] Physico-chemical and polarimetric data of the isolated amino acids L-*allo*-O-methylthreonine and L-*allo*-O-ethelthreonine correspond to the literarture data.[13]

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REFERENCES

1. Proctor, G. *Asymmetric synthesis*; Oxford University Press: Oxford, 1996.
2. Scott, J. Enantioselective synthesis of non-racemic chiral molecules on an industrial scale. In *Topic in stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; John Wiley & Sons: New York, 1989; Vol. 19, p. 209.
3. Krause, N.; Röder, A. H. Recent advances in catalytic enantioselective Michael addition. *Synthesis* **2001**, 171–196.
4. Nojori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994; pp. 207–212.
5. Perlmutter, P. *Conjugate Addition Reactions of Organic Synthesis*; Pergamon Press: Oxford, 1992.
6. Shibasaki, M. *Catalytic Asymmetric Synthesis*, 2nd Ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000Chapter 8D.
7. Tomioka, M.; Nagaoka, Y. *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999, Chapter 31.1.
8. Yamaguchi, M. *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999Chapter 31.2.
9. Fang, C.; Ogawa, T.; Suemune, H.; Sakai, K. Asymmetric conjugate addition of organometallic reagents to chiral α,β-unsaturated esters. *Tetrahedron: Asymmetry* **1991**, *2* (5), 389–398.
10. Van Heeredn, P. S.; Bezuidenhoudt, B. C. B.; Ferreira, D. Dibutylboron triflate promoted conjugate addition of benzylic and allylic organocopper reagents to chiral α,β-unsaturated N-Acyl imidazolidinones. *Tetrahedron Lett.* **1997**, *38* (10), 1821–1824.
11. Oppolzer, W.; Kingma, A. J. Asymmetric induction on copper(I) chloride catalyzed 1,4-addition of alkyl magnesium chlorides to α,β-disubstituted (E)-endylsultams and subsequent protonation. *Helv. Chim. Acta* **1989**, *72*, 1337–1345.
12. Melnyk, O.; Stephan, E.; Pourcelot, G.; Cresson, P. Additions Diastéréosélectives D'alkyl, Alcényl, Aryl et Allyl Cuprates à des Imides Chirales Insaturées. *Tetrahedron* **1992**, *48* (5), 841–850.
13. Belokon, Yu. N.; Sagiyan, A. S.; Djamgaryan, S. M.; Bakhmutov, V. I.; Vitt, S. V.; Batsanov, A. S.; Struchkov, Yu. T.; Belikov, V. M. General method for the asymmetric synthesis of anti-diastereoisomers of β-substituted L-2-aminobutanoic acids via chiral nickel (II) Schiff's base complexes of dehydroaminobutanoic acid. X-ray crystal and molecular structure of the nickel (II) complex of the Schiff's base from [(Benzylprolyl)amino]benzophenone and dehydroaminobutanoic acid. *J. Chem. Soc. Perkin Trans. 1* **1990**, 2301–2310.
14. Belokon, Yu. N.; Maleev, V. I.; Petrosyan, A. A.; Savel'eva, T. F.; Ikonnikov, N. S.; Peregudov, A. S.; Khrustalev, V. N.; Saghiyan, A. S. Halo-substituted (*S*)-N-(2-Benzoylphenyl)-1-benzylpyrolidine-2-carboxamides as new

chiral auxiliaries fort asymmetric synthesis of (*S*)-α-amino acids. *Russian Chemical Bulletin, Int. Ed.* **2002**, *51* (3), 1593–1599.

15. Belokon, Y. N. (S)-2-[N-(N-benzylprolyl)amino]benzophenone (BPB) a reagent for the synthesis of optically pure α-amino acids. *Janssen Chimica Acta* **1992**, *10* (2), 4–13.
16. Belokon, Yu. N.; Saghiyan, A. S.; Djamgaryan, S. A.; Bakhmutov, V. I.; Belikov, V. M. Asymmetric synthesis of β-substituted α–amino acids via a chiral Ni^{II} complex of dehydroalanine. *Tetrahedron* **1988**, *44* (17), 5507–5514.
17. Saghiyan, A. S.; Geolchanyan, A. V.; Petrosyan, S. G.; Ghochikyan, T. V.; Haroutunyan, V. S.; Avetisyan, A. A.; Belokon, Yu. N.; Fisher, K. Asymmetric synthesis of heterocycle substituted L-α-amino acids. *Tetrahedron: Asymmetry* **2004**, *15* (4), 705.