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Asymmetric Aldol Reactions of Chiral Ni(II)-Complex of Glycine with Aliphatic Aldehydes. Stereodivergent Synthesis of *syn*-(2*S*)- and *syn*-(2*R*)-β-Alkylserines

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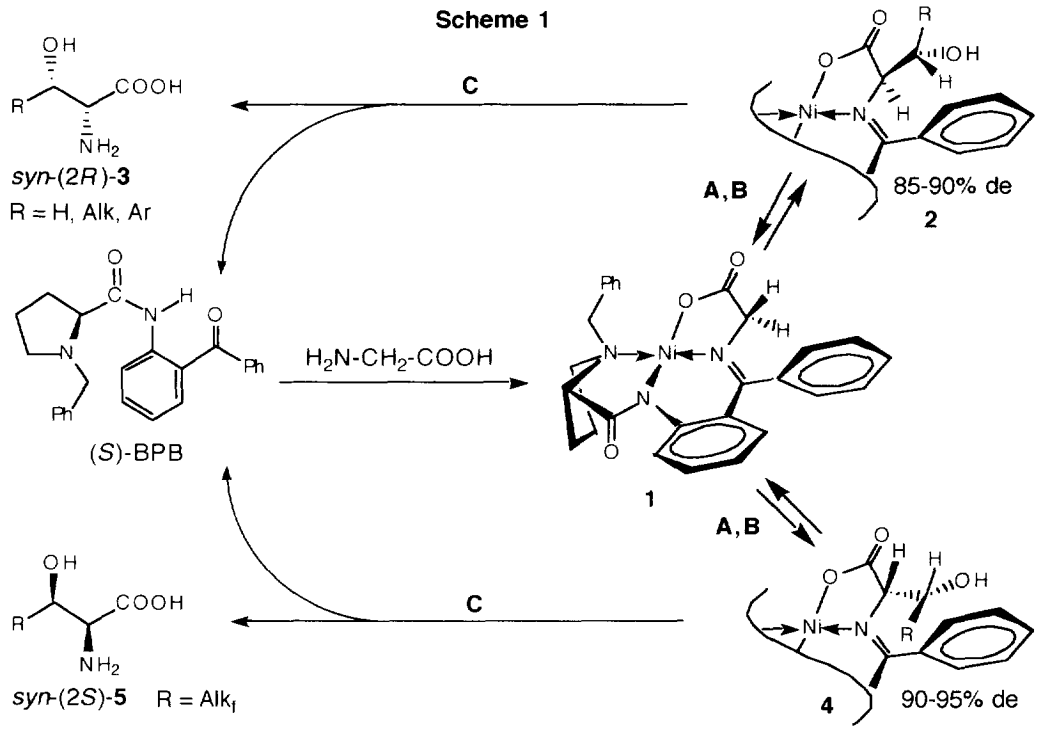
Abstract: Stereoselectivity of aldol reactions between aliphatic aldehydes and Ni(II)-complex of chiral non-racemic Schiff base of glycine with (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone (BPB) in the presence of excess of MeONa, has been studied as a function of time, reaction conditions and nature of an aldehyde. Two salient features of the reaction, very high pseudokinetic *syn*-(2*S*)-diastereoselectivity, and dependence of thermodynamic *syn*-(2*R*)-diastereoselectivity on the steric bulk of an aldehyde side chain, were disclosed and used for efficient (more than 90% de and ee) asymmetric synthesis of both *syn*-(2*S*) and *syn*-(2*R*)-3-alkyl substituted serines. Synthetic potential and reliability of this asymmetric method are demonstrated with the large scale (2-20 g) preparation of enantiomerically pure amino acids.

INTRODUCTION

The development of stereocontrolled aldol methodology in recent decades has had a huge impact on the present state-of-the-art of organic synthesis in general and natural product synthesis in particular.[1] Available nowadays approaches to the highly stereoselective aldol reaction and nearly complete understanding of the parameters governing *syn/anti* stereoselection of carbon-carbon bond formation can ensure successful synthesis of stereodefined structures of various natural compounds.[2] However, despite the synthetic power and flexibility of comprehensive aldol methodology, each method itself possesses its own limitations, therefore further elaboration of known methods and creation of new ones, for instance with application of bifunctional chiral auxiliaries[3] or asymmetric homogeneous catalysis,[4] are going on.

Among the synthetic targets accessible by an aldol reaction, α-amino-β-hydroxy carboxylic acids are of particular interest, that had been greatly stimulated in recent years by the increasing awareness of these amino acids' biological and pharmaceutical importance both in free form and as essential structural components of more complex naturally occurring molecules.[5] The most synthetically valuable strategies developed to date for the stereocontrolled preparation of α-amino-β-hydroxy carboxylic acids include aldol reaction of chiral glycine equivalent with carbonyl compound.[6] Along this line aldol reactions between aldehydes and Ni(II)-complex of chiral non-racemic Schiff base of glycine with (*R*)- or (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone (BPB)[7]

Scheme 1



Conditions: **A**, MeOH/1.5*N* MeONa, RCHO; **B**, H_2O/AcOH; **C**, HCl/MeOH, Dowex-50/NH_4OH

1 is particularly attractive since the structure of complex **1** offers the advantage of relatively high CH acidity of glycine α-protons[8], allowing to use wide range of weak and strong bases under the various reaction conditions. Moreover, chiral auxiliary BPB, providing high level of unusual 1,8-asymmetric induction at α-position of new amino acid formed,[9] is readily recoverable and can be used in many synthetic cycles without any loss in optical purity. Generally, aldol reaction of complex (*S*)-**1** with formaldehyde, acetaldehyde, and substituted benzaldehydes in the presence of an excess of MeONa provides *syn*-(2*R*)-3-substituted serines with up to 90% of both chemical yield and diastereomeric excess (de) (Scheme 1, compounds **1**-**3**), that renders this reaction as one of the most successful stoicheiometric approaches to α-amino-β-hydroxy carboxylic acid synthesis.

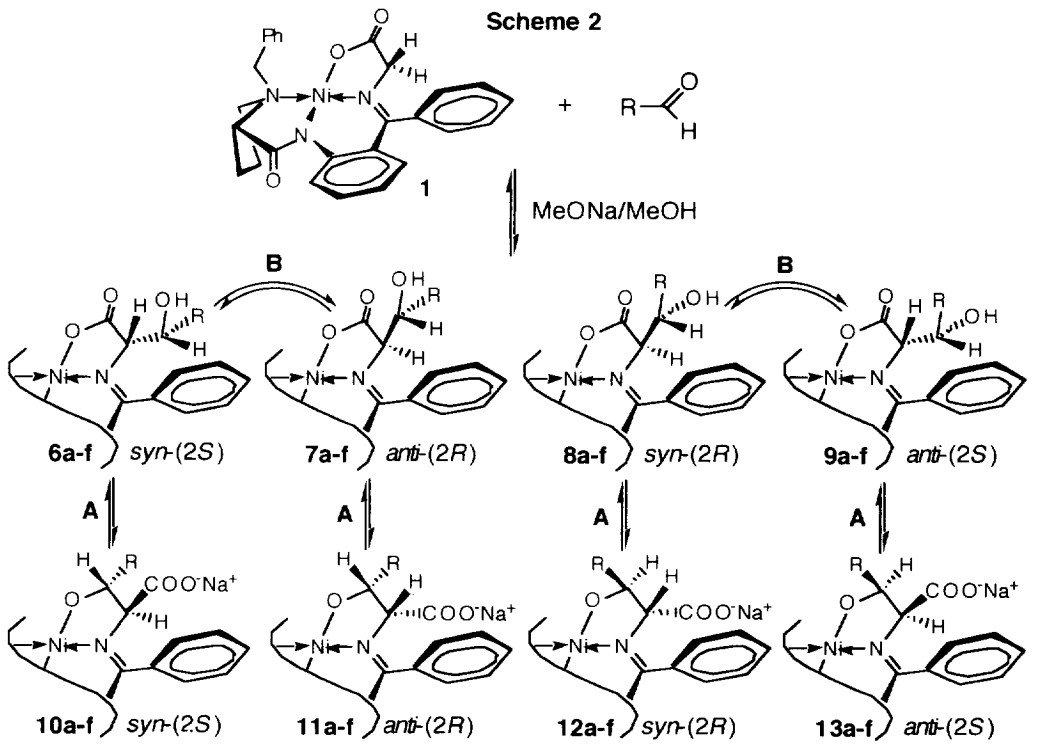
Previous investigations into the aldol reaction of **1** with carbonyl compounds[10] had defined many of the key parameters of complex **1** reactivity and origins of stereoselectivity, however, not all of the experimental results can be adequately explained. A striking example of this complication is offered by the reactions of complex (*S*)-**1** with fluorine-containing aldehydes[11] (Scheme 1, compounds **1**,**4**,**5**). The MeONa promoted reaction of (*S*)-**1** with trifluoroacetaldehyde gave (*S*)-4,4,4-trifluorothreonine [(2*S*,3*S*)-2-amino-3-hydroxy-4,4,4-trifluorobutanoic acid][12] in 92% ee[11a] but under similar conditions the reaction with acetaldehyde and benzaldehyde produced respectively (*R*)-threonine [(2*R*,3*S*)-2-amino-3-hydroxybutanoic acid] in 84% ee[10a] and *syn*-(2*R*)-phenylserine [(2*R*,3*S*)-2-amino-3-hydroxy-3-phenylpropanoic acid] in 88% ee.[10a] The existing mechanistic model of the aldol reaction between complex **1** and carbonyl compound, and rationale for stereochemistry of the products [in methanol solution at high pH (>0.1 *N* MeONa)][13,10a] invariably necessitates the formation of corresponding *syn*-(2*R*)-3-substituted serine-containing complexes (Scheme 1, compound **2**) as

the most thermodynamically stable products (thermodynamic control), therefore the specific influence of fluorine atoms was suggested to rationalize unexpected stereochemical outcome (Scheme 1, **2** vs **4**) in the reaction of complex (*S*)-**1** with trifluoroacetaldehyde.[14] These results have clearly shown the necessity of more detailed study of the aldol reaction itself and particularly its earlier stages that did not previously receive due attention. In continuation of our studies on the origin of stereocontrol in the aldol reactions of complex (*S*)-**1** with carbonyl compounds we have now investigated diastereoselectivity of aliphatic aldehyde condensation with (*S*)-**1** as a function of time, conditions and the nature (steric bulk) of an aldehyde.

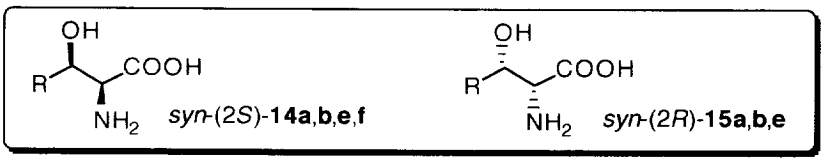
RESULTS

Initially, we reexamined the reaction of complex **1** with acetaldehyde, known to be effective for the synthesis of (2*R*)-threonine.[10] Thus, the solution of complex **1** in 1.2 *N* MeONa (MeOH solution) at 24 °C was treated with acetaldehyde. Parts of the solution were withdrawn at certain time intervals and quenched with aqueous acetic acid solutions and worked up as described in the experimental. The diastereomeric ratio of the

Scheme 2



A = rearrangement; **B** = epimerization



R = CH_3 (**a**), $CH_3(CH_2)_5$ (**b**), $CH_3(CH_2)_7$ (**c**), $(CH_3)_2CHCH_2$ (**d**), $(CH_3)_2CH$ (**e**), $(CH_3)_3C$ (**f**)

Table 1. MeONa-Promoted Asymmetric Aldol Reactions of Aldehydes with Ni(II)-Complex **1**[a]

entry	aldehyde	time	ratio of diastereomers[b]			yield[c] (%)
			syn-(2*S*) **6a-f**	*syn*-(2*R*) **8a-f**	*anti*-(2*R*)/(2*S*)[d] **7a-f** and **9a-f**	
1	CH_3CHO	0.5 min	95	5	trace	82
2	CH_3CHO	1 min	77	15	8	86
3	CH_3CHO	10 min	70	18	12	95
4	CH_3CHO	2 hr	16	84	trace	—
5	CH_3CHO	24 h	5	95	trace	78
6	$CH_3(CH_2)_5CHO$	0.5 min	91	9	trace	94
7	$CH_3(CH_2)_5CHO$	1 min	83	15	2	90
8	$CH_3(CH_2)_5CHO$	10 min	51	37	12	89
9	$CH_3(CH_2)_5CHO$	24 h	11	85	4	78
10	$CH_3(CH_2)_7CHO$	0.5 min	>95	<5	trace	78
11	$CH_3(CH_2)_7CHO$	1 min	73	15	12	75
12	$CH_3(CH_2)_7CHO$	10 min	52	35	13	85
13	$CH_3(CH_2)_7CHO$	24 h	10	90	trace	76
14	$(CH_3)_2CHCH_2CHO$	0.5 min	97	3	trace	94
15	$(CH_3)_2CHCH_2CHO$	1 min	68	20	12	82
16	$(CH_3)_2CHCH_2CHO$	10 min	55	40	5	—
17	$(CH_3)_2CHCH_2CHO$	24 h	9	91	trace	75
18	$(CH_3)_2CHCHO$	3 min	90[f]	10[f]	trace	99.6
19	$(CH_3)_2CHCHO$	30 min	47.5[f,g]	52.5[f,g]	trace	99.8
20	$(CH_3)_2CHCHO$	3 h	25.5[f,h]	74.5[f,h]	trace	—
21	$(CH_3)_3CCHO$	10 min	>98	<2	trace	97
22	$(CH_3)_3CCHO$	15 min	97[f]	3[f]	trace	95
23	$(CH_3)_3CCHO$	2 h	93[f]	7[f]	trace	—
24	$(CH_3)_3CCHO$	24 h	78[f]	22[f]	trace	80
25	$(CH_3)_3CCHO$	96 h	75[f]	25[f]	trace	—
26	$(CH_3)_3CCHO$	240 h	42.5[f]	57.5[f]	trace	—
27	$(CH_3)_3CCHO$	480 h	42.5[f]	57.5[f]	trace	—

[a] The reactions were carried out in methanol solution at room temperature under argon atmosphere. Ratio (*S*)-**1**/MeONa greater than 1/3; for details see experimental part. [b] Determined by ^1H NMR analysis of crude reaction mixture. [c] Total isolated yield of all diastereomeric complexes formed. [e] The values were obtained spectrophotometrically after the chromatographic separation of the mixture of the diastereomeric complexes **6e**, **8e**. [f] Determined by the enantiomeric GC analysis of free amino acids isolated after the decomposition of the initial mixture of the diastereomeric complexes. [g] The isomer ratio was determined by weighting the preparatively isolated **6e**, **8e**. [h] The de of the reaction was the same after another 24 h.

complexes formed was analyzed either by ^{1}H NMR of the crude reaction mixture or by GLC of the amino acids recovered from the complexes. As Table 1 (entries 1-5) illustrated, the stereochemical outcome of the aldol reaction of complex **1** with acetaldehyde dramatically depended upon reaction time. At the beginning of the reaction it was (*S*)-threonine-containing diastereomer **6a** (Scheme 2) which was formed in 90% de and after 2 and 24 hours the reaction mixture contained a large excess of (*R*)-threonine-containing complex **8a** (68% and 90% de respectively).

With these results in hands, we next designed series of short (0.5-3 min), middle (10-15 min) and long (1 day and more) run experiments which were done under the same reaction conditions using 1-heptanal (Table 1, entries 6-9), 1-nonanal (entries 10-13), 3-methyl-1-butanal (entries 14-17), 2-methyl-1-propanal (entries 18-20), and 2,2-dimethyl-1-propanal (entries 21-27), to explore the dependence of the diastereoselectivity of the aldol reaction under study upon both, reaction time and steric bulk of the aldehyde side chain. In all cases examined (see Table 1) the general pattern of the acetaldehyde reactivity was repeating itself. At the beginning of the reaction one almost pure diastereoisomer **6** was formed and after a period of time another one **8** along with minute amounts of additional diastereoisomeric complexes **7**, **9** appeared in the reaction mixture and their final ratio depended on the structure of the aldehyde. The absolute configurations of the side chains of the amino acid moieties in Ni(II)-complexes **6-9** were assigned as described below.

The absolute configuration of the amino acid side chain in **6f** was determined as (2*S*,3*R*)[or *syn*-(2*S*)] by X-ray analysis data (see Fig. 1).[15] Absolute configuration of the threonines in their Ni(II)-complexes **6a-9a** was assigned by comparison of ^{1}H NMR spectra and $[\alpha]_D$ values of these complexes and amino acids released from them, with that of previously reported for complexes *syn*-(2*S*)-**6a**, *syn*-(2*R*)-**8a**, *anti*-(2*S*)-**7a**, *anti*-(2*R*)-**9a,f**[10,11] and corresponding amino acids. The *syn*- (or *threo*-) configuration of the β-hydroxyleucine furnished by the condensation of *i*-PrCHO with **1** was confirmed by TLC on cellulose and by the comparison of the R_f value with that of the racemic authentic sample obtained by the reaction of *i*-PrCHO with copper(II) glycinate (*syn*/*anti* 3:1).[16] For all other cases the configuration at the α-carbon of the amino acids in corresponding

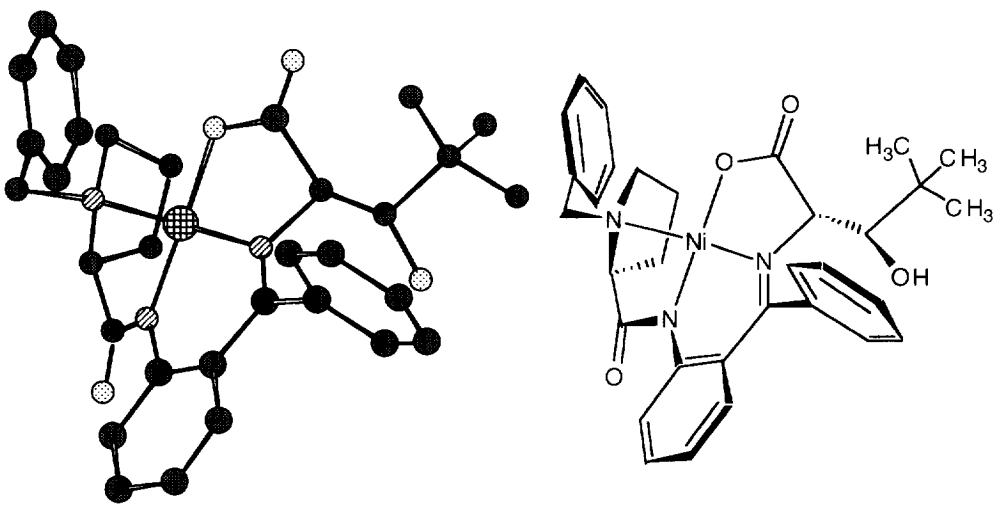


Figure 1. Structure of Ni(II)-complex of *syn*-(2*S*)-3-*tert*-butylserine Schiff's base with (*S*)-*o*-[(*N*-benzylprolyl)amino]benzophenone **6f**.

Ni(II)-complexes was established using their optical rotary dispersion (ORD) curves, as described previously.[17] Complexes **6b-e** and **8b-e** were each decomposed to give free amino acids relative stereochemistry of which was established by proton NMR. Thus, ^{1}H NMR spectra of crude amino acids released from complexes **6b-e** were identical to that of compounds obtained from **8b-e** and their corresponding mixtures (**6c** and **8c**, for instance) shown the same single set of signals. This data strongly suggest enantiomeric relationship between amino acids contained in complexes **6b-e** and **8b-e**, that combined with the known absolute configuration of threonines, β-hydroxyleucines, and *syn*-(2*S*)-3-*tert*-butylserine in complexes **6a,e,f** and **8a,e** allowed us to assign *syn* relative stereochemistry to the amino acid moieties of **6a-f** and **8a-f**. The (*S*)- and (*R*)-*anti*-configuration of the amino acid moieties were assigned to **7a** and **9a** on the basis of previous data.[10,11] In other cases the configuration of the complexes **7b-d** and **9b-d** were assigned on the bases of strong similarity in chemical shifts of aromatic protons of **7a** and **7b-d** and **9a** and **9b-d** respectively.

As one can see from the Table 1, the early stage of an aliphatic aldehyde aldol reaction with complex **1** provided formation of almost exclusively *syn*-(2*S*)-3-substituted serine-containing complexes **6a-f** in all cases examined. Thus, length (entry 1 vs 6,10) and bulkiness (entry 1 vs 14,18,21) of an aldehyde side chain have little influence on stereochemical result; being increased some improvements in de of complexes **6** formation were observed (90% de, entry 1vs >95 de, entries 10,14,21). By contrast, steric bulk of an aldehyde side chain has critical influence on the formation of *syn*-(2*R*)-**8** as the final products of the aldol reactions under study (entries 20,23-27 vs 5,9,13,17). Thus, although it were still *syn*-(2*R*)-**8e,f** which were formed under thermodynamically controlled conditions of *i*-PrCHO and *tert*-BuCHO condensation with **1**, the de of the reaction was only 49% and 15% respectively (entries 20,27).

Diastereo- and enantiomerically pure complexes **6**, **8** obtained were decomposed in their methanol solutions by the action of conc hydrochloric acid at 40-50 °C to release corresponding 3-substituted serines **14**, **15**, and chiral auxiliary (*S*)-BPB (Scheme 2). In free form amino acids were isolated by means of cation exchanger Dowex-50. For details see Experimental.

DISCUSSION

Like other aldol reactions of glycine metal complexes with carbonyl compounds,[18] the mechanism of carbon-carbon bond formation in the reaction under study is assumed to consist of two main steps, namely, base-catalyzed abstraction of an α-proton from glycine fragment followed by reversible addition of the resulting carbanion with carbonyl group.[10a,11a] On the other hand, unlike most known chiral equivalents of nucleophilic glycine, methylene group of glycine in complex **1** as well as methyne one in corresponding aldol products possess relatively high α-CH acidity and owing to this aldol products can easily undergo α-epimerization under the basic reaction conditions (Scheme 2, route B) giving rise to new complexes with opposite absolute configuration at α-position. Furthermore, because of aldol reaction of complex **1** with aldehydes is a reversible process, the stereochemistry of the products could reflect kinetic, thermodynamic or a mixed case of diastereoselection. Nevertheless, the consideration of basic structural features of the complexes might help to rationalize the thermodynamic diastereoselectivity observed in the reaction. Two limiting cases should be considered. First case: thermodynamic diastereoselectivity of the complexes of the α-amino acids with aliphatic side chain (at all the pH of the solution) and β-hydroxy-α-amino acids at low pH of the solution (Et_3N in MeOH). If the hydroxy group of the amino acid side chain was not ionized and the complex had a regular structure with a pseudoaxial orientation of the amino acid side chain, the thermodynamic effects favored (*S*)-

configuration of the α-carbon atom of the amino acid side chain[11a] in the same manner as was observed for all the other Schiff's base complexes of amino acids derived from (*S*)-BPB and Ni(II).[19] The unfavorable interaction of the amino acid side chain with the phenyl substituent at the C=N bond (as for instance structures **7**, **8** on the Scheme 2) was believed to be responsible for the instability of the corresponding (*R*)-amino acid-containing diastereomer.[10b] It seemed there were no significant thermodynamic diastereoselection at the β-carbon atom of the amino acid moiety under low pH conditions.[11a] Second case: thermodynamic diastereoselectivity of the complex of the β-hydroxy-α-amino acids at high pH of the solution (greater than 0.1M MeONa, ratio MeONa/(*S*)-**1** ≥ 3/1). As was shown earlier for the acetaldehyde and benzaldehyde condensations with complex (*S*)-**1**, in a solution of high pH, the sense of asymmetric induction was reversed as a consequence of ionization of the hydroxy group and concomitant rearrangement with substitution, by this group, of the ionized carboxy group in the main co-ordination plane of the complex (see Scheme 2, route A, compounds **10-13**).[10a,11a] Complexes **8** containing *syn*-(2*R*)-β-hydroxy-α-amino acids, existing in the MeOH/MeONa solution as **12**, were the main products of this thermodynamically controlled reversible process, in agreement with molecular mechanics calculations. The non-bonding interaction of the ionized carboxy group with the phenyl substituent at the carbon atom of the C=N bond, as it takes place in the case of structures **10**, **13**, might be implicated as the main reason for the reversal of the sense of asymmetric induction at the α-carbon atom of the amino acid moiety.[11a] The postulated rearrangement stabilizes the addition product and allows the involvement of sterically demanding aldehydes in the condensation. For example, there was no reaction of **1** with *t*-BuCHO catalyzed by triethylamine.

Relative stereochemistry within amino acid moiety in the hydroxy-co-ordinated complexes could be apparently determined by an energetic advantage of *trans*-relationship between substituents at five-membered chelate ring. Among four possible structures of hydroxy-co-ordinated complexes **10-13** the only **12**, containing *syn*-(2*R*)-3-substituted serine meets all requirements for stereochemistry and is expected to be the product of final thermodynamic control in the aldol reactions of chiral Ni(II)-complex **1** with aldehydes. Thus, it was expected that the MeONa-promoted reactions of complex (*S*)-**1** with aliphatic aldehydes used in this study under the conditions of thermodynamic control (long run reactions in the Table 1) will provide a great excess of *syn*-(2*R*)-3-substituted serine-containing complexes **12a-f**. By contrast, thermodynamically controlled 25.5/74.5 and 42.5/57.5 ratios of complexes **6e/8e** and **6e/8e** in the reaction of (*S*)-**1a** with *i*-PrCHO and pivalaldehyde respectively were rather surprising. As it follows from the results, the elongation of the alkyl side chain from C_1 and up to C_7 (entries 5,9,13) or its branching at β-position (entry 17) only slightly affect thermodynamic *syn*-(2*R*)-diastereoselectivity diminishing it from 90% de (entry 5) to 80% de (entry 13). Dramatic decrease in the yield of complexes **8e,f**, as compared with that of complexes **8a-d**, and consequently less favorable formation of **12e,f** is not obvious and probably comes from the specific changes in geometry of chelate rings that are brought about by steric demands of bulky *i*-propyl and *tert*-butyl groups. In contrast to the experimental results, the molecular mechanics calculations, without taking into account any electrostatic effects, predict a regular increase in the de of *syn*-(2*R*)-diastereomers as the size of R of the amino acid moiety is increased and the energetic difference between **10f** and **12f** is the largest in the series of the diastereoisomers. However, introduction of a positive charge (+1) on the metal[20] made the calculated structure of **10f** energetically similar to **12f**. The rationalization of the phenomena might be sought in the different distances between the carboxyl group and the metal center in **10f** and **12f**. Thus, in structure **10** the distance between the metal and the negatively charged oxygen atom of the carboxy group is shorter than in **12** for all the complexes

under study. Moreover, as the size of R increased, the distance between the carboxy group and the metal in **10** becomes shorter with the concomitant greater electrostatic stabilization of *syn*-(2*S*)-**10** relative to *syn*-(2*R*)-**12**. In the case of **10a-d** the effect of electrostatic attractive interaction between positively charged metal and ionized carboxy group is not sufficient to overcome the steric repulsive interactions, but becomes sizable in the structure **10e** bearing *i*-propyl group. Finally, the electrostatic effects in **10f** outweigh the steric non-bonding interactions rendering **10f** almost as stable as **12f**.

At first sight the invariable formation of *syn*-(2*S*)-β-hydroxy-α-amino acids at the earlier stages of the condensation reaction (Table 1, entries 1,6,10,14,18,21) seemed to reflect kinetic stereoselectivity of the aldehyde attack on the carbanion of (*S*)-**1**. However at a low pH of the solution (Et_3N in MeOH) the initially observed stereoselectivity of the condensation reaction of acetaldehyde and (*S*)-**1** led to *syn/anti* ratio close to 1/1. Also the condensation of pentafluorobenzaldehyde and polyfluoroaliphatic aldehydes with (*S*)-**1** catalyzed by such a weak bases as Et_3N and DABCO in $CHCl_3$ solution gave a mixture of *syn/anti*-(2*S*) close to 1/1.[11] In addition, there was relatively low kinetic stereoselectivity of C-alkylation of the carbanion of (*S*)-**1** in a series of Michael addition reactions.[9j] Evidently, a more sophisticated mechanism was responsible for the observed diastereoselectivity of the reaction at the earlier stages at a high pH in MeOH.

We believe that the real kinetically controlled ratio of diastereomers could not be observed under the experimental conditions at high pH. Whatever amounts of the initially formed isomers of regular structure with the unionized hydroxy group immediately equilibrate at a high pH (most likely *via* a reversible C-C bond formation) to give initially the thermodynamically controlled excess of (2*S*)-*syn* + (2*S*)-*anti*-isomers (Scheme 2, **6a-f** + **9a-f**) in a ratio of 1:1. It were (2*S*)-*syn*-isomers **6a-f** that were converted further to the rearranged form **10a-f** *via* path A and become stabilized both to C-C bond dissociation and α-proton labilization. On the other hand (2*S*)-*anti*-isomers **9** being unable to rearrange and become stabilized because of unfavorable formation of structures like **13**, as was discussed earlier,[11a] undergo decomposition back to (*S*)-**1** and aldehyde. The thermodynamic equilibration of the rearranged product **10a-f** was a much more slow process and numerous condensation - decomposition cycles of the regular built (2*S*)-*anti*-isomers **9a-f** within seconds led to the predominant formation of the large excesses of (2*S*)-*syn*-isomers at the beginning of the process at a high pH. Thus the high (2*S*)-*syn*-stereoselectivity at the earlier stages of the reaction was not kinetically controlled and reflected an unusual case of the formation of a metastable intermediate complex **10**.

CONCLUSIONS

Diastereoselectivity of aldol reaction between aliphatic aldehydes and Ni(II)-complex of chiral Schiff base of glycine with (*R*)- or (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone (BPB) **1** has been studied as a function of time, reaction conditions and nature of aldehyde. The results obtained revealed that both *syn*-(2*S*)- and *syn*-(2*R*)-α-amino-β-hydroxy carboxylic acids containing in β-position long chain or β-branched alkyl groups can be effectively prepared in high optical purity under the corresponding pseudokinetically and thermodynamically controlled conditions employing the same chiral auxiliary BPB.

The method elaborated in this work is suitable for the production of at least 20 g quantities of enantiomerically and diastereomerically pure α-amino-β-hydroxy carboxylic acids starting from glycine and the commercially available recoverable chiral auxiliary BPB. It seems there are no difficulties in increasing the scale of the syntheses.

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EXPERIMENTAL

General. ^{1}H-NMR was performed on a Varian VXR-300 (299.94 MHz), Gemini-200 (199.98 MHz) and Brucker WP-200 spectrometers. TMS and HCOOH were used as internal standards in $CDCl_3$ and D_2O solutions respectively. NMR data are reported in δ units. Optical rotations were measured using a Perkin-Elmer 241 polarimeter. ORD curves were recorded on Jasco ORD/UV-5 instrument. X-Ray crystal structure analysis was performed with a four-circle automated Siemens P3/PC difractometer. Enantiomeric and diastereomeric analysis of amino acids was carried out by GC in the form of their *O*-isopropyl *N*-trifluoroacetyl derivatives using stationary phase Chirasil-val type.[21] TLC were run on silica gel 60 PF_{254} and 50 PF_{245} Merck plates, column chromatographies were performed with silica gel $L_{5/40}$ and $L_{40/60}$ obtained from Chemapol and Aldrich respectively. Melting points (mp) are uncorrected and were obtained in open capillaries. Reagents and solvents were purified in the usual way.[22]

Molecular mechanics calculations were performed on a IBM-compatible 386-processor computer, using the MMX force field, 'PC-model' program, 1988 year version, available from Serene Software, as described earlier.[11a]

Ni(II)-Complex of the Schiff Base's of (*S*)-BPB and Glycine 1. Synthesis of complex **1** was accomplished by a modified procedure given in ref. 19, starting from commercially available[7] chiral auxiliary (*S*)-BPB. A solution of NaOH (56 g, 1.4 mol) in 400 mL of MeOH was poured into a mixture of 75 g (1 mol) of glycine, 76.8 g (0.2 mol) of BPB, 116.3 g (0.4 mol) of $Ni(NO_3)_2 \times 6H_2O$ and 800 mL of MeOH with energetic stirring under N_2 at 50-60 °C. After the addition had been completed the reaction mixture was stirred at the same temperature for another 30-40 min and then 90 mL AcOH was added. The solution was transferred into a 5 L beaker and water was gradually added to the stirred mixture. As soon as the solution became turbid, a few crystals of **1** were added to the mixture to speed up the crystallization of the complex and then another portion of water was slowly added with stirring until the volume became 4.5-5 L and the mixture was left overnight at rt. The red precipitate was filtered, thoroughly washed with water and air dried. 92.5 g (93%) of complex **1** was obtained and used without further purification. KOH could be used in place of NaOH. BPB·HCl could also be used for the synthesis of **1**, the only alteration of the procedure was that additional base was used for the neutralization of HCl.

Aldol Reaction of Complex (S)-1 with Aliphatic Aldehydes. General Procedures. Synthesis of Complexes* 6a-d,f *containing syn-(2S)-3-Substituted Serines.

To a solution of 0.5 g (1 mmol) of complex **1** in 1.5 mL of MeOH was added 0.5 mL of 4.8 *N* solution of MeONa. The mixture was stirred for 1-2 min to homogeneous solution, and then 0.17g (1.5 mmol) of neat heptanal was added under the stirring at ambient temperature. The reaction mixture was vigorously stirred for 0.5 min and then quenched with 5% aqueous acetic acid. The crystals formed were filtered off, washed with

H_2O and dried over P_2O_5 in vacuum. The crude product obtained was purified on silica gel (column 25 × 4 cm, eluent $CHCl_3$). The main fraction isolated yielded compound **6b**.

Ni(II)-Complex of Schiff's base of (*S*)-BPB and (2*S*, 3*R*)-β-hexylserine 6b: yield 83%, mp 80 °C. $[\alpha]_D^{25}$ = +2540.0 (*c* 0.4, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 0.93 (3H, t, *J* = 8.2 Hz, CH_3) 1.20-1.55 [10H, m, $(CH_2)_5$], 1.62-3.53 (7H, m, Pro-H), 3.20 (1H, m, β-CH), 3.62, 4.38 (2H, AB, *J* = 12.3 Hz, $C\underline{H}_2Ph$), 4.15 (1H, d, *J* = 4.5 Hz, α-CH), 6.61-7.62 (11H, m, ArH), 8.02-8,07 (2H, m, ArH), 8.20-8.24 (1H, m, ArH). Anal. Calcd for $C_{34}H_{39}N_3NiO_4$: C, 74.38; H, 7.16; N, 7.65. Found: C, 74.61; H, 7.19; N, 7.82.

The rest of the complexes **6a**,**c**,**d**,**f** were prepared from complex (*S*)-**1** and appropriate aldehyde as it described for complex **6a**. In the case of oil product formed after quenching of reaction mixture with 5% aqueous acetic acid, filtration could be substituted with $CHCl_3$ extraction, drying over $MgSO_4$ and evaporation.

Ni(II)-Complex of Schiff's base of (*S*)-BPB and (2*S*, 3*R*)-threonine 6a: yield 76%, mp 189-192 °C. $[\alpha]_D^{25}$ = +3175.0 (*c* 0.04, $CHCl_3$); lit.,[9b] $[\alpha]_D^{25}$ = +3244.0 (*c* 0.00127, MeCN). ^{1}H-NMR ($CDCl_3$): 1.97 (3H, d, *J* = 6.5 Hz, CH_3), 1.91-3.70 (8H, m, Pro-H, β-CH), 3.62, 4.36 (2H, AB, *J* = 12.0 Hz, $C\underline{H}_2Ph$), 4.11 (1H, d, *J* = 5.3 Hz, α-CH), 6.55-7.60 (11H, m, ArH), 8.02-8.08 (2H, m, ArH), 8.22-8.28 (1H, m, ArH).

Ni(II)-Complex of Schiff's base of (*S*)-BPB and (2*S*, 3*R*)-β-octylserine 6c: yield 74%, mp 76-78 °C. $[\alpha]_D^{25}$ = +1443.3 (*c* 0.1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 0.90 (3H, t, *J* = 6.7 Hz, CH_3), 1.02-1.55 [14H, m, $(CH_2)_7$], 1.56-3.49 (7H, m, Pro-H), 3.20 (1H, m, β-CH), 3.62, 4.38 (2H, AB, *J* = 12.6 Hz, $C\underline{H}_2Ph$), 4.14 (1H, d, *J* = 4.2 Hz, α-CH), 6.59-7.66 (11H, m, ArH), 8.02-8.06 (2H, m, ArH), 8.20-8.25 (1H, m, ArH). Anal. Calcd for $C_{36}H_{43}N_3NiO_4$: C, 67.51; H, 6.77; N, 6.56. Found: C, 67.80; H, 6.93; N, 6.82.

Ni(II)-Complex of Schiff's base of (*S*)-BPB and (2*S*, 3*R*)-β-*i*-butylserine 6d: yield 85%, mp 178-181 °C. $[\alpha]_D^{25}$ = +1615.8 (*c* 0.04, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 0.89 (3H, d, *J* = 6.8 Hz, CH_3), 1.12 (3H, d, *J* = 6.6 Hz, CH_3), 1.20 (3H, m, CH_2, CH) 1.66-3.57 (8H, m, Pro-H, β-H), 3.56, 4.32 (2H, AB, *J* = 12.7 Hz, $C\underline{H}_2Ph$), 4.11 (1H, d, *J* = 5.0 Hz, α-CH), 6.59-7.58 (11H, m, ArH), 7.93-8.03 (2H, m, ArH), 8.10-8.20 (1H, m, ArH). Anal. Calcd for $C_{32}H_{35}N_3NiO_4$: C, 65.75; H, 5.99; N, 7.19. Found: C, 65.94; H, 6.17; N, 7.03.

Ni(II)-Complex of Schiff's base of (*S*)-BPB and (2*S*, 3*R*)-β-*tert*-butylserine 6f: yield 94%, mp 157-159 °C. $[\alpha]_D^{25}$ = +3215.0 (*c* 0.04, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 1.28 [9H, s, $(CH_3)_3$], 1.60-3.55 (7H, m, Pro-H), 3.60, 4.42 (2H, AB, *J* = 12.6 Hz, $C\underline{H}_2Ph$), 4.06 (1H, d, *J* = 6.6 Hz, β-CH), 4.23 (1H, d, *J* = 6.6 Hz, α-CH), 6.58-7.60 (11H, m, ArH), 8.04-8.08 (2H, m, ArH), 8.27-8.32 (1H, m, ArH). Anal. Calcd for $C_{32}H_{35}N_3NiO_4$: C, 65.75; H, 5.99; N, 7.19; Ni, 10.1. Found: C, 66.31; H, 6.16; N, 7.11; Ni, 9.87.

Synthesis of Complexes* 8a-d,f *containing syn-(2R)-3-Substituted Serines.

To a solution of 0.5 g (1 mmol) of complex **1** in 1.5 mL of MeOH was added 0.5 mL of 4.8 N solution of MeONa . The mixture was stirred for 1-2 min to homogeneous solution, and then 0.17g (1.5 mmol) of neat heptanal was added under the stirring at ambient temperature. The reaction mixture was stirred for 24 hr and then quenched with 5% aqueous acetic acid. The crystals formed were filtered off, washed with H_2O and dried over P_2O_5 in vacuum. The crude product obtained was purified on silica gel (column 25 × 4 cm, eluent $CHCl_3$). The main fraction isolated yielded compound **8b**.

Ni(II)-Complex of Schiff's base of (*S*)-BPB and (2*R*, 3*S*)-β-hexylserine 8b: yield 60%, mp 150-152 °C. $[\alpha]_D^{25}$ = –670 (*c* 0.4, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 0.91 (3H, t, *J* = 8.0 Hz, CH_3) 1.18-1.55 [10H, m, $(CH_2)_5$], 1.79-3.62 (7H, m, Pro-H), 3.85, 4.73 (2H, AB, *J* = 13.2 Hz, C$\underline{H_2}$Ph), 4.01 (1H, m, β-CH), 4.10 (1H, d, *J* = 5.1 Hz, α-CH), 6.60-7.61 (11H, m, ArH), 7.84-7.90 (2H, m, ArH), 8.43-8.49 (1H, m, ArH). Anal. Calcd for $C_{34}H_{39}N_3NiO_4$: C, 74.38; H, 7.16; N, 7.65. Found: C, 74.53; H, 7.21; N, 7.67.

The rest of the complexes **8a,c,d,f** were prepared from complex (*S*)-**1** and appropriate aldehyde as it described for complex **8b**.

Ni(II)-Complex of Schiff's base of (*S*)-BPB and (2*R*, 3*S*)-threonine 8a: yield 73%, mp 163-166 °C. $[\alpha]_D^{25}$ = –617 (*c* 0.08, MeCN); lit.,[9b] $[\alpha]_D^{25}$ = -609.0 (*c* 0.02 MeCN). ^{1}H-NMR ($CDCl_3$): 1.68 (3H, d, *J* = 6.6 Hz, CH_3), 1.72-3.83 (7H, m, Pro-H), 3.88, 4.67 (2H, AB, *J* = 12.8 Hz, C$\underline{H_2}$Ph), 3.86 (1H, m, β-H), 4.06 (1H, d, *J* = 5.2 Hz, α-CH), 6.70-7.65 (11H, m, ArH), 7.83-7.91 (2H, m, ArH), 8.45-8.49 (1H, m, ArH).

Ni(II)-Complex of Schiff's base of (*S*)-BPB and (2*R*, 3*S*)-β-octylserine 8c: yield 67%, mp 141-143 °C. $[\alpha]_D^{25}$ = –611 (*c* 0.04, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 0.89 (3H, t, *J* = 6.9 Hz, CH_3), 1.20-1.54 [14H, m, $(CH_2)_7$], 1.56-3.62 (7H, m, Pro-H), 3.86, 4.75 (2H, AB, *J* = 13.2 Hz, C$\underline{H_2}$Ph), 4.01 (1H, m, β-CH), 4.10 (1H, d, *J* = 5.1 Hz, α-CH), 6.69-7.59 (11H, m, ArH), 7.84-7.89 (2H, m, ArH), 8.45-8.49 (1H, m, ArH). Anal. Calcd for $C_{36}H_{43}N_3NiO_4$: C, 67.51; H, 6.77; N, 6.56. Found: C, 67.77; H, 6.86; N, 6.74.

Ni(II)-Complex of Schiff's base of (*S*)-BPB and (2*R*, 3*S*)-β-*i*-butylserine 8d: yield 65%, mp 147-149 °C. $[\alpha]_D^{25}$ = –618 (*c* 0.04, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 0.86 (3H, d, *J* = 6.3 Hz, CH_3), 1.00 (3H, d, *J* = 6.6 Hz, CH_3), 1.15-3.70 (10H, m, CH, CH_2, Pro-H), 3.78, 4.72 (2H, AB, *J* = 13.2 Hz, C$\underline{H_2}$Ph), 3.94 (1H, m, β-CH), 4.08 (1H, d, *J* = 5.4 Hz, α-CH), 6.55-7.51 (11H, m, ArH), 7.79-7.84 (2H, m, ArH), 8.36-8.41 (1H, m, ArH). Anal. Calcd for $C_{32}H_{35}N_3NiO_4$: C, 65.75; H, 5.99; N, 7.19. Found: C, 65.85; H, 6.03; N, 7.24.

Ni(II)-Complex of Schiff's base of (*S*)-BPB and (2*R*, 3*S*)-β-*tert*-butylserine 8f: yield 18%. $[\alpha]_D^{25}$ = –605 (*c* 0.01, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 1.09 [9H, s, $(CH_3)_3$], 1.57-3.55 (7H, m, Pro-H), 3.69 (1H, d, *J* = 6.6 Hz, β-CH), 3.99, 4.75 (2H, AB, *J* = 13.5 Hz, C$\underline{H_2}$Ph), 4.06 (1H, d, *J* = 6.6 Hz, α-CH), 6.65-7.57 (11H, m, ArH), 7.67-7.71 (2H, m, ArH), 8.50-8.55 (m, 1H, ArH).

Ni(II)-Complex of Schiff's base of (*S*)-BPB and (2*S*, 3*S*)-*allo*-threonine 9a: isolated from the 1 min experiment in the 0.2 M MeONa/MeOH (Table 1, entry 2); yield 21%, mp 199-201 °C. $[\alpha]_D^{25}$ = +3005.0 (*c* 0.03, CH_3CN); lit.,[10b] $[\alpha]_D^{25}$ = +2990 (*c* 0.078, MeCN). ^{1}H-NMR [$CDCl_3$/$(CD_3)_2CO$ = 1/1]: 1.09 (3H, d, *J* = 8 Hz, CH_3), 2.02-3.99 (8H, m, β-H, Pro-H), 3.52, 4.28 (2H, AB, *J* = 12.3 Hz, C$\underline{H_2}$Ph), 3.73 (1H, d, *J* = 4.5 Hz, α-CH), 6.59-7.63 (11H, m, ArH), 8.11-8.19 (1H, m, ArH), 8.28-8.36 (2H, m, ArH).

Isolation of Amino Acids from the Ni(II)-Complexes and Recovery of Chiral Auxiliary (S)-BPB. General Procedure. The solution of Ni(II)-complex in methanol was added in portions to a diluted aqueous HCl solution (1 mL of conc HCl and 2 mL H_2O for 1 g of the complex). The mixture was refluxed for 10-20 min and then cooled to rt, the precipitated crystalline BPB·HCl was filtered, thoroughly washed with water and air dried (the recovery of BPB·HCl was 90-92%). The filtrate was evaporated to dryness in vacuum. The residue was dissolved in water, neutralized with conc NH_3 until pH 7 and extracted 3

times with $CHCl_3$. From the combined organic layers an additional amount (5%) of BPB was isolated. From the water layer the crude amino acid was isolated using a cation exchange technique (10 mL of resin with the capacity 2 mmol/mL was used per 1 g of the decomposed complex). The crude amino acid was dissolved in a minimum volume of boiling water and upon addition of 4-5 volumes of EtOH the amino acid crystallized immediately. This mixture was kept overnight at rt and the amino acid was filtered and dried.

(2*S*)-Threonine (**14a**), (2*R*)-threonine (**15a**) were isolated from complexes **6a**, and **8a** in 67%, and 73% yield respectively. Amino acids obtained **14a**, **15a** have shown physical characteristics in good accord with previously reported data.[10]

(2*S*, 3*R*)-β-hexylserine (14b): yield 57%, mp 201-204 °C. $[\alpha]_D^{25}$ = +6.9 (*c* 1, 6 *N* HCl). ^{1}H-NMR (0.1 *N* DCl in D_2O): 0.58 (3H, t, *J* = 6.5 Hz, CH_3), 0.91-1.23 [8H, m, $(CH_2)_4$], 1.23-1.43 (2H, m, CH_2), 3.78 (1H, d, *J* = 3.4 Hz, α-CH), 3.85-4.01 (1H, m, β-CH). Anal. Calcd for $C_9H_{19}NO_4$: C, 57.12; H, 10.12; N, 7.40. Found: C, 57.34; H, 10.19; N, 7.41.

(2*R*, 3*S*)-β-hexylserine (15b): yield 67%, mp 202-205 °C. $[\alpha]_D^{25}$ = –7 (*c* 1, 6 *N* HCl). ^{1}H-NMR (D_2O): 0.61 (3H, t, *J* = 6.5 Hz, CH_3), 0.94-1.25 [8H, m, $(CH_2)_4$], 1,26-1.47 (2H, m, CH_2), 3.70 (1H, d, *J* = 3.6 Hz, α-CH), 3.88-4.02 (1H, m, β-CH). Anal. Calcd for $C_9H_{19}NO_4$: C, 57.12; H, 10.12; N, 7.40. Found: C, 57.21; H, 10.17; N, 7.35.

Data for **(2*S*, 3*R*)-, (2*R*, 3*S*)-β-*i*-propylserines (14e), (15e) and (2*S*, 3*R*)-β-*tert*-butylserine (14f)** are given in corresponding protocols for large scale preparations.

Detailed Protocols for Large Scale Preparation of syn-(2R)-, syn-(2S)-β-i-Propylserine and syn-(2S)-β-tert-Butylserine.

Synthesis of *syn*-(2*R*)-, *syn*-(2*S*)-β-*i*-Propylserines in a Single Experiment. A 4.93 *N* solution of MeONa in MeOH (122 mL, 0.6 mol) was poured into a stirred mixture of 200 g (0.4 mol) of complex **1**, 108.8 mL (86.4 g, 1.2 mol) *i*-PrCHO and 800 mL EtOH under N_2 at rt. In order to obtain both enantiomers of *syn*-β-hydroxyleucine in approximately equal amounts (Table 1, entry 19) the reaction was quenched after 30 min by addition of AcOH (48 mL, 50.4 g, 0.84 mol) to the stirred reaction mixture. After 1 h at rt a semicrystalline slurry was formed. It was filtered, thoroughly sucked and washed successively with 600 mL of water-acetone (1:1) mixture and 600 mL of waster and then air dried. 121.6 g (51.3%) of **8e** with de 90% was obtained. The filtrate was diluted with water to 5 L volume, the precipitated oil crystallized slowly. The precipitate was filtered, washed with water and dried in air, furnishing 111.2 g (48.5%) of **6e** with de 80%.

Analytical samples of **8e** and **6e** were obtained by chromatography on SiO_2 (**8e** had higher R_f value than **6e**, THF-PhH, 1:1) and additional purification on Sephadex LH-20 (PhH-EtOH 3:1). Anal. **6e**. Calcd for $C_{31}H_{33}N_3NiO_4$: C, 65.29; H, 5.83; N, 7.36. Found: C, 65.29; H, 6.25; N, 6.82. Anal. **8e**. Calcd for $C_{31}H_{33}N_3NiO_4$: C, 65.29; H, 5.83; N, 7.36. Found: C, 65.61; H, 6.02; N, 6.85.

Crude *syn*-(2*S*)-β-hydroxyleucine **14e** obtained from 111.2 g (0.195 mol) of **6e** with ee 80% was recrystallized twice from aqueous EtOH. The additional amount of amino acid (60% ee) could be isolated from the combined evaporated filtrates. Recrystallization from a minimum volume of hot water gave a sample with ee ca 80%. Further recrystallization twice from aqueous EtOH gave enantiomerically pure compound. The optically pure samples were combined and dried in vacuum over P_2O_5 at 80 °C to give 17.6 g (61.4%) of *syn*-(2*S*)-β-hydroxyleucine **14e**. $[\alpha]_D^{25}$ +18.5 (*c* 1, 5 *N* HCl) [lit.[23]: for hydrate of *syn*-(2*S*)-β-hydroxyleucine $[\alpha]_D^{25}$ +15 (*c* 2, 5 *N* HCl). ^{1}H-NMR (D_2O): 0.85 (3H, d, *J* = 7.0 Hz, CH_3), 0.90 (3H, d, *J* = 7.0 Hz, CH_3),

1.65 (1H, m, CH), 3.67 (1H, dd, J = 4.0, 8.0 Hz, β-CH), 3.77 (1H, d, J = 4.0 Hz, α-CH). Anal. Calcd for $C_6H_{13}NO_3$: C, 48.97; H, 8.9; N, 9.51. Found: C, 49.08; H, 9.09; N, 9.46.

Crude *syn*-(2*R*)-β-hydroxyleucine **15e** obtained from 121.6 g (0.213 mol) of complex **8e** with de 90% was recrystallized from aqueous EtOH. An additional amount of the amino acid was obtained after the evaporation of the filtrate and two recrystallizations of the residue. The combined crops after being dried in vacuum over P_2O_5 at 80 °C gave 27.4 g (87.5%) of *syn*-(2*R*)-β-hydroxyleucine with ee > 99%. $[\alpha]_D^{25}$ -18.5 (*c* 2, 5 *N* HCl). ^{1}H NMR spectra was identical with that of *syn*-(2*S*)-isomer. Anal. Calcd for $C_6H_{13}NO_3$: C, 48.97; H, 8.9; N, 9.51. Found: C, 48.82; H, 9.24; N, 9.64.

Synthesis of *syn*-(2*S*)-β-*i*-Propylserine under Pseudokinetically Controlled Conditions. A 4.26 *N* solution of MeONa in MeOH (142 mL, 0.6 mol) was added at once to a stirred mixture of 100 g (0.2 mol) of complex **1**, *i*-PrCHO (54.4 mL, 43.2 g, 0.6 mol) and MeOH (140 mL) under N_2 at 0 °C. After 3 min AcOH (60 mL, 62.8 g, 1.05 mol) was added with stirring followed by 400 mL of water. The crystallization began immediately. After 1 h the precipitate was collected, thoroughly washed with water and dried in air to give 114 g (99.6%) of complex **6e** with de 80% identical to that described above. (The reaction can be carried out in EtOH, but complex **6e** precipitated as an oil which crystallized very slowly). The isolation and purification of *syn*-(2*S*)-β-hydroxyleucine was performed as described above.

Synthesis of *syn*-(2*S*)-β-*tert*-Butylserine. To a stirred mixture of 49.8 g (0.1 mol) of (*S*)-**1**, 16.3 mL (13 g, 0.15 mol) *tert*-BuCHO and 100 mL of MeOH a solution of MeONa (3.94 *N*) in MeOH (76 mL, 0.3 mol) was added. The resulting solution was stirred for 20 min at ambient temperature and then quenched with 24 mL AcOH. After addition of ca 300 mL of water the precipitated solid was filtered, thoroughly washed with water and dried on air to afford 54.4 g (95%) of complex **6f** (de ca 90%). This was decomposed and amino acid isolated according to the above procedures to give crude amino acid with ee 89%. The latter was recrystallized from boiling water to give 7.9 g of optically pure **14f**. Additional crop (2.5 g) of **14f** with ee 98.8% was obtained after evaporation of mother liquor and recrystallization of residue from water. The combined yield of hydrate of **14f** with ee >99% was 10.4 g [58%, based on starting (S)-**1**]. $[\alpha]_D^{25}$ +5.35 (*c* 1, 5 *N* HCl); +6.08 (*c* 1, 6 *N* HCl). ^{1}H NMR (D_2O): 0.92 [9H, s, $(CH_3)_3$], 3.86 (1H, d, J = 2.0, Hz, β-CH), 4.13 (1H, d, J = 2.0 Hz, α-CH). Anal. Calcd for $C_7H_{15}NO_3 \cdot H_2O$: C, 46.92; H, 9.49; N, 7.82. Found: C, 46.53; H, 9.02; N, 7.53.

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5 α-Amino-β-hydroxy carboxylic acids are naturally occurring compounds. Some of them being proteinogenic and/or essential amino acids are involved in various physiological processes in living organisms therefore, analogs of these amino acids are very interesting as biomedical tools or potential inhibitors. Other α-amino-β-hydroxy carboxylic acids are constituents of complex natural products such as cyclosporin, bouvardin, peptides and glycopeptides, which usually posses high antibiotic activity. In addition, these amino acids are valuable precursors to β-lactam antibiotics.

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8 The glycine fragment in complex **1** has a significant CH acidity, and corresponding carbanion can be easily generated under the action of such a weak bases as triethylamine or Dabco. Thus, pK_a value of (*S*)-**1** in DMSO is 18.8, that is greater than that of acetophenone (pK_a = 24.7) and fluorene (pK_a = 22.6) and comparable with that of mononitro compounds ($pK_a \approx 17$). For pK_a value of complex **1** see: (a) Terehova, M. I.; Belokon', Yu. N.; Maleev, V. I.; Chernoglazova, N. I.; Kochetkov, K. A.; Belikov, V. M.; Petrov, E. G. *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1986**, 905. (b) Belokon', Yu. N.; Maleev, V. I.; Vitt, S. V.; Ryzhov, M. G.; Kondrashov, Y. D.; Golubev, S. N.; Vauchskii, Y. P.; Novikova, M. I.; Krasutskii, P. A.; Yurchenko, A. G.; Dubchak, I. L.; Shklover, V. E.; Struchkov, Y. T.; Bakhmutov, V. I.; Belikov, V. M. *J. Chem. Soc., Dalton Trans.* **1985**, 17. For pK_a values of fluorene, acetophenone, and mononitro compounds see: Matthews, W. S.; Baras, J. E.; Bartmess, J. E.; Bordwell, F. G.; Cornoforth, F. J.; Drucker, G. E.; Margolin, Z.; McCallum, R. S.; McCallum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.*, **1975**, *97*, 7006.

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14 The electrostatic repulsion between trifluoromethyl (or in general perfluoroalkyl) group and negatively charged ionized carboxylic group, and electrostatic attraction between the positively charged Ni(II)-ion and fluorine atoms of fluoroalkyl group of an amino acid moiety was suggested with some hesitation by us to explain this unexpected result: see ref. 11a.

15 Crystals of compound **6f** were grown up from chloroform. Crystal data for **6f**: $C_{32}H_{35}N_3NiO_4$, red prisms, 0.5 × 0.3 × 0.2 mm, monoclinic, $P2_1$. Unit cell: a = 11.742(3), b = 10.612(4), c = 13.603(4) Å,

β = 90.36(2)°, V = 1695.0(9) Å^3, Z = 2, D_X = 1.306 Mg/m^3. Full crystallographic data have been deposited at the Cambridge Crystallographic Data Center and are available from the principal authors.

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