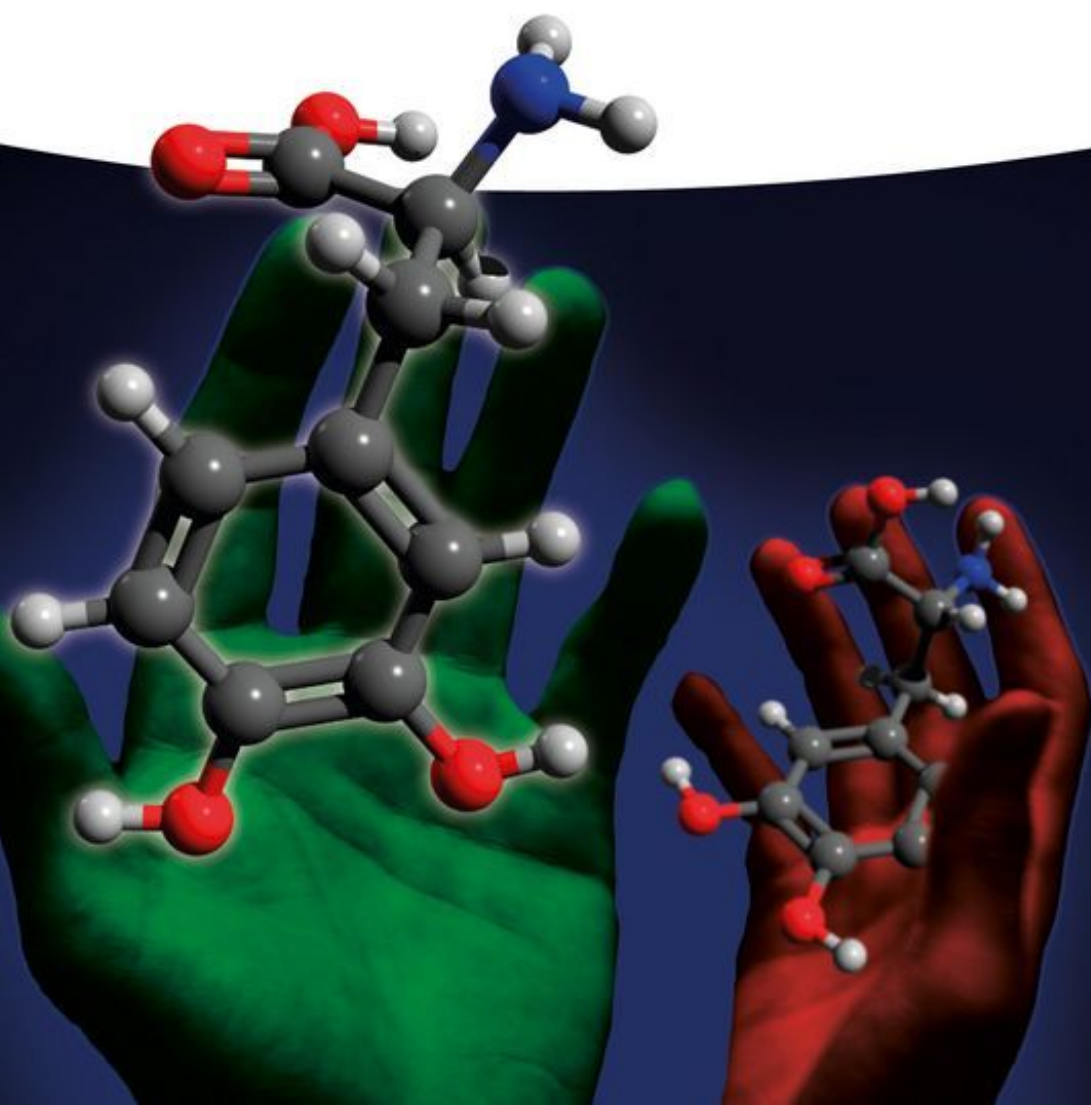


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WILEY-VCH
Verlag GmbH & Co. KGaA

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Library of Congress Card No.: applied for

British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library.

Bibliographic information published by the Deutsche Nationalbibliothek

The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at <<http://dnb.d-nb.de>>.

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Print ISBN: 978-3-527-34041-5

ePDF ISBN: 978-3-527-80448-1

ePub ISBN: 978-3-527-80447-4

Mobi ISBN: 978-3-527-80446-7

oBook ISBN: 978-3-527-80449-8

Cover Design Schulz Grafik-Design,

Fußgönheim, Germany

Typesetting SPi Global, Chennai, India

Printing and Binding

Printed on acid-free paper

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List of Abbreviations

AA	amino acid
Ala	alanine
AS	asymmetric synthesis
BBA	(<i>S</i>)-2-[<i>N</i> -(<i>N'</i> -benzylpropyl)amino]benzaldehyde
BBX	(<i>S</i>)- <i>N</i> -[2-(2,5-dimethylphenyl)-benzoyl]-1-benzylpyrrolidine-2-carboxamide
BPB	(<i>S</i>)-2-[<i>N</i> -(<i>N'</i> -benzylpropyl)amino]benzophenone
CD	circular dichroism
Dabco	diazobicyclooctane
DAST	(diethylamino)sulfo trifluoride
de	diastereomeric purity
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DOPA	3,4-dihydroxyphenylalanine
EDTA	ethylenediaminetetraacetate
ee	enantiomeric purity
GABA	gamma-Aminobutyric acid or γ -Aminobutyric acid
GLC	gas-liquid chromatography
Glu	glutamic acid
Gly	glycine
HPLC	high-performance liquid chromatography
Iva	isovaline
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
Nle	norleucine
ORD	optical rotatory dispersion
PBA	(2-formylphenyl)-amidopyridyl-2-carboxylic acid
PBP	(2-benzoylphenyl)-amidopyridyl-2-carboxylic acid
PET	positron emission tomography
Phe	phenylalanine
PP	pyridoxal phosphate
Pro	proline
PTC	phase-transfer catalysis

RM	reaction mixture
RPD	radiopharmaceutical drug
Ser	serine
TBAB	tetrabutylammonium bromide
THF	tetrahydrofuran
XRD	X-ray diffraction analysis
(+)-NLE	positive nonlinear effect
(<i>R</i>)-BINOL	(<i>R</i>)-2,2'-dihydroxy-1,1'-binaphthyl
(<i>R</i>)-NOBIN	(<i>R</i>)-2-amino-2'-hydroxy-1,1'-binaphthyl
(<i>R,R</i>)-TADDOL	(4 <i>R</i> ,5 <i>R</i>)-2,2-dimethyl- $\alpha,\alpha,\alpha',\alpha'$ -tetraphenyl-1,3-dioxolane-4,5-dimethanol
(<i>S</i>)-[¹¹ CH ₃]MET	(<i>S</i>)-[¹¹ Cmethyl]methionine
(<i>S</i>)-[¹⁸ F]FET	(<i>S</i>)- <i>O</i> -2-([¹⁸ F]fluoroethyl)tyrosine
(<i>S</i>)-[¹⁸ F]-FPT	(<i>S</i>)- <i>O</i> -3-([¹⁸ F]fluoropropyl)tyrosine
(<i>S</i>)-2-[¹⁸ F]FTYR	(<i>S</i>)-2-[¹⁸ F]fluorotyrosine
(<i>S</i>)-2-CBPB	(<i>S</i>)- <i>N</i> -(2-benzoylphenyl)-1-(2-chlorobenzyl)pyrrolidine-2-carboxamide
(<i>S</i>)-3,4-DCBPB	(<i>S</i>)- <i>N</i> -(2-benzoylphenyl)-1-(3,4-dichlorobenzyl)pyrrolidine-2-carboxamide
(<i>S</i>)-3,4-DMBPB	(<i>S</i>)- <i>N</i> -(2-benzoylphenyl)-1-(3,4-dimethylbenzyl)pyrrolidine-2-carboxamide
TLC	thin-layer chromatography
[¹⁸ F]FDG	2-[¹⁸ F]fluoro-2-deoxy-D-glucose

Introduction

Even from the very beginning of writing this book, I thought about its impending introduction. It seemed to me that some clarification of the reasons that prompted me to write this book may be useful for a reader.

One of the major challenges currently facing the chemical science and industry is the synthesis of enantiomerically pure and physiologically active compounds of unusual structure. This branch of science under the general title “Biotechnology,” has undergone rapid development over the past decades due to brilliant achievements in the field of biochemistry, bioorganic, and biomimetic chemistry.

To develop efficient methods for the asymmetric synthesis of active chiral molecules, it is necessary, first of all, to simulate the processes that occur in nature under the influence of enzymes. Such advances in stereochemistry, as identifying the chirality of molecules, the manifestation of different reactivity of enantiotopic substituents in enzymatic transformations, and many others have always been highly appreciated by scientists of different disciplines.

At first, these achievements seemed to be far from the needs of everyday life, and, as the experts of stereochemistry joked – “the majority of mankind does not care in what configuration the chiral molecule is used.” However, the situation changed when it was found that the enantiomers in racemic drugs had different, sometimes opposite effects. Then, the problem of stereoselective synthesis of chiral molecules immediately moved into the area of interest of both producers and businessmen who invest heavily in the promotion of these drugs on the market.

This book reflects my research interests over the past 30 years, and, therefore, its content is highly subjective. It is dedicated to a rather narrow and important class of physiologically active compounds: enantiomerically pure amino acids of nonprotein origin.

Recently, these compounds have been in the focus of scientists working in the field of pharmacology, medicine, microbiology, synthesis of physiologically active peptides, and other pharmaceuticals.

The book contains results of our studies and research of scientists known worldwide in the area of stereoselective synthesis of amino acids.

Chapter 1 summarizes data on the natural origin of nonprotein amino acids and aspects of their use. Chapter 2 provides pathways of natural transformations of

amino acids under the influence of pyridoxal phosphate (PP)-dependent enzymes and the results of biomimetic studies of the mechanisms of these transformations.

At a glance, it may seem unusual to include material on the synthesis of natural protein amino acids in the monograph devoted to the main methods for obtaining enantiomerically pure nonprotein amino acids. However, carefully looking at the presentation of the material, the reader will understand that without a clear understanding of the mechanisms of natural transformation of amino acids it is unreal to construct realistic biomimetic systems for the asymmetric synthesis of nonprotein amino acids.

Chapter 3, the main one of the monograph, is devoted to the modern methods for the asymmetric synthesis of nonprotein amino acids. In this chapter, the known methods of stoichiometric and catalytic asymmetric syntheses of amino acids, obtaining and testing of both known and new modified chiral catalysts and auxiliary reagents in asymmetric synthesis reactions of (*S*)- and (*R*)- α -amino acids, including aliphatic, aromatic, and heterocyclic-substituted amino acids and their isotope-labeled analogs are discussed in detail. I thought it appropriate to include in this chapter information on the original technology for isolation and purification of proline amino acid from microbial fermentation solutions, developed by us, which is connected with the subject of this monograph. A flow diagram of small-tonnage production of optically active nonprotein amino acids, which was developed with the financial support of the ISTC, is presented at the end of the chapter.

The present monograph exclusively concentrates on chemical methods for the synthesis of α -amino acids. β -Amino acids and biological (enzymatic) methods for the synthesis are not covered.

I want to note that, in the world literature, recently there appeared several review articles on the synthesis of optically active nonprotein amino acids; however, they do not describe in detail biomimetic methods for the asymmetric synthesis of amino acids with the use of metal complexes. In our view, this monograph can be a useful source for researchers, graduate students, and doctoral candidates working in the field of asymmetric synthesis of amino acids and other chiral molecules. I also want to indicate a high degree of accuracy of the data presented in the monograph, verified with such modern physical and chemical methods of analysis as ^1H and ^{13}C NMR, X-ray diffraction analysis (XRD), chiral high performance liquid chromatography (HPLC), GLC, IR, circular dichroism (CD), optical rotatory dispersion (ORD) curves, and so on.

I think that the knowledge of a relatively young field of stereoselective synthesis of chiral molecules intensively developing worldwide together with its successes and opportunities available today will inevitably contribute to a wide range of experts, synthetic chemists, biochemists, pharmacologists, and biotechnologists. The aspects described in this monograph will benefit the country's science and contribute to the development of the pharmaceutical industry.

I take this opportunity to thank some of my colleagues and employees. In particular, I acknowledge the contributions of Doctor of Science, Professor of RAS Belokon Yuri N., who is the main contributor of many developments that

are reflected in this monograph and of my assistant Doctor of Science Anna F. Mkrtchyan for the rendered help in making the monograph. I am very grateful to a number of my research associates from the Institute of Biotechnology and Department of Pharmaceutical Chemistry, Yerevan State University, who worked under my supervision in recent years. Finally, I thank my family for the fact that during the writing of this monograph (at the same time of another textbook, “Chemistry of amino acids, peptides and proteins”), they took all my moods with patience and love.

Academician of NAS RA, Professor Ashot Saghyan
Prof. Dr h.c. mult. Peter Langer

1

Non-Proteinogenic α -Amino Acids, Natural Origin, Biological Functions

α -Amino acids are an important class of physiologically and pharmacologically active compounds. There are more than 1000 different amino acids in microbial cells and plant tissues. However, only 26 of them are found in protein compositions, from which only 20 amino acids can be considered typical components of proteins.

In recent years, the need for significant amounts of α -amino acids has been steadily increasing due to their extensive use in biotechnology, medicine, food, microbiology, and other areas of science and technology [1, 2]. If in the past, the need for most of α -amino acids was met by obtaining them from protein *hydrolysates* or other natural sources, from the second half of the twentieth century microbiological and synthetic directions of obtaining α -amino acids have been intensively developed.

Selection of a particular method for producing amino acids is mainly determined based on the requirements to chemical and optical purity of the final products and the area of their further use.

Synthetic methods can be considered general only if starting materials necessary for the synthesis are readily available, and reaction conditions and experimental techniques at each stage of the synthesis are similar for all amino acids. However, this is not always possible because the side chains of amino acids can have diverse structures. In addition, the main drawback of the achiral methods of chemical synthesis is the formation of amino acids in the form of racemic mixtures that could be separated on their optically active antipodes by enzymatic or microbiological methods only in the case of protein α -amino acids. In connection with this, achiral chemical methods for amino acid synthesis have found a practical application only for the production of several protein α -amino acids.

Despite this, the current total production of α -amino acids worldwide is about half a million tons per year. A large-scale production of mainly protein amino acids is due to their wide use in medicine, agriculture (growth-stimulating food additives), and food industry (flavoring substances and preservatives). The practical importance of individual amino acids is proved by the scale of their biotechnological and chemical production: tryptophan is produced in the amount of 0.2–0.3 thousand tons, glycine at 7–10 thousand tons, lysine at about

50 thousand tons, methionine at 150–200 thousand tons, glutamic acid at more than 200 thousand tons per year, and so on.

Specifically, methionine is used in medicine for the treatment and prevention of hepatotoxicity and diabetes, while a mixture of methionine and cysteine is used for the treatment of different kinds of poisoning. A mixture of glycine and glutamic acid is used to control gastric acidity. Pure glutamic acid is used for the treatment of CNS disorders (epilepsy, psychosis in children with polio, and mental retardation), and its sodium salt as flavoring and preservative in food. Vitamin B₃ (pantothenic acid), which contains a fragment of the nonprotein amino acid β -alanine (3-aminopropionic acid) is used in polyneurites, dermatoses, bronchitis, venous ulcers. Nonprotein γ -aminobutyric acid, detected in mammalian brain in 1950, acts as a mediator in the transmission of nerve impulses. γ -Aminobutyric acid (GABA) (aminolon, gammalon) is used to treat nervous system disorders, speech disorders, memory loss, cerebral vascular atherosclerosis, and mental retardation in children. 6-Aminohexanoic acid (ϵ -aminocaproic acid) is used in medicine to stop severe bleeding, as it helps in effective blood clotting.

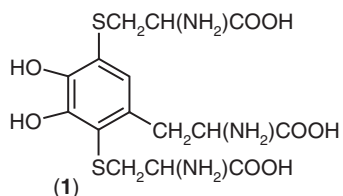
Several oligomers of α -amino acids play an important role in body functions, and some of them are used in medical practice. Thus, methyl ether of L-asparagyl-L-phenylalanine dipeptide (aspartate, aspartame) is used for diabetes as low calorie sugar substitute (150 times sweeter than glucose); a natural antibiotic *Gramicidin*, *S*-cyclic decapeptide – [Val-Orn-Leu(D)-Phe-Pro]₂, produced by *Bacillus brevis*, has bacteriostatic and bactericidal action and is used to treat wounds, burns, and inflammatory diseases. It is also interesting to note that this antimicrobial peptide includes a D-form of phenylalanine. Recently, a number of small natural peptides (of leather tree frogs, snails ganglion, and poison spiders), containing one or two D-amino acids were isolated. It has been found that the D-form of the amino acid moiety in such peptides greatly increases their resistance to hydrolytic action of exo- and endoproteases. This fact is taken into account when oligopeptide drug substances with prolonged action are created [3].

Organisms can vary greatly in their metabolism because of the differences in their amino acid structure. Lately, researchers are more and more attracted by nonprotein α -amino acids with unusual structures. These include those amino acids that do not exist in the main chains of the proteins due either to the lack of specific tRNA or corresponding triplet codon or to the fact that nonprotein amino acids are not subject to a posttranslational modification. Many of these compounds are the end products of secondary metabolism, others occur as intermediates or as a result of metabolism or detoxification of foreign compounds. Due to the nature of bacterial metabolism, formation of many new compounds is possible by biosynthetic processes by adding the corresponding cell compounds to the substances of nutrient medium. These unusual amino acids can be also obtained synthetically; however, the number of “artificially” obtained amino acids of unusual structure is limited in the literature.

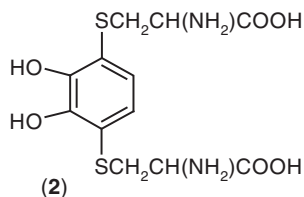
In essence, the nonprotein amino acids are functionally substituted derivatives of protein amino acids (substituted by α -NH₂, α -COOH, SH, OH, β , and γ -COOH,

δ -NH₂, imidazole, guanidine groups, etc.) and C-alkylated analogs (α , β , γ , etc.) with a variety of aliphatic, aromatic, and heterocyclic substituents.

One of the first isolated and identified nonprotein amino acid is *dicysteinyldopa* [4]. Study of a major constituent of yellow pigment *Tapetum*, isolated from a sea pike *Lepisosteus*, revealed a new sulfur-containing product, which was purified by chromatography (*Sephadex* L1120, *Dowex* 50) and identified by physicochemical methods of analysis. Spectral analysis showed the presence of sulfur-containing *ortho*-diphenyl amino acid. After reductive hydrolysis of the isolated substance in hydrochloric acid, cysteine and dihydroxyphenylalanine (DOPA) in a ratio of 2/1 attached by thioester bond were obtained as the main products (¹H NMR data) (1).



This structure (1) was partially confirmed by biological synthesis. Tyrosinase oxidation of *L*-DOPA in the presence of an excess *L*-cysteine resulted in the same amino acid with 5- and 3-*S*-cysteinyldopa, indicating the substitution in positions 2 and 5 of the aromatic ring. Under the same conditions, catechol and cysteine formed 3,5-cysteinylcatechol and 3,6-*S,S*-dicysteinylcatechine (2), which is an additional argument in favor of the 3,5-substituted phenyl ring (3,6-*S,S*-dicysteinylcatechine – symmetric structure of compound 1).



(2 *S*,2¹*S*,2¹¹*S*) – absolute configuration of the isolated product was established by comparing the data of polarimetric measurements of natural and synthetic product samples obtained from *L*-DOPA and *L*-cysteine.

The unusual amino acid, 2,4-diamino-3-methylbutyric acid [5], was found in the amino acid composition of root nodules of *Lotus* plant, which is produced by the bacterial strain of *Rhizobium*. Chromatographic and spectral analysis (NMR, mass spectroscopy, and chiral Gas-liquid chromatography (GLC) of the fraction isolated from the acid hydrolysate of the ethanol extract of this plant by ion-exchange methods (*Amberlite* IR 120, *Dowex* 50) established its (2*R*,3*S*)-absolute configuration. In the same plant species, among the protein amino acids, ninhydrin-positive compounds with unusual *R*_f values were also found.

In general, more than 1000 nonprotein amino acids are found in nature, extracted from plants, microorganisms, and other sources. Complete information on nonprotein amino acids are presented in the book by Barrett [6].

The main sources of known nonprotein amino acids are fauna and microorganisms that are responsible for excreting many compounds into the environment [7]. Many microbiological products show antibiotic properties, and by analogy with the fungi products, contain unusual amino acids included in more complex structures such as depsipeptides [8]. In these structures, D- and L-amino acids of common and unusual nature are connected to each other by peptide as well as by other bonds with components such as carboxylic acids and hydroxy acids. These natural molecules are rich sources of new amino acids with unusual structure.

In higher plants, unusual amino acids are most often found in free state or in the form of low-molecular-weight complexes, such as with glutamic acid. The concentration of these compounds in plant tissues can be very high. Many of the unusual amino acids from plants and animals are components of a number of pigment structures [9, 10].

Bacteria and plants differ from animal organisms by the content and chemical nature of nonprotein amino acids which affect their metabolism. In products of metabolism of animal organisms, there are no secondary by-products such as nonprotein amino acids, alkaloids, phenols, and other substances that are characteristic of lower organisms and plants.

A significant portion of nonprotein amino acids in plants have aliphatic structure, with no more than six carbon atoms in chain length, although there are also large molecules. The diversity in their structures is achieved by limited branching, substitution of hydroxyl, carboxyl, and amino groups, as well as inclusion of unsaturated allene and alline groups into the molecule. Despite the variety of halogenated aromatic compounds in marine organisms [11] and the possibility of substitution of the phenolic ring by halide atoms, the discovery of such a small number of free halogen-containing aromatic amino acids in natural sources was unexpected. In fact, any type of halogenated amino acids is relatively rare among chlorine-containing bacterial products, even in algae and marine invertebrates that are known to produce proteins and other halogenated by-products [12].

In contrast to cyclic aromatic amino acids, heterocycles of both aromatic and nonaromatic series are part of many amino acids. It is expected that most of these are nitrogen-containing heterocycles, although many of them also contain oxygen or sulfur in the ring. A number of nitrogen-containing heterocyclic amino acids derived from tryptophan are substituted in the indole ring analogs. Other nitrogen heterocycles are closely related to pyrrolidone ring and are homologs of proline.

Although there are many heterocyclic imino acids, many developments are aimed at expanding a limited number of aliphatic imino-acids with pyruvate and the products derived from amino acids such as strombine and alanopine, which are added to the octopine as components of anaerobic metabolism in invertebrates [13, 14].

Based on the diversity of the structures, it is not surprising that the clear pattern of biosynthetic origin of nonprotein amino acid is difficult to predict. If we

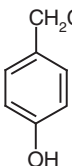
take into account the impact of environmental and other effects that lead to the accumulation of specific components, it seems likely that there are three or four general ways for the emergence of nonprotein amino acids in nature.

A possible synthesis route for many well-known products is modification of existing amino acids by mechanisms similar to those involved in posttranslational modification of protein amino acids, that is, a simple replacement of certain positions in the structure of protein amino acids. Obtaining dihydroxyphenylalanine in plants from the synthesis cycles of tyrosine [15], β -acetyl-ornithine [16], or *O*-acetylserine [17] are well-grounded examples of such modifications. The emergence of hydroxyproline [18], desmosine, and isodesmosine [19] in protein chains or pyridinoline [20] in the urine of mammals is as an example of appearance of new amino acids as posttranslational modifications of amino acids.

Thus, it is potentially possible to form many simple analogs of known amino acids by simple postsynthetic modification of 20 protein amino acids in different ways. In fact, certain amino acids are more involved in this type of modification than others. For example, in nature, there are quite many lysine analogs and very few products obtained from valine. It is obvious that the reactivity of the side chains is in favor of such modifications. The reactive thiol group of cysteine promotes the formation of a relatively large number of amino acids, and the formation of α -amino- α -carboxyl group in α -amino acids occurs by amination of keto acids in the initial stages of the synthesis of amino acids. If the formation of the functional groups in the side chain of amino acids includes several enzymatically catalyzed steps, then it is easy to imagine how the modification in intermediate stages can lead to the formation of one or more new amino acids. Perhaps, many free amino acids are formed in such a way that intermediates are actually involved in the formation of a particular amino acid. In the absence of metabolic function, the existence of these amino acids may be temporary. As examples can serve the formation of phosphoserine in the route to serine synthesis from 3-phosphoglycerate or glutamyl- γ -semialdehyde [21], or the accumulation of homoserine in the route to methionine and threonine synthesis from aspartate, or the accumulation of ornithine in the route to arginine [21]. The precursor of amino acids in the latter synthesis is glutamyl- γ -semialdehyde, while the related derivative of aspartate affords homoserine, which in turn is formed from aspartyl phosphate [21]. If we consider all possible intermediates of those types of derivatives, the list of nonprotein amino acids will be much greater.

Accumulation of homocysteine along with other unusual sulfur-containing amino acids in the blood and urine of patients with homocystinuria indicates an anomaly in the metabolism of methionine. This process can be treated as a side condensation reaction of homocysteine with serine with the formation of cystathionine, which is catalyzed by cystathionine synthase [22, 23]. Pyroglutamic acid (5-oxoproline) can appear in the urine as a result of abnormal metabolism, due to the lack of 5-oxoprolinase, which is a component of γ -glutamyl cycle [22].

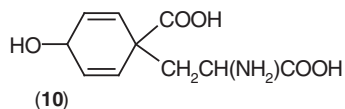
The most reasoned example of abnormal metabolism is the formation of shikimate from chorismate (see Scheme 1.1). Common amino acids phenylalanine and tyrosine are synthesized from shikimate (3) through chorismate (4) and



Scheme 1.1

prephenate (5). Vegetal amino acids β -(3-carboxyphenyl)alanine (6) and β -(3-carboxy-4-hydroxyphenyl)alanine (7) are synthesized by the same path directly from both chorismate and transformation of chorismate to isochorismate (8), and then to isoprephenate (9) followed by the aromatization of the ring where the modification may only exclude the decarboxylation stage [23, 24]. However, sometimes there is a deviation from this principle.

During the formation of other new aromatic amino acids from chorismate, such as the synthesis of *p*-aminophenylalanine in *Vigna*, amination of chorismate is observed [25]. An interesting variant of such a modification is an alternative route for the synthesis of tyrosine from chorismate in *Pseudomonas*, proceeding through a specific compound pterosine or arogenate (10) [26].

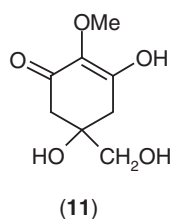


Although the new amino acids are the result of “tuning” of the metabolic pathways and metabolites, as described earlier, it is equally clear that this path cannot fully provide the formation of many unusual compounds.

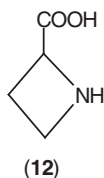
Sometimes, even those nonprotein amino acids, structures of which seem to be very similar to the structures of protein amino acids, are products of convergent rather than parallel development. L- β -Aspartic acid in *Clostridium tetanomorphum* is formed not from aspartate, but by means of a new rearrangement of L-glutamate involving 5'-deoxyadenosylcobalamine in the aerobic enzymatic reaction [21].

A similar methyl derivative – *erythro*-methyl- γ -glutamic acid is formed into *Gleditsia triacanthos* not from glutamic acid, but from L-leucine by the oxidation of the methyl group [27].

Currently, the actual data on the biosynthesis are available only for several groups of nonprotein amino acids. Possible ways of formation of the majority of nonprotein amino acids can only be assumed based on the known metabolic pathways for the synthesis of their protein counterparts. For example, mycosporine-like mutilins and related amino acids are probably formed by the condensation of protein amino acids of glycine, serine, and threonine with the original diketone (11) obtained by shikimate pathway [28]. Strombine and alanopine are formed by the condensation of pyruvate with glycine or alanine in the presence of NADH and dehydrogenase [13]. This reaction has common features with the synthesis of glutamate from α -ketoglutarate and ammonium ion by means of glutamate dehydrogenase and NADH.



To the unusual amino acids belongs the heterocyclic amino acid azetidine-2-carboxylic acid (12), which, as it was expected, is synthesized by a totally new pathway, and for its formation the hypothetical scheme of synthesis from homoserine via 2,4-diaminobutanoate to 4-amino-butanoate with subsequent cycle closure and dehydration was proposed.



Unusual amino acids can play many roles *in vivo*; however, presently, for most of these compounds, the specific functions are not determined. It should be noted that nonprotein amino acids of plant origin exhibit physiological activity in animals, but in some cases, these compounds cannot perform certain functions.

A significant aspect of plant metabolism is the need to retain nitrogen, thus to limit the loss of nitrogen through the synthesis of secreted nitrogen compounds. Since animals do not need to retain nitrogen, they are able to produce and excrete nitrogen-containing compounds. The nitrogen that is required for the synthesis of proteins in plants can be accumulated in large amounts in the form of alanine, asparagine, arginine, acetylornithine, allantoin, citrulline, and glutamine, which makes the protein synthesis easily traceable. However, in many cases, accumulation of high concentration of unusual amino acids does not guarantee this pathway, it is possible that some of the substances are not intended to serve as a nitrogen source or they cannot participate in metabolism.

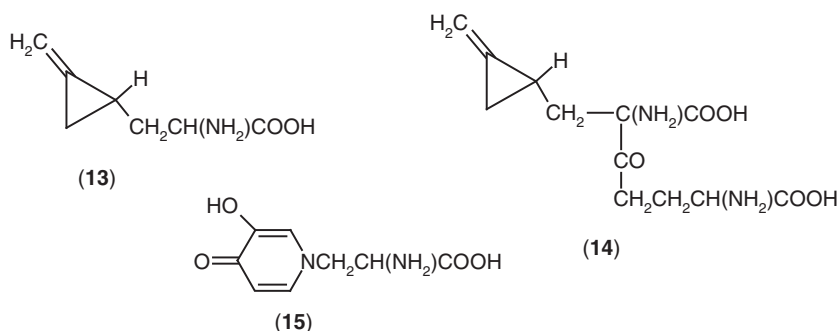
An important property of many nonprotein amino acids is their toxicity or the ability to adversely affect the metabolism of other compounds. Many plant non-protein amino acids structurally are very similar to protein amino acids. In this sense, the accuracy of translation system is not surprising. In spite of the relative abundance of such compounds, it almost does not allow any errors, nor includes these compounds in the composition of the protein. However, nonprotein amino acid can be included in the composition of the protein, if it has a very similar structure to protein amino acids. A classic example is the introduction of azetidine-2-carboxylic acid by tissues of *Phaseolus aureus* as a replacement of proline moieties in protein [29].

Introduction of abnormal amino acid into proteins of organisms, for which this amino acid is a foreign compound, significantly alters the properties of these proteins and generally increases their toxicity.

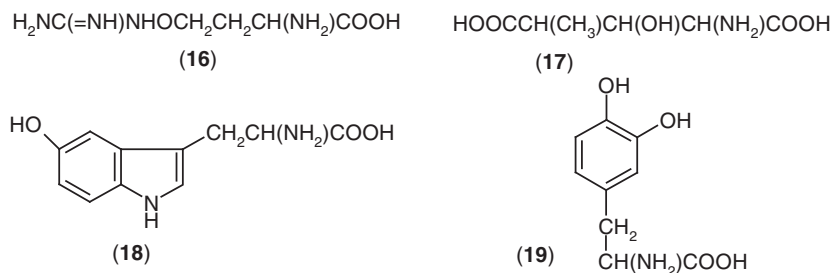
In plants, β -aminopropionitrile is formed by the decarboxylation of β -cyano alanine. It is known that β -cyano alanine and its γ -glutamyl derivative are present in the legume *Vicia sativa* and few other *Vicia* species, and are neurotoxins that cause neurological disorders [30]. Isolation of cystathionine in unusually high amounts in the urine is another manifestation of this condition, suggesting interference in the synthesis of homocysteine. Since the nature of the action of β -cyano

alanine and β -aminopropionitrile in these diseases is not fully understood, the relationship with pyridoxine and pyridoxal phosphate may be partly responsible for their toxicity. It should be noted that the lack of pyridoxine decreases the activity of amine oxidase *in vivo*, and induces the formation of defective elastin, while pyridoxal phosphate is not only required for the conversion of cystathionine to methionine but also eliminates the toxic effects of β -cyanoalanine [21, 22].

Many toxic effects on humans have been recorded in case of other plant unusual amino acids. Hypoglycines A and B (**13** and **14**) are responsible for hypoglycemia, which is caused by human consumption of unripe ackee (fruit) [31, 32]. Mimosine (**15**) causes hair and fur loss in animals and sheep fed on *Leucaena leucocephala* [33]; numerous selenium analogs of sulfur amino acids, found in many plants, also have a wide range of toxic effects on livestock.

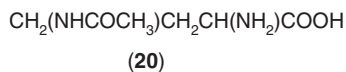


Toxic effects of nonprotein amino acids are also observed on invertebrates, especially insects. Canavanine (**16**) and β -hydroxy- γ -methylglutamate (**17**) can act as repellents (insect repellent) for certain species and can also be toxic, whereas the 5-hydroxytryptophan (**18**) and 3,4-dihydroxyphenylalanine (**19**) are toxic to beetles, weevils [34, 35], and other insects.

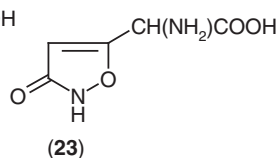
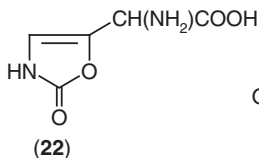
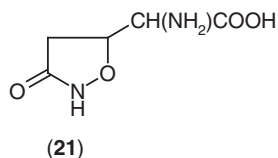


It is possible that the compound related to structure **18** and neurotransmitter play a certain role because 5-hydroxytryptamine is the major neurotransmitter in the muscles of digestive tract of insects [36]. DOPA simultaneously is the predecessor of neurotransmitters and cuticle of cross agents in insects; dihydroxyphenylalanine and a series of quinonoids and β -substituted ketocatechols [37, 38] are synthesized through DOPA.

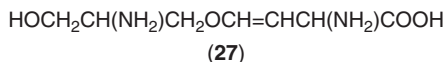
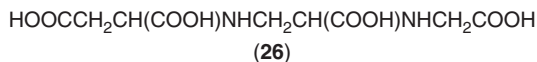
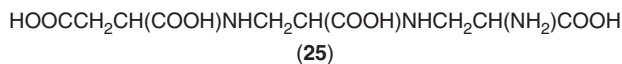
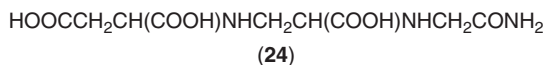
High toxicity of such a wide range of plant products suggests that the cause of some nonspecific diseases in humans and domestic animals can surely arise from toxic amino acids, which are widely spread in edible plants. For example, *N*⁸-acetyl-L- α,γ -diaminobutyric acid (**20**), which is converted to a α,γ -diaminobutyric acid toxin, inhibits urinary ornithine transcarbamylase cycle and is present in small amounts in sugar beets [39].



It seems that hydroxyisoleucine is responsible for the toxicity of amotoxins because its replacement by a leucine in amanulline leads to a nontoxic drug [40]. Apparently, the toxic outcome of the drug is due to its effect on RNA polymerase, inhibiting protein synthesis, which explains the slow action of the toxin. Tricholomic acid (**21**) and muscazone (**22**) are the causes of various injuries of vision, memory, and spatial or temporal orientation in humans, whereas the two compounds of *Tricholoma muscarium* and *Amanita muscaria* with ibotenic acid (**23**) from *Amanita pantherina* are potential insecticides [40]. All of these unusual amino acids comprise a fragment of oxoxazole.



Fungi also produce nonprotein amino acids, phytotoxins, and imino acids. Lycoramasine (**25**) and aspergillomarasamine (**26**) of *Fusarium* cause wilt in tomato leaves by forming complexes with iron ion, whereas fusaric acid (**26**) from the same source causes yellowing of leaves. Soybean leaf necrosis is caused by rizo-bitoksin (**27**), which blocks the conversion of cystathionine to homocysteine.



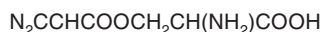
The action range of many antibiotics is still insufficiently elucidated, but it is obvious that many of them have a cyclic structure with a content of nonprotein

amino acids or amino acids with D-configuration. Among such compounds are gramicidins or enniatins that act on the bacterial cell membrane level by affecting the permeability of ions.

Penicillin derived from penicillamine (28) acts at the level of inhibition of peptidoglycan biosynthesis, similar to D-alanyl-D-alanine, and bind to the active site of the bacterial transacylase. Cephalosporins are related to penicillin [21] and contain D- α -aminoadipic acid in the side chain. The nonprotein amino acids with antibacterial properties also include azaserine (29) and L-2-amino-4-(4'-amino-2',5'-cyclohexadienyl)butyric acid [41].



(28)



(29)

Animals, unlike plants and microorganisms, produce little toxin-containing unusual amino acids. However, certain shellfish poisons are mixtures of peptides and proteins containing nonprotein amino acids. For example, gomarin, which is present in the venoms of some molluscs has curare-like effects [40].

Based on the foregoing, it follows that most of the biological functions of the unusual amino acids in plants and microorganisms can be associated not directly with the physiology of the organism itself, but with its relationship to other organisms in the environment. The question of physiological functions of nonprotein amino acids in higher plants is still doubtful for the majority of researchers and it is keenly debated. To a large extent, the role of such compounds is perceived as nitrogen retention.

Physiological functions of nonprotein amino acids are evaluated at various stages of plant development according to the age, time of the year, and/or stress. Studies have shown that the depletion or accumulation of specific amino acids is observed in various conditions. For example, γ -hydroxy- γ -methylglutamic acid can be detected in *Asplenium* in certain years, but not every year [42], canavanine accumulation in seeds can disappear during its growth [43], and so on. There is also no doubt that the osmotic control under stresses caused by lack of water can be achieved by changes in the concentration of free amino acids [44]. Free amino acids can also be involved in the binding of iodine – a factor that can have implications for the marine and freshwater algae [45].

Some unusual amino acids are found on the path to the synthesis of well-known plant metabolites. For example, it has been shown that the plant hormone *Ethylene* is produced from methionine through (S)-adenosyl methionine, and 1-aminocyclopropane-1-carboxylic acid [46].

In invertebrates, the function of some unusual amino acids is associated with energy supply to tissues under anoxic conditions. In particular, the biosynthesis of strombine, alanopine, and octopine serves to maintain the base rate of energy formation [13, 14].

The effect of different phosphorylated amino acids in invertebrates is similar to phosphocreatine effect on muscles of vertebrates. *N*-Phosphoryl arginine, phospho glycocyamine, and lombricine relate to such compounds.

On the other hand, similar to irreversible enzyme inhibitors with increased duration of action, nonprotein α -amino acids are also potentially biologically active compounds, and more recently successfully have been used in medicine, pharmacology, peptide synthesis, microbiology, and other areas of science and technology [1, 2].

According to the marketing, need for nonprotein α -amino acids annually increases by approximately 10%. In this regard, the researchers' attention is increasingly attracted to the synthesis of nonprotein α -amino acids of unusual structure with potential biological activity [47, 48].

Many nonprotein α -amino acids are part of modern high-level antitumor, hypertensive, and analgesic drugs, agents used to fight drug and alcohol addiction, and other important pharmacological agents [49, 50].

A special place among them occupy α -methyl-substituted α -amino acids, which are specific inhibitors of many enzymes capable of irreversibly binding to the active site of enzymes by covalent bonds. This principle is applied in biochemistry and enzymology to clarify the mechanism of action of many enzymes [51, 52]. α -Substituted- α -amino acids have a potent antihypertensive and antiseptic activity along with antitumor and radioprotective effects [53].

In particular, the inclusion of α -methyl-L-dihydroxyphenylalanine in the medication DOPA eliminates unwanted side effects in the treatment of Parkinson's disease [54–56]; α -methyltryptophan is used for the treatment of staphylococcal infections [57]; and α -methyltyrosine is an inhibitor for tyrosine-hydroxylase enzyme, which is responsible for tyrosine conversion to 3,4-dihydroxyphenylalanine, an important intermediate of adrenaline biosynthesis [54].

Nonprotein α -amino acids are also used as important pharmacologically active aglycones in the synthesis of various drugs. Thus, a strong antibiotic *Leucinostatin A*, having antitumor activity, comprises three moieties of (*S*)- α -methylaminopropionic acid [58]; *O*-methyl-L-threonine is used for the synthesis of an important physiologically active peptide 3-*O*-methylthreonine-oxytocin [59]; β -N-amino substituted derivatives of amino acid are part of *Tuberactinomycin* [60], *Bleomycin* [61], *Edeine* [62], *Capreomycin* [63], *A-19003* [64] antibiotics, and so on. β -Hydroxy- α -amino acids of different structures are important components of physiologically active cyclic peptides (*Vancomycine*), and enzyme inhibitors [65]. Thus, for example, *D*-*allo*-threonine is included into the composition of *Katanosins* [66] and *Accurninatur* [67] antibiotics; (+)-*Lactacystine* [68] and *Cyclosporin* [69] contain β -hydroxyisoleucine moiety. (*S*)-Substituted cysteine is used for the synthesis of physiologically active cysteine-containing peptides [70]. Inclusion of *D*-*allo*-isoleucine into the antibiotic *Dactinomycin D* imparts to the drug anticarcinogenic activity [71]. Sympathomimetic drug *N*-carboxyphenylprolyllysine is part of the antihypertensive drug *Lysinopril* [72]; derivatives of L-lysine, L-oxyproline, and *D*-phenylalanine are parts of anticancer drugs *Leuprolide* [73], *Octreotide* [74],

and *Tuftsia* [75]; (*S*)-2-methyl-3,4,5-trihydroxy-phenylalanine possesses antitumor activity [76]; and (2*S*,4*S*)-4-fluoroglutamic acid is an important component of antitumor drug *Methotrexat* [77], and so on.

Figure 1.1 shows the structures of some important pharmaceuticals based on nonprotein α -amino acids.

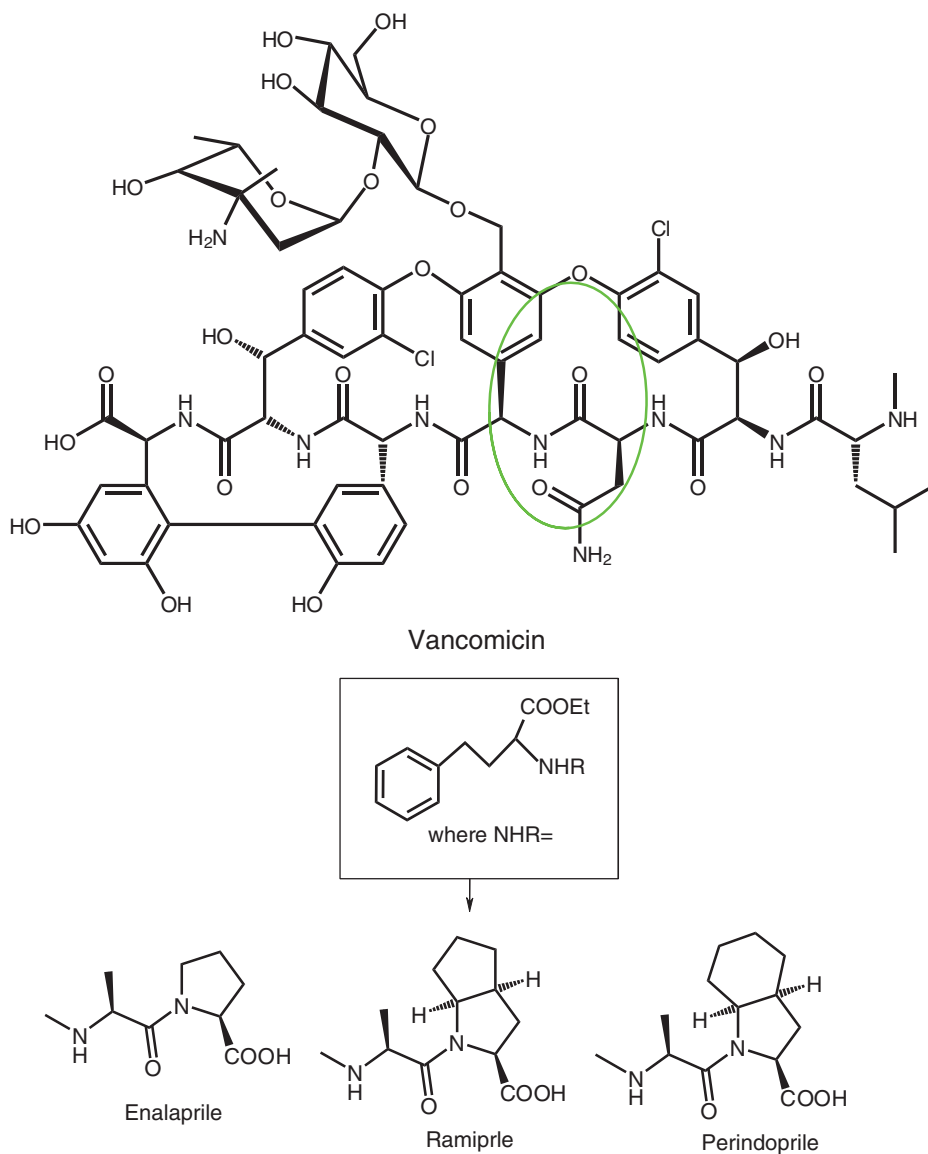


Figure 1.1 The structures of some drugs based on nonprotein amino acids.

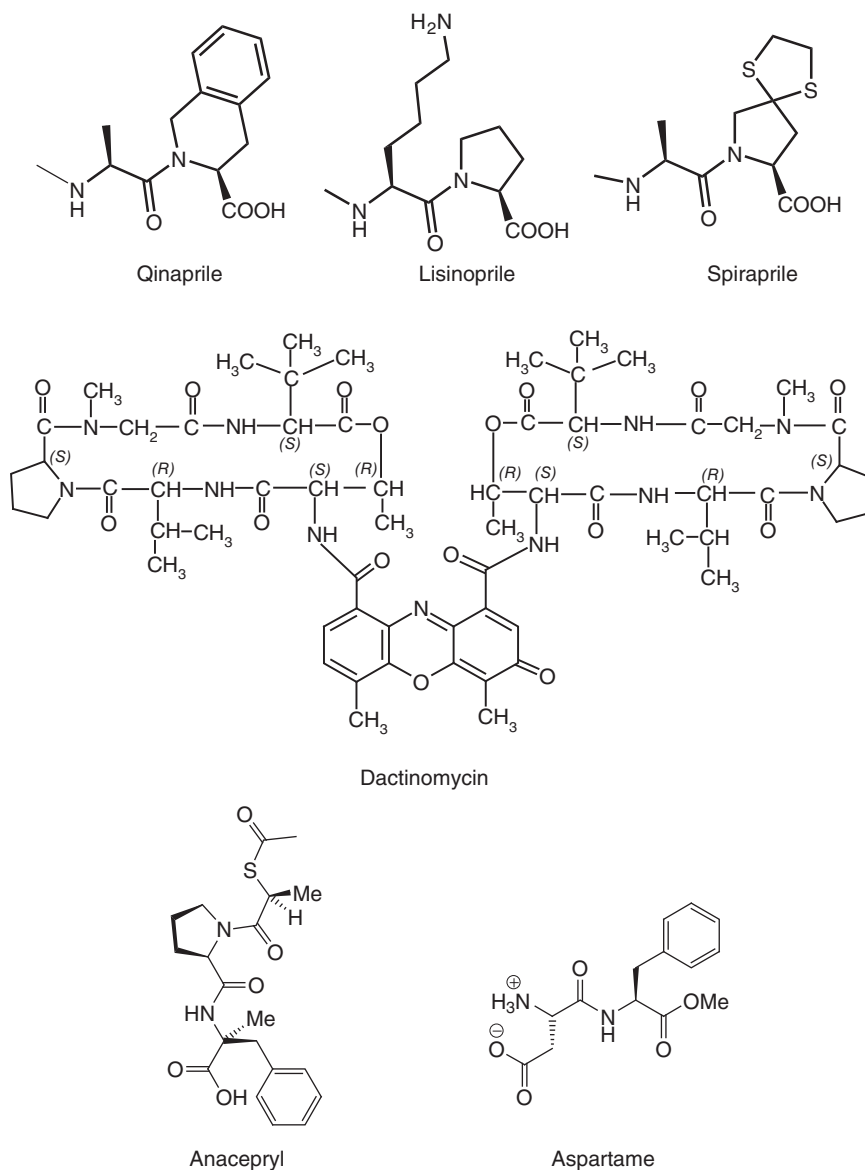


Figure 1.1 (Continued).

Non-natural D-amino acids widely found as common intermediates for the preparation of many chiral drugs, biologically active molecules, chiral auxiliaries and some useful chiral building blocks have attracted intensive attention over the past decades regardless of the fact that natural L-amino acids are readily available. Among all the non-natural amino acids, aliphatic D-amino acids stand out as elegant intermediates for the synthesis of many chiral drugs which include

the orally administered anti-diabetic drugs in the DPP-4 inhibitor class, among which, alogliptin, linagliptin, sitagliptin, and saxagliptin are just to name a few. Moreover, due to the significance of chiral aliphatic D-amino acids, the worldwide market value of these valuable compounds is estimated at 2 billion dollars annually [78].

Nonprotein α -amino acids are also successfully used in microbiology as analogs of natural α -amino acids for the selection of their highly active strain-producers. For example, *S*-(2-aminoethyl)-L-cysteine is an effective analog of L-lysine [79], β -hydroxyleucine is an analog of L-threonine [80], *O*-methyl-L-serine is an effective analog of L-methionine [81], and β -hydroxyleucine is an analog of L-leucine [82]. Recently, in pharmaceutical and agrochemical industries, much attention is paid to methods for producing enantiomerically pure forms of biologically active compounds. Indistinguishable in their physical and chemical properties, enantiomers often sharply differ from each other in their physiological action. Thus, levorotatory nicotine in tobacco is several times more toxic than the dextrorotatory. Enantiomers of amino acids also differ in their taste. Thus, the natural amino acids L-asparagine and L-tryptophan are tasteless but L-leucine and L-tyrosine have a bitter taste, whereas their unnatural D-isomers have a sweet taste.

Enantiomers of many compounds used as drugs have various physiological effects. Thus, the racemate of antibiotic *Chloromycetin* contains 50% of physiologically inactive dextrorotatory isomer, whereas the levorotatory isomer, *Laevomycetin*, has antibiotic activity. Moreover, (+)-isopropyl nora-drenaline has 800-fold more potent bronchodilator action than the (–)-isomer; (–)-5-(1,3-dimethylbutyl)-5-ethylbarbituric acid exhibits usual for barbiturates sedative action, whereas (+)-antipode causes convulsions [83]. *Thalidomide* widely known in late 1950s as a sedative drug used to eliminate insomnia and morning sickness in pregnant women has its (*S*)-(–)-antipode, which causes limb hypoplasia in newborns [84]. The drug was very popular; however, it became clear that due to its use the number of children with severe congenital deformities of the upper and lower extremities has increased. This was explained by the fact that the drug was used as a mixture of two optically active enantiomers (racemate) from which (+)-(*R*)-enantiomer has a sedative action and is nontoxic, and its (–)-(*S*)-antipode causes teratogenicity (congenital malformations) (see Figure 1.2).

According to US Senate and European Commission decisions, only enantiomerically pure drugs are needed in the drug market because the optical antipode of the

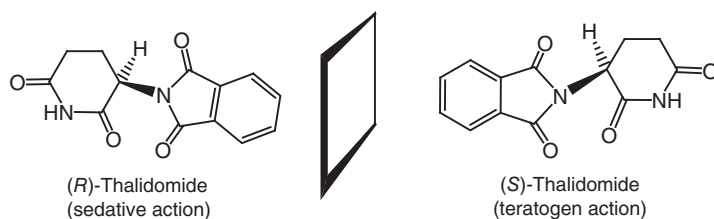


Figure 1.2 The structure of the optical antipodes of thalidomide.

pharmacologically active drugs usually has adverse effects, and at best, it remains neutral. In this regard, recently pharmaceutical companies pay more attention to the production of optically pure drugs. Thus, the total sales of enantiomerically pure drugs worldwide were more than 133 billion dollars (40% of all drugs), and the rate of production growth of chiral drugs was 18% per year [85].

Besides, the use of enantiomerically pure agrochemicals reduces their environmental impact [86]. Based on this, a large number of research laboratories have begun to develop methods for the asymmetric synthesis of chiral organic compounds used in agriculture.

A separate interesting class of nonprotein amino acids is isotopically labeled α -amino acids, which are successfully used in both biochemical research, and in positron emission tomography (PET) for fast and effective diagnosis of various diseases, including diagnosis of tumor cells in the early stages of development.

The basis of *positron emission tomography* (PET) is the use of positron-emitting radioisotope-labeled compounds. As the radioisotope undergoes positron emission decay (also known as *positive beta decay*), it emits a positron, an antiparticle of the electron with opposite charge. The emitted positron travels in the tissue for a short distance (typically less than 1 mm, but depends on the isotope), losing kinetic energy at that, until it decelerates to a point where it can interact with an electron. The encounter annihilates both electron and positron, producing a pair of annihilation (gamma) photons moving in approximately opposite directions. The most significant fraction of electron–positron annihilations results in two 511 keV gamma photons being emitted at almost 180° to each other.

Fixing these paired γ -rays with the help of PET camera's detector rings allows to determine the exact location of the annihilation place in the space.

After intravenous administration of the radiopharmaceutical drug (RPD), its distribution in the body tissues can be studied using a special external system detector (PET scanner). Therefore, for the PET method the nature and characteristics of the used isotopes are very important.

Using short-lived isotopes with high specific activity enables to conduct PET studies introducing “trace” amounts of radiopharmaceuticals without any pharmacological effect, and allows to obtain high-quality PET images with a low dose load on patients. Detecting equipment for PET is based on the registration of quantum annihilation radiation with opposing detector system (coincidence circuit).

This makes possible to determine annihilation (autocollimation) directly. Due to registering annihilation radiation using the coincidence, the conventional collimation used in single photon emission computed tomography (SPECT) is no longer necessary, which causes higher resolution of the PET method.

PET scanner comprises an array of detectors arranged in a ring in pairs included in the matching circuit. The detection system is calibrated using phantoms with a certain concentration of a radioactive isotope. Data obtained by a PET scanner are processed by “image reconstruction” special algorithms, and the result is presented in the form of distribution of the radiopharmaceutical in the body in terms of activity/volume.

Table 1.1 Main characteristics of radioisotopes and their sources.

Isotope	Half-life (min)	Nuclear reaction
^{11}C	20.4	$^{14}\text{N}(\text{p},\alpha)^{11}\text{C}$
^{13}N	9.96	$^{16}\text{O}(\text{p},\alpha)^{13}\text{N}$
^{15}O	2.03	$^{14}\text{N}(\text{d},\text{n})^{15}\text{O}$
		$^{15}\text{N}(\text{p},\text{n})^{15}\text{O}$
^{18}F	109.8	$^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$
		$^{20}\text{Ne}(\text{d},\alpha)^{18}\text{F}$

Nowadays, isotopes of the following elements ^{11}C , ^{13}N , ^{15}O , ^{18}F that make up the majority of organic molecules are widely used. These isotopes are produced in cyclotron targets by the nuclear reactions listed in Table 1.1.

Due to the very small half-lives of ^{13}N and ^{15}O , these isotopes are mainly used in the composition of the simplest compounds: ^{15}O O_2 , ^{15}O CO , ^{15}O CO_2 , ^{15}O H_2O , and ^{13}N NH_3 . The ^{11}C isotopes are of the greatest interest because of their longer half-lives as compared with ^{13}N and ^{15}O isotopes and in the case of ^{11}C it becomes possible to synthesize rather complex and diverse organic compounds.

The use of ^{11}C radiopharmaceuticals in clinical practice substantially restrains the need to produce RPD in close proximity to the PET chamber for patients' examination because the half-life ($\tau_{1/2}$) is 20.4 min, and to deliver such radiotracers to the PET centers that do not have cyclotrons is impossible. Therefore, in recent PET studies, there is a trend to replace clinically used ^{11}C RT with ^{18}F RT. Analysis of the literature devoted to PET shows that the most promising radiotracers are labeled with ^{18}F isotope. For the preparation of ^{18}F isotope in the form of molecular fluorine, $^{20}\text{Ne}(\text{d},\alpha)^{18}\text{F}$ nuclear reaction is used, implemented in the gas target filled with Ne in the presence of nonradioactive molecular fluorine ($\sim 0.1\%$) [87], and nuclear reaction of $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$ is carried out in the target filled with gaseous molecular oxygen [88].

Most of the operating cyclotron accelerators currently produce ^{18}F isotope by $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$ nuclear reaction. In this reaction, the ^{18}F isotope can be prepared from ^{18}O H_2O in the form of fluoride anion, (^{18}F) F^- (aq) with an activity of up to 100 GBq, with a specific activity of up to 30 000 GBq/mmol, as well as in the form of molecular fluorine (^{18}F) F_2 in the gas target of high pressure (^{18}O) O_2 with an activity of up to 34 GBq and specific activity of 350–600 GBq/mmol [88].

From the sources of ^{18}F -labeled reagents, the most promising is the ^{18}F F^- , produced by the ^{18}O H_2O nuclear reaction, since this method has several advantages:

- higher selectivity of labeling compared with the administration of electrophilic fluorinating reagents while using;
- ability to work with ^{18}F isotope nongaseous sources;

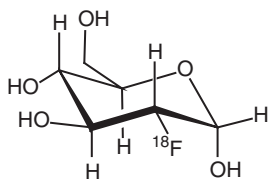


Figure 1.3 The most common radiotracer – [^{18}F] FDG.

- the possibility of obtaining radiolabel [^{18}F] F^- with high specific activity;
- easiness to purify the [^{18}F] F^- by chromatography or electrochemical methods.

Thus, [^{18}F] F^- in many studies has been selected as a fluorinating agent for the preparation of ^{18}F radiotracers. Therefore, in recent PET studies, a trend to replace clinically used [^{11}C]RT with [^{18}F]RT was observed. This is due to the fact that half-life of the ^{18}F isotope is sufficiently long as compared with ^{11}C , ^{13}N , ^{15}O isotopes, and this allows to employ the strategy of using several PET cameras served by a cyclotron located at some distance, implemented in the case of the most common radiotracer of 2- ^{18}F fluoro-2-deoxy-D-glucose ([^{18}F]FDG) (see Figure 1.3).

On the one hand, the size of the F atom is slightly higher than the size of the hydrogen atom (van der Waals radius of hydrogen is 1.5 Å, and that of fluorine is 1.65 Å), and, on the other hand, the F atom has a significant negative inductive effect, and its introduction into the molecule significantly polarizes the part adjacent to the C–F bond.

Introduction of fluorine into the known biological compound can affect its biochemical and physicochemical properties in an unpredictable manner. In case of replacement of the hydroxyl group of the glucose molecule by ^{18}F atom, the [^{18}F]FDG is transported into tissues similar to glucose but [^{18}F]FDG metabolism in cells is stopped at the phosphorylation stage, which leads to accumulation of [^{18}F]FDG in the areas of increased energetic metabolism of glucose.

Therefore, the distribution of [^{18}F] FDG in the body tissues is described in terms of a simple pharmacokinetic model, and PET findings can be quite easily interpreted.

In accordance with the modern concepts, the use of ^{18}F -labeled amino acids (^{18}F -AAs) as diagnostic agents is determined by their accumulation in the tumor, which reflects the increased amino acid transport rate into tumor cells compared with the intact tissue. Besides, the accumulation of amino acids in the gray matter of the brain is low that advantageously distinguishes them from [^{18}F]FDG, which often gives false-positive results in cases of brain tumors [89].

Moreover, in recent studies it has been shown that amino acid transport in infected cells (foci of infection) is significantly lower than in the tumor tissue. Thus, in the inflammation site, induced in the rat's body by injection of turpentine, the accumulation of [^{18}F]FDG was 21.2%, while the accumulation of 2- ^{125}I -iodo-L-tyrosine reached only 8% [90]. Studies in experimental animals with (O-2- ^{18}F fluoroethyl)tyrosine [^{18}F]FET showed that unlike [^{18}F]FDG and L- ^{11}C]MET, accumulation of fluorinated tyrosine analog in nonmalignant cells and inflamed lymph nodes was extremely negligible [91].

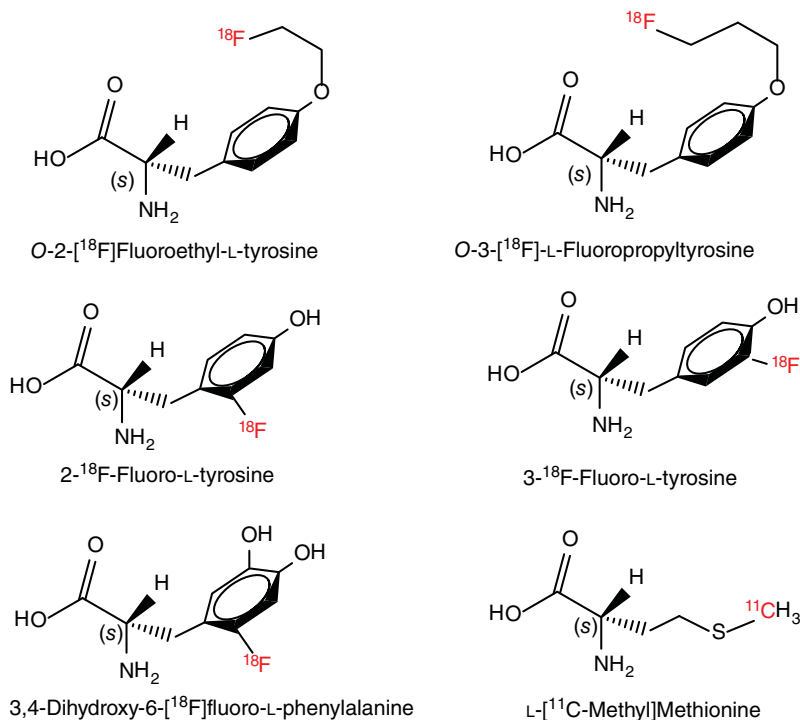


Figure 1.4 PET radiotracers based on α -amino acids.

We can hope that the use of fluorine-labeled amino acids would solve a huge problem in PET diagnostics – the inability to differentiate tumor and inflammation process in the brain by the conventionally used [^{18}F]FDG [92].

The most well-known radiopharmaceutical based on fluorine-labeled amino acids is the 3,4-dihydroxy-6-[^{18}F]fluoro-L-phenylalanine (6-[^{18}F]-L-DOPA) – a fluorinated analog of L-DOPA, the metabolic precursor of dopamine neurotransmitter (see Figure 1.4).

Pharmacokinetic behavior of 6-[^{18}F]-L-DOPA coincides with the behavior of the natural metabolite, which enables a quantitative assessment of dopaminergic neuron density by PET method in the diagnosis and selection of treatment of Parkinson's disease and other disorders associated with a lesion of the dopaminergic system [93]. Recently, the possibility of using 6-[^{18}F]-L-DOPA in the diagnosis of tumors of the gastrointestinal tract and of some other organs was reported [94].

Fluorinated analogs of tyrosine containing fluorine-18 in both the aromatic ring (2- ^{18}F -fluoro-L-tyrosine (2- ^{18}F -FTYR) and 3- ^{18}F -fluoro-L- α -methyl-tyrosine (3- ^{18}F -FAMT), and in the side chain – ^{18}F -FET, O-3-[^{18}F]-fluoropropyl-L-tyrosine (^{18}F -FPT) [95, 96], are being intensively investigated in a number of PET centers in Europe, Japan, and United States as promising radiopharmaceuticals for PET oncology (see Figure 1.4).

2- ^{18}F]FTYR was among the first amino acids used in PET diagnostics as far back as in 1989 [97]. However, the lack of methods for the synthesis of this RPD in acceptable PET amounts prevents its introduction into clinical practice.

The comparative study of 2- ^{18}F -FTYR and L- ^{11}C [methyl]methionine ($^{11}\text{CH}_3$]MET) in rats with F98 [98] glioma showed similarity in biodistribution and accumulation of 2- ^{18}F]FTYR and L- $^{11}\text{CH}_3$]MET in tumors, indicating the prospectivity of using 2- ^{18}F]FTYR in studies traditionally performed with L- $^{11}\text{CH}_3$]MET.

The study of metabolism and biodistribution of 2- ^{18}F]FTYR in organs of healthy mice [99] as well as human [100] PET studies have shown that the metabolism of 2- ^{18}F]FTYR is characterized by a simpler mechanism as compared with L- $^{11}\text{CH}_3$]MET, the molecule of which rapidly loses radiolabel in the demethylation reaction. Application of 2- ^{18}F -FTYR in PET is intensively conducted in many PET centers [100], and the interest in this RPD and other tyrosine derivatives is growing fast.

In Russia, radiopharmaceuticals based on ^{18}F -amino acids have not yet been introduced into clinical practice. Their development and clinical evaluation are highly relevant to expand the possibilities of the method and its implementation in practice of nuclear medicine. The Institute of Human Brain RAS accumulated vast experience of L- ^{11}C]MET used in clinical diagnostics in addition to the ^{18}F]FDG. The development of 2- ^{18}F]FTYR as a new drug for the diagnosis of tumors by PET is being conducted.

Since nonprotein α -amino acids are physiologically active and suitable for incorporation into pharmaceuticals and for the use as PET radiotracers only in the form of optically active enantiomers, development of methods for their preparation as such is a very important problem of bioorganic chemistry and biotechnology. Unfortunately, traditional microbiological and enzymatic methods for the synthesis of α -amino acids, including chemical synthesis of racemates with their subsequent enzymatic cleavage, are of little use for producing optically active nonprotein α -amino acids because of unusual structures of substrates. Therefore, the asymmetric synthesis is the most applicable approach for the production of such compounds.

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Part I

Natural Synthesis of Amino Acids, Mechanisms, and Modeling

It is well known that one of the most interesting challenges to date is the implementation of the asymmetric synthesis from prochiral precursors using the principles of enzyme action, that is, development of biomimetic approaches [1].

Synthetic organic molecules, having the characteristic features of enzyme systems, are typically used as biomimetic enzyme systems. They are smaller in size and simpler by structure as compared with enzymes. Imitation of enzymes is an attempt to reproduce a key parameter of the enzyme function on a much simpler level. By using synthetic chemistry techniques, it is possible to create a “miniature enzyme,” which lacks the macromolecular structure of the peptide but contains active chemical groups correctly oriented in accordance with the geometry of the active site of the enzyme. This approach is called *biomimetic chemical approach* to study the biological systems.¹⁾ Thanks to the biomimetic approach it becomes possible to simulate features, typical for enzyme-catalyzed reactions, such as high speed and substrate selectivity [2].

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1) The term *biomimetic* was first introduced in 1972 by Breslow.

2

Some Regularities of Mechanisms for the Natural Synthesis of Amino Acids

In nature, amino acid synthesis is carried out by pyridoxal phosphate (PP)-dependent enzymes, which are mainly responsible for the metabolic conversions of amino acids (including racemization, decarboxylation, transamination, β -substitution, elimination, and condensation) (see Scheme 2.1).

The principle of PP-enzyme operation is the conversion of amino acid to CH-acid by the formation of a Schiff base between the amino acid and pyridoxal aldehyde at the active site of enzymes and catalysis of cleavage of various bonds in amino acid molecule. The specifics of each PP-enzyme determine which amino acid bond is broken or replaced.

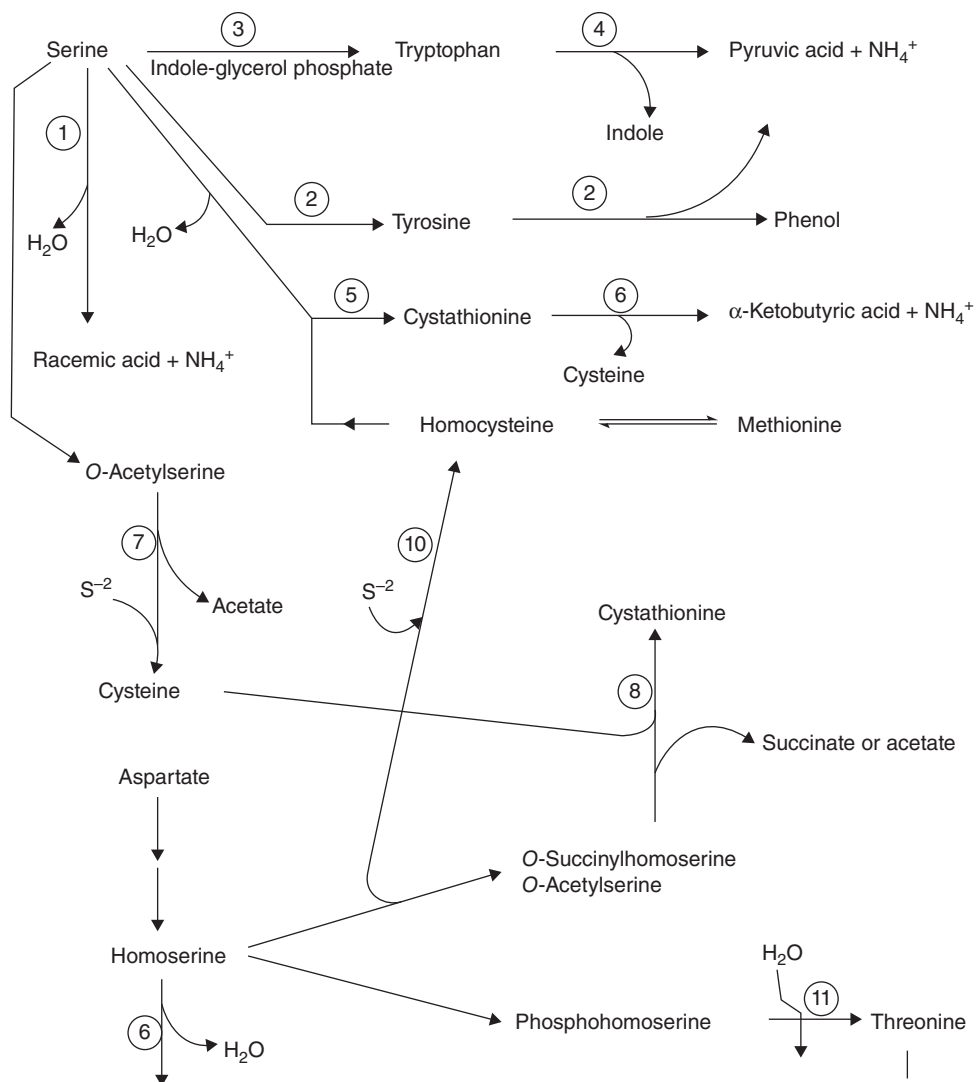
Cleavage of the α -H of amino acid followed by C-alkylation, α,β -elimination of β -hydroxy- α -amino acids followed by the addition to the active C=C bond of dehydroamino acids are among these reactions.

In mid-1950s, *Braunstein* and *Shemyakin* in the USSR [1] and *Metzler* and *Snell* in the United States [2] simultaneously created a new theory of pyridoxal catalysis. According to this theory, a key step is the formation of Schiff base (1) at the active center of the enzyme between the substrate-amino acid, containing electronegative substituent at the β -position and pyridoxal (or PP) (see Scheme 2.2).

In the resulting Schiff base, the pyridoxal fragment is an electron-withdrawing moiety that reduces the electron density at the α -carbon atom of the amino acid that facilitates the cleavage of bonds at that atom.

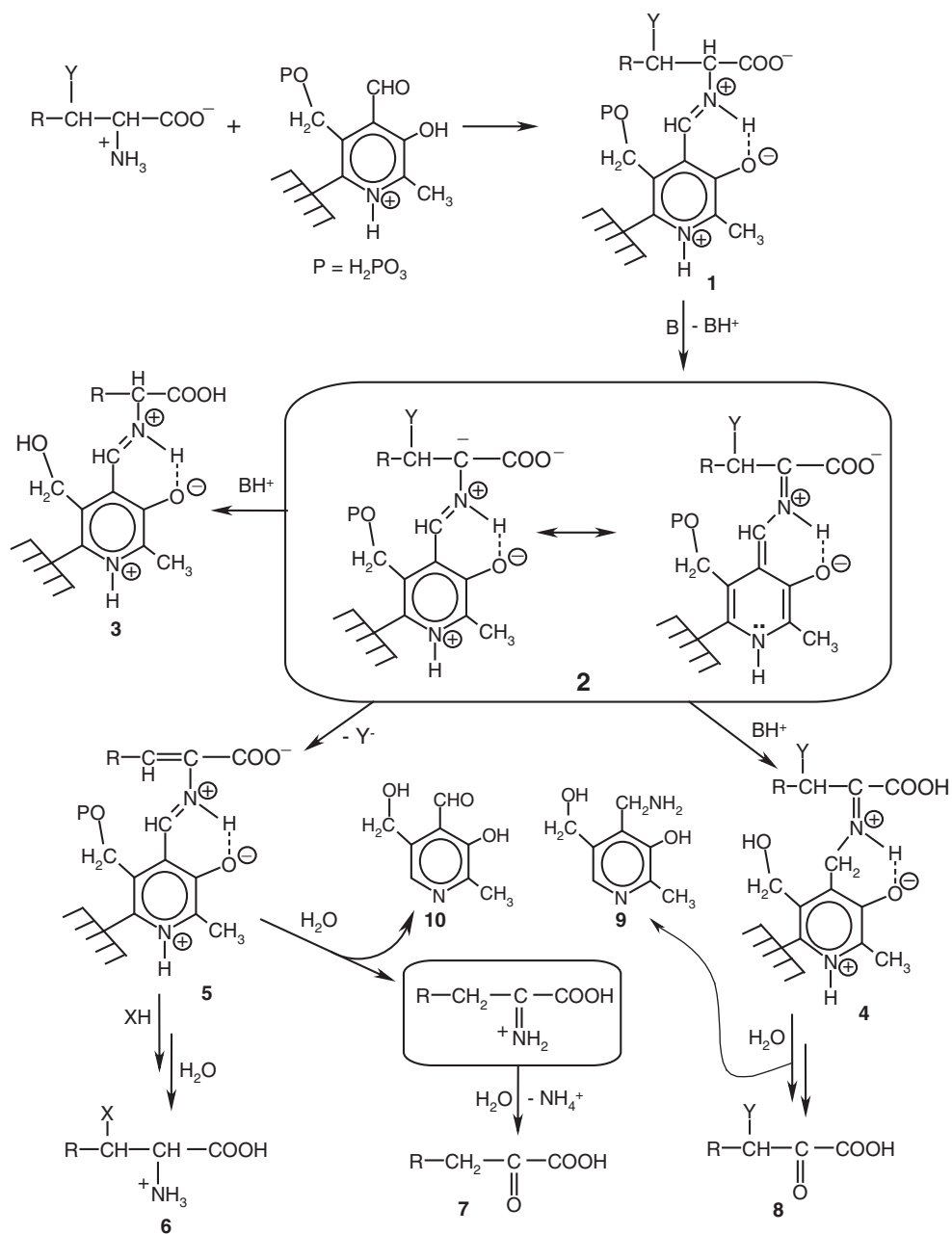
Under the influence of base during cleavage of α -proton of the amino acid fragment, a planar intermediate carbanion (2) is formed. The electron densities in this carbanion are distributed in such a way that the negative maximum charge is localized on α -carbon atom of amino acid and phenyl carbon of pyridoxal moieties. The carbanion (2) can undergo the following transformations (see Scheme 2.2):

- 1) If the amino acid has an asymmetric α -carbon, then by the cleavage of its α -proton the system becomes prochiral, and if the reverse protonation of α -carbon of the carbanion occurs from two equal sides of the Schiff base plane, this leads to racemization (3);
- 2) Protonation of the benzylic carbon, accompanied by a tautomeric shift with the formation of 4. Hydrolysis of the formed pyridoximine acid affords keto acid 8 and pyridoxamine 9;



Where: 1. Threonine, serine dehydratase; 2. Tyrosine phenol-lyase; 3. Tryptophan synthetase; 4. Tryptophanase; 5. β -cystathionine synthetase; 6. γ -istationase, homoserine dehydratase; 7. O-acetylserine sulfhydrylase (cysteine synthetase); 8. Cystathionine γ -synthetase; 9. β -cystathionase; 10. Homocysteine synthetase; 11. Threonine synthetase.

Scheme 2.1



Scheme 2.2

- 3) The carbanion can be further stabilized by the release of the Y-group, thereby forming a Schiff base of dehydroamino acid (5), wherein the double $C_\alpha-C_\beta$ bond is characterized by a deficiency of electrons. This compound reacts with other nucleophiles to form addition products (6). Hydrolysis of the Schiff base of dehydroamino acid affords keto acid (7), ammonia, and pyridoxal aldehyde (10).

PP is attached to the active center of the enzyme via covalent, ionic, and hydrophobic interactions, as well as by hydrogen bonds formed between the functional groups of apoenzyme and coenzyme. In particular, covalent interactions are implemented through the formation of a Schiff base between the PP and the ω -amino group of the lysine moiety in the active site of the enzyme [3], and ionic bonds are implemented by ionized phosphate and hydroxy groups of PP [4]. It has been shown that the rate of the formation of enzyme–substrate complex significantly increases the rate of the model reaction – pyridoxal condensation with an amino acid. Thus, one of the important functions of the enzyme is the catalysis of base formation from the amino acid and pyridoxal at active center of the enzyme.

It can be claimed that the amino acid fragment in the enzyme–substrate complex becomes a CH-acid. Cleavage of α -proton of the amino acid fragment and formation of a carbanion occur at the active site of the enzyme due to the basic functional groups of the enzyme. The cleavage of α -proton of amino acid catalyzed by the enzyme can become the rate-limiting step of elimination. An imidazole fragment of histidine [5] and ω -amino group of lysine [2] moieties can be functional groups engaged in the general base catalysis in the active site of the enzyme. Snell was the first to suggest that the ω -amino group of a lysine moiety [2] plays a role of the base catalyst in such reactions.

It is considered that the formed carbanion resulting from the cleavage of α -proton from the amino acid fragment of Schiff base of type 2 (see Scheme 2.2) is characterized by strong absorption in the range of 450–500 nm. Similar absorptions were recorded for many enzyme–substrate complexes [6].

Apoenzyme function is the control of the course of the reaction strictly by one way. In 1966, *Danatan* [7] proposed a stereoelectronic hypothesis to explain the selective action of enzymes. According to this hypothesis, the cleaving bond of amino acid–substrate under the action of the PP-dependent enzymes should be located in the plane perpendicular to the plane of the π -system of substrate–coenzyme imine. This orientation reduces the transition state energy to the minimum, as it allows the greatest possible σ – π overlap of the cleaving bond and conjugated π -system of imine cofactor. Figure 2.1 shows three types of orientation of amino acid in which α -hydrogen, a carboxyl group, and the side chain are in a position optimal for the bond cleavage.

From the data presented in Figure 2.1, it is obvious that PP serves as a coenzyme in transformations of amino acids such as decarboxylation, transamination, racemization, and synthesis of amino acids. One of the most important features of the reactivity of pyridoxal-dependent enzymes is stereochemistry of transformations catalyzed by them. These systems except racemases [8] are selecting between

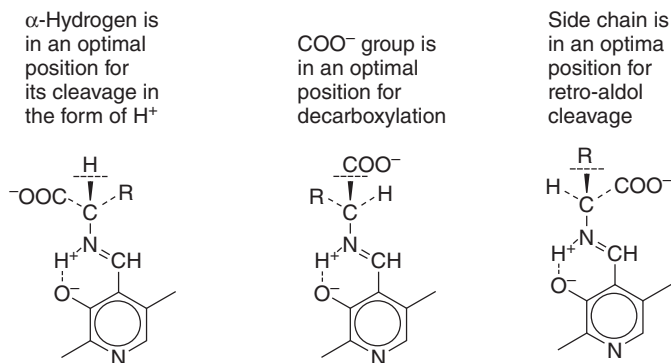


Figure 2.1 Stereochemical aspects of catalysis of PP-dependent enzymes. (The cleaving bond is located perpendicular to the π -system of the Schiff base.)

both enantiomers of amino acids and enantiotopic groups of amino acid fragments. The cleavage and formation of the C–C and C–H bonds catalyzed by these enzymes proceed enantioselectively.

Research of *Vederas* and *Floss* [9] showed that in such systems elimination of β -electronegative substituent and addition of appropriate nucleophiles (or electrophiles) occurred from one side of amino acid Schiff base plane, fixed at the active site of the enzyme. Intramolecular transfer of isotope label from α -position of (*S*)-tryptophan or (*S*)-tyrosine to phenol or indole leaving moiety in reactions catalyzed by tryptophanase or tyrosinase indicates that one and the same basic group implements both the cleavage of α -proton of α -amino acid and transfer of this proton to the leaving indole or phenol. Thus, the Schiff base is fixed in the active site of tryptophanase in the conformation with α -hydrogen oriented perpendicular to the Schiff base plane. In such a system, elimination of the leaving indole moiety and reverse protonation of the forming dehydroalanine Schiff base occur by the *syn*-type.

Analysis of results of the stereochemical action of α,β - and β,γ -eliminating and substituting enzymes [10] allows us to formulate the following rule: all chemical reactions occur on one side of Schiff base plane (see Figure 2.2).

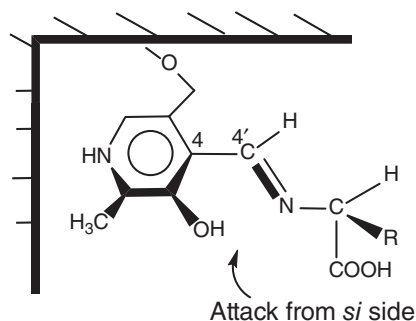


Figure 2.2 The preferred protonation of imine intermediate compound in the active site of PP-dependent enzymes.

However, in some cases, there are deviations from the general rule. First of all, these are racemases, in the active site of some of them there are two main groups, one of which cleaves the amino acid proton and the other one returns it from the opposite side [11].

The summarized data on the mechanism [12] of pyridoxal enzyme action allow to conclude the following: the amino acid forms with pyridoxal a Schiff base and is converted to CH-acid or electrophilic dehydroamino acid, which enters into C-alkylation or nucleophilic addition reactions (in the case of dehydroamino acids) to form more complex optically active α -amino acids. Thus, the stereochemistry of the amino acid conversions is completely controlled by chiral environment of the PP active center, which provides the flow of all pyridoxal catalysis reactions (substitution, elimination, addition, etc.) strictly on one side of the planar Schiff base.

Analysis of the data on pyridoxal catalysis mechanism shows that due to the formation of Schiff base in the active site of the enzyme, the amino acids acquire the following important properties:

- stiffness of the system due to intramolecular hydrogen bonds;
- stereochemical inertness of the system;
- high CH-acidity of amino acid and electrophilicity of dehydroamino acid moieties;
- emergence of high enantioselective effects due to the specific chiral environment around the active center of enzyme by apoenzyme.

Studies have shown that these properties are responsible for nearly 100% asymmetric synthesis of amino acids in the body. It can be assumed that systems designed to model the action of the pyridoxal enzymes and implement the asymmetric biomimetic synthesis of optically active α -amino acids should have these properties.

It is known that free β -hydroxyamino acids readily undergo retroaldol cleavage in the presence of simple pyridoxal and metal ions [13]. Retroaldol cleavage of threonine is also observed in octahedral Co^{3+} complexes of Schiff base of this amino acid with salicyl aldehyde [14]. This suggests that similar amino acid conversions can be performed not only in the presence of pyridoxal, but its simplest analogs, including salicyl aldehyde.

Actually, further studies have shown that both β -elimination of activated amino acid substituents with the formation of Schiff bases of dehydroamino acids and addition of nucleophiles to the double bond of dehydroamino acid moiety occur even with the simplest pyridoxal analogs.

Optimal systems suitable simultaneously to clarify the stereochemical aspects of pyridoxal catalysis and to construct reagents for the asymmetric synthesis of amino acids, should be based on stereochemically rigid designs with substituents uniquely oriented in space. Such systems are stereochemically inert complexes built by some transition metal ions and Schiff bases. In the complex, metal ion performs a role of the apoenzyme, and the role of active site in case of the PP-enzymes can bear pyridoxal or its simplest analog, for example, salicylaldehyde or its derivatives.

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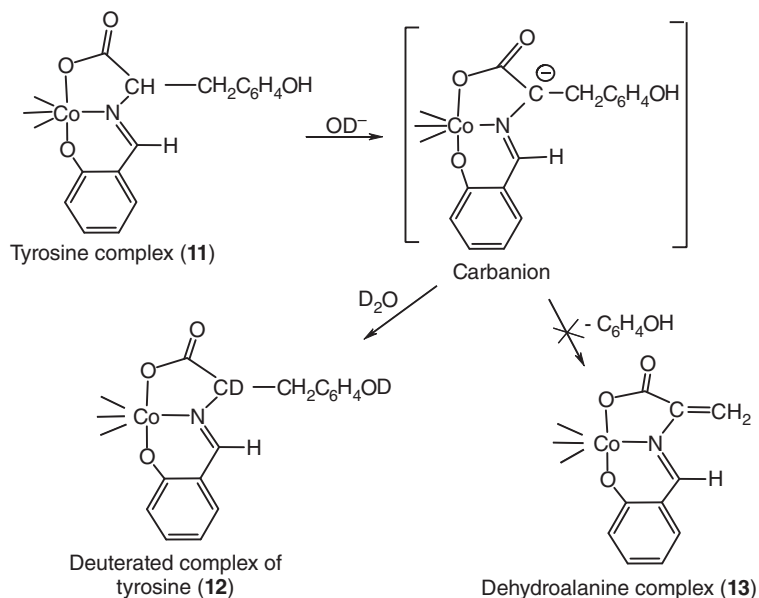
Systems for Modeling Some Aspects of Pyridoxal Enzyme Action

Much of what is known about the pyridoxal catalysis is obtained based on the studies of model systems containing pyridoxal, metal ions, and amino acid. One of the first in this respect are the studies of Snell and his students who showed that serine and cysteine in the presence of metal ions and pyridoxal in neutral, acidic, and alkaline environments converted to pyruvic acid [1–3]. Furthermore, it was shown that under the same conditions pyruvic acid was formed by other β -substituted α -amino acids: phosphothreonine [4], phosphoserine [5–7], β -chloro- α -aminobutyric acid [6, 7], β -chloroalanine [6, 7], *S*-ethylcysteine [7], *S*-phenylcysteine [8].

Kinetic study of dehydrochlorination of ethyl ester of β -chloroalanine in the presence of pyridoxal and its metachloride conducted by a team of Japanese scientists [9] on the whole confirms this conclusion. Thus, the order of catalytic activity of metal ions in these reactions is also opposite to that which provides maximum mobility of amino acid α -proton. This observation fits into the same framework of the relative reactivity of amino acids in β -elimination reactions. In the studied literature, amino acids having easily leaving groups (Cl, OPO_3 , SR, etc.) in β -position were subjected to β -elimination.

Free β -oxyamino acids readily undergo retroaldol cleavage in the presence of pyridoxal and metal ions [1, 10, 11]. Against this background, it is difficult to see the β -elimination reaction, since the hydroxyl ion is a poor leaving group. However, in the case of phenylserines, forming a stabilized system of amino cinnamic acids during β -elimination, it became possible under these conditions to observe both parallel reactions, namely retroaldol cleavage with the formation of aldehyde and glycine and β -elimination [12]. Retroaldol cleavage of threonine was observed in Co^{3+} complexes of Schiff bases of this amino acid with salicyl aldehyde [13]. All this taken together suggests that β -elimination of amino acids with the easily leaving group can be carried out not only in the presence of pyridoxal, but also its simplest analogs, including salicyl aldehyde.

β -Elimination of other substituents, such as indole and phenol (models of tryptophanase and tyrosinephenollyase) from tryptophan and tyrosine, respectively, under the action of salicylaldehyde does not occur to an appreciable extent even at high pD of a solution. Thus, in the octahedral complex of Co^{III} ion of Schiff base of salicylaldehyde and (*S*)-tyrosine (**11**), there is an exchange of α -proton of amino



Scheme 3.1

acid fragment with deuterium under the action of 0.1 N NaOD with the formation of deuterated complex **12** without destroying the structure of the amino acid (see Scheme 3.1) [14].

Elimination of phenol moiety from tyrosine complex **11** and formation of dehydroalanine Schiff base complex (**13**) under these conditions were not observed.

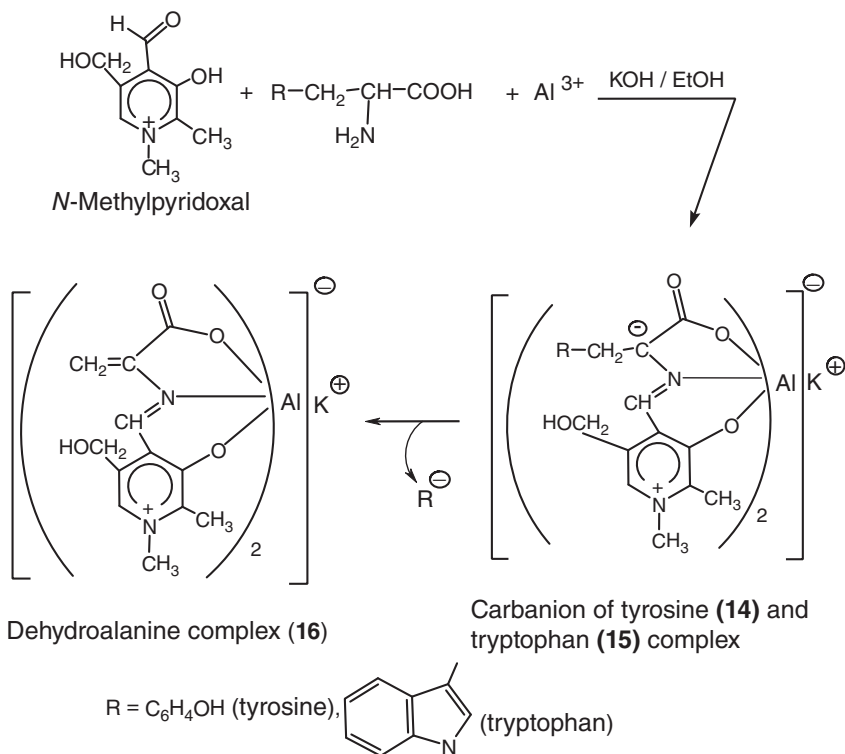
It was further shown that tyrosine and tryptophan nevertheless were subjected to elimination in octahedral Al^{III} ion complexes of their Schiff base of *N*-methylpyridoxal with intermediate formation of Schiff base complex of dehydroalanine (**16**). In this case, phenol from tyrosine complex (**14**) and indole from tryptophan complex (**15**) [15] were correspondingly eliminated (see Scheme 3.2).

The formed system of dehydroalanine Schiff base with electrophilic double bond is able to attach nucleophiles, for example, *n*-chlorothiophenol to form *S*-*n*-chlorophenylcysteine.

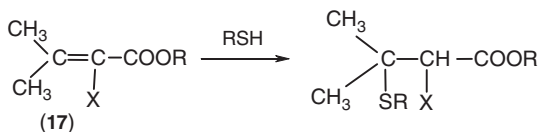
Thiols are also attached to a dehydroamino acid fragment of Schiff bases with benzaldehyde, salicylaldehyde [16], and even *N*-acyldehydroamino acids [17], as illustrated in the example of dehydrovaline Schiff base (**17**) [18] (see Scheme 3.3).

Thus, electrophilicity of double bond in the reaction increases dramatically during the transition from a benzylidene derivative to salicylidene and marginally increases in the transition from salicylidene to pyridoxylidene derivative.

Similar systems of dehydroamino esters in which the electrophilicity of the $\text{C}=\text{C}$ double bond upon addition of thiols is four times higher than that in the initial acids [19] were also studied.



Scheme 3.2

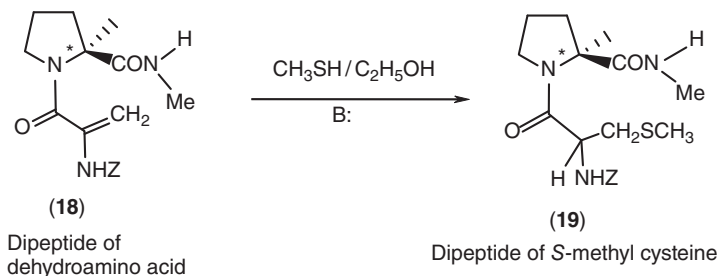


Where: $\text{R} = \text{C}_2\text{H}_5$; $\text{X} =$ benzylidenamino, salicylidenamino, *n*-nitrosalicylidenamino and pyridoxylidenamino

Scheme 3.3

These results indicate that both β -elimination of activated substituents forming Schiff bases of dehydroamino acids and addition of some nucleophiles to dehydroamino acid moieties occur even with the simplest pyridoxal analogs.

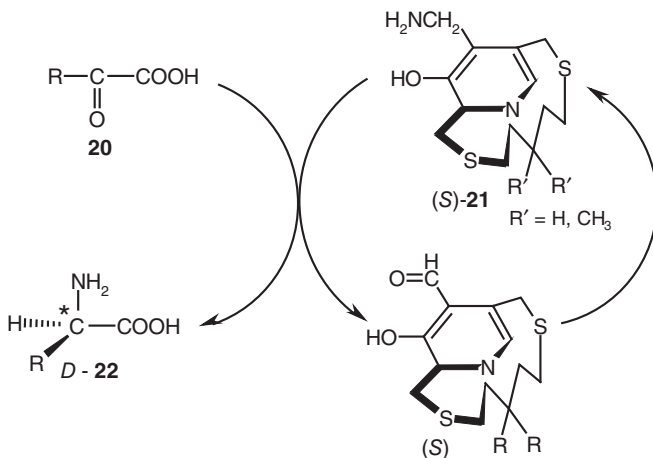
The principal possibility of the asymmetric synthesis of sulfur-containing amino acids by nucleophilic addition of thiols to dehydroamino acid fragments was demonstrated by Schmidt's group [20] by adding methylthiol to the dehydropeptide derivative (**18**) in ethanol (see Scheme 3.4). Thus, from a precursor containing proline and dehydroamino acid derivatives, dipeptide (**19**) containing D-methyl cysteine in excess (>84%) was obtained.



Scheme 3.4

Transamination reaction involving achiral pyridoxamine and α -keto acid (20) leads to the formation of D,L-amino acid.

In case of using optically active pyridoxamine analog – (*R*)- or (*S*)-15-aminomethyl-14-hydroxy-5,5-dimethyl-2,8-dithio[9](2,5)-pyridinophane (21), in the presence of Zn^{2+} ion as a result of transamination, α -ketoacids, respectively, convert to L- or D-amino acids (22). The highest yield of optically active isomer of D-phenylalanine (23–61%) was observed in the transamination reaction of phenylpyruvic acid catalyzed by a chiral pyridoxamine (see Scheme 3.5) [21]. The enzyme is capable of catalyzing the formation of α -keto acid only from one optical isomer of the amino acid.

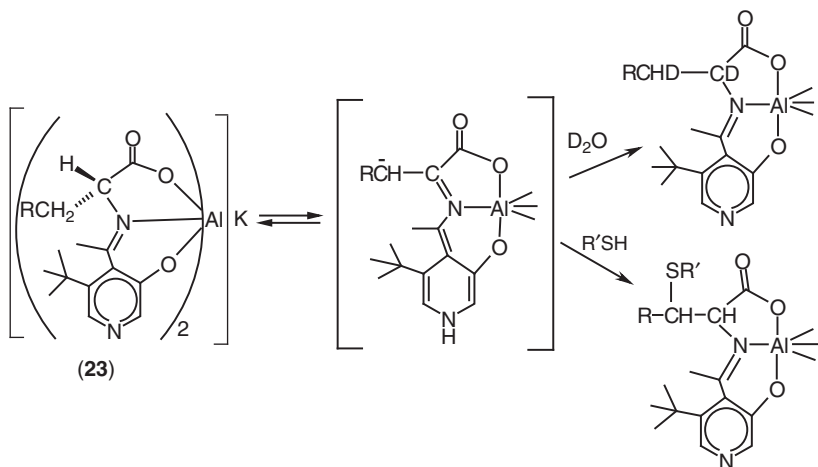


Scheme 3.5

In all the studied enzyme systems till date, protonation of the intermediate imine is always done from the *si* side. In catalysis by α -decarboxylases, the spatial arrangement of atoms around the $\text{C}\alpha-\text{N}$ bond is defined by binding a peripheral group in the fully extended side chain of the amino acid moiety. The intermediate imino compound is usually protonated by α -carbon atom, which ultimately leads to the release of the amine. Theoretically, it can be protonated from both sides

of the plane of the imine, but it was found that the decarboxylation of L-tyrosine, L-lysine, L-glutamate, and L-histidine by the action of respective decarboxylases proceeds with retention of configuration.

In contrast to the reactions of β -elimination and addition, the reactions of γ -eliminating and coupling enzymes can be modeled only in the systems containing positively charged pyridoxal heterocycle. Thus, these processes were simulated in the octahedral Al^{III} ion complexes of Schiff bases of the amino acids with pyridoxal aldehyde derivative (**23**) [22] (see Scheme 3.6).



Scheme 3.6

Substitution in γ -position was observed with the reaction of pyridoxal-N-metachloride, aluminum nitrate, thiophenol, and methionine sulfone from which phenylhomocysteine was formed [15].

Despite the fact that Danatan's hypothesis about the role of stereoelectronic effects is widespread, without modeling studies it is impossible to obtain convincing experimental confirmation.

First, *Fisher* and *Abbott* revealed that the relative rates of cleavage of two C–H bonds of the glycine moiety in bis-[pyridoxalidenglycinate]sodium cobaltate (III) complexes were different [23]. According to the authors, this is due to the different orientation of hydrogens relative to the Schiff base plane. In favor of this view are the ^1H NMR spectroscopy data – the allyl constants of spin–spin interaction of these protons with the aldimine hydrogen are different. The difference in mobility of α -protons of the glycine moiety found earlier for similarly constructed complexes of bis-[*N*-3-methylsalicylidenglycinate]sodium cobaltate (III) (**24**) [14, 24] can be easily explained by the steric hindrance of attack of base on one of the protons of the glycine moiety, as shown in Figure 3.1.

The absolute configuration of isolated mono-deuterated chiral glycine after 50% deuterium exchange corresponds to this stereochemical picture [14].

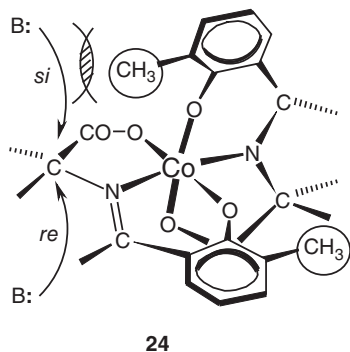


Figure 3.1 Steric hindrances of attack of the base on pro-S proton in the complex Δ -bis[*N*-3-methylsalicylidene]glycinate]sodium cobaltate (III) (24).

In another study, Tsai and coworkers associate the mobility of α -hydrogen of amino acid in the Schiff base with a specific weight of the conformer with a perpendicular arrangement of the C–H bond relative to the Schiff base plane [25].

However, to date, in known works there is no clear correlation of influence of stereoelectronic effects on the choice of the direction of cleavage and formation of individual bonds of amino acid moiety in pyridoxal model systems, which is very important to mimic biological processes and develop biomimetic methods for the synthesis of amino acids.

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4

Modeling of Processes Associated with Cleavage of C α -H and C α -C β Bonds

As has been previously shown, chiral bis-salicylidene and pyridoxalidene octahedral complexes of So^{III} , Al^{III} , and Fe^{III} ions can be successfully used to simulate and to some extent model the reactivity of pyridoxal-dependent aldolase [1].

Co^{III} ion complexes are stereochemically inert and do not change their configuration in chemical conversions of ligands. Depending on the location of the tridentate ligands to the right or left to the helix relative to the C_2 axis, complexes are referred either to Λ - or Δ -series (see Figure 4.1).

Assignment of Λ - and Δ -configuration to the isomers of octahedral complexes of bis- $[N\text{-salicylideneaminoacetate}]$ sodium cobaltate (III) was carried out using optical rotatory dispersion (ORD) curves, CD (circular dichroism) spectra, and X-ray diffraction (XRD) analysis [2–4].

In salicylidene complexes, salicylaldehyde moiety acts as a pyridoxal, in which heterocyclic nitrogen is deprotonated as CH-acidity of amino acid fragments of Schiff bases of deprotonated on the heterocyclic nitrogen of pyridoxal and salicylaldehyde is close to each other [5]. Stereochemical inertness of transition metal ion complexes allows some compounds that do not exist in a free form to exist as complexes. Among these compounds are also dehydroamino acid complexes, and this chapter is dedicated to them.

As model systems, to study some aspects of pyridoxal catalysis, such as α,β -elimination of β -hydroxy- α -amino acids with the formation of active electrophilic moieties of dehydroamino acids and asymmetric addition of nucleophiles to the $\text{C}=\text{C}$ bond of dehydroamino acids with the formation of β -functionally substituted α -amino acids, the chiral octahedral Co^{III} complexes of Schiff base of threonine with salicylic, 3-methylsalicylic, and 7-methylsalicylic aldehydes were chosen [6]. Initial threonine complexes were synthesized by reacting (*S*)-threonine with $\text{Na}_3\text{Co}(\text{CO}_3)_3$, and salicylaldehyde or its derivatives in water (see Scheme 4.1).

It has been shown that the enantioselective effects (optical properties) in such octahedral complexes of chiral amino acids arise due to the “configuration” and “vicinal” components [3, 4]. ORD curves of the two diastereomers of the threonine complex with *o*-oxyacetophenone (or 7-methylsalicylic aldehyde) (Λ -27 and

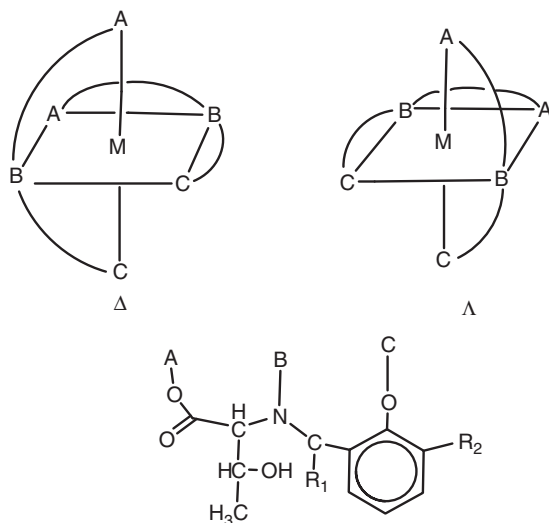
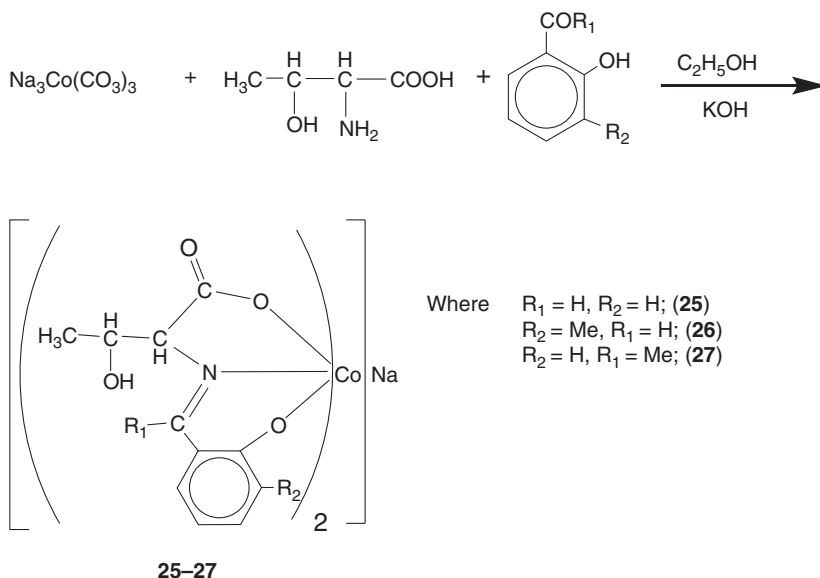


Figure 4.1 Location of tridentate ligands relative to the C₂ axis.



Scheme 4.1

Δ -27) are shown in Figure 4.2. Comparison of the calculated “configuration” component of these curves with the ORD curve of similarly constructed complex of glycine (glycine is an achiral amino acid and “vicinal” contribution is absent in its complexes) shows that the isomer of complex 27 with a higher R_f value on Al_2O_3 has Λ -configuration, and a slow-moving diastereomer – Δ configuration.

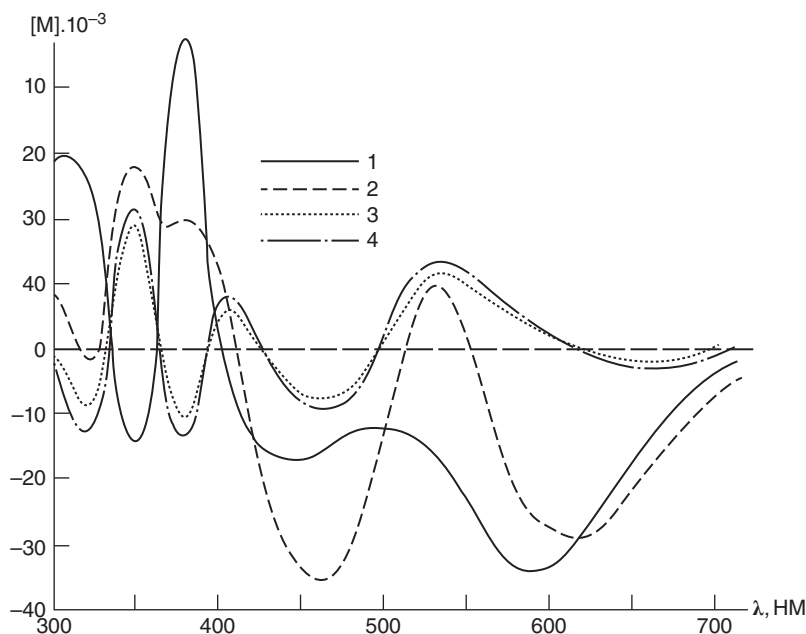


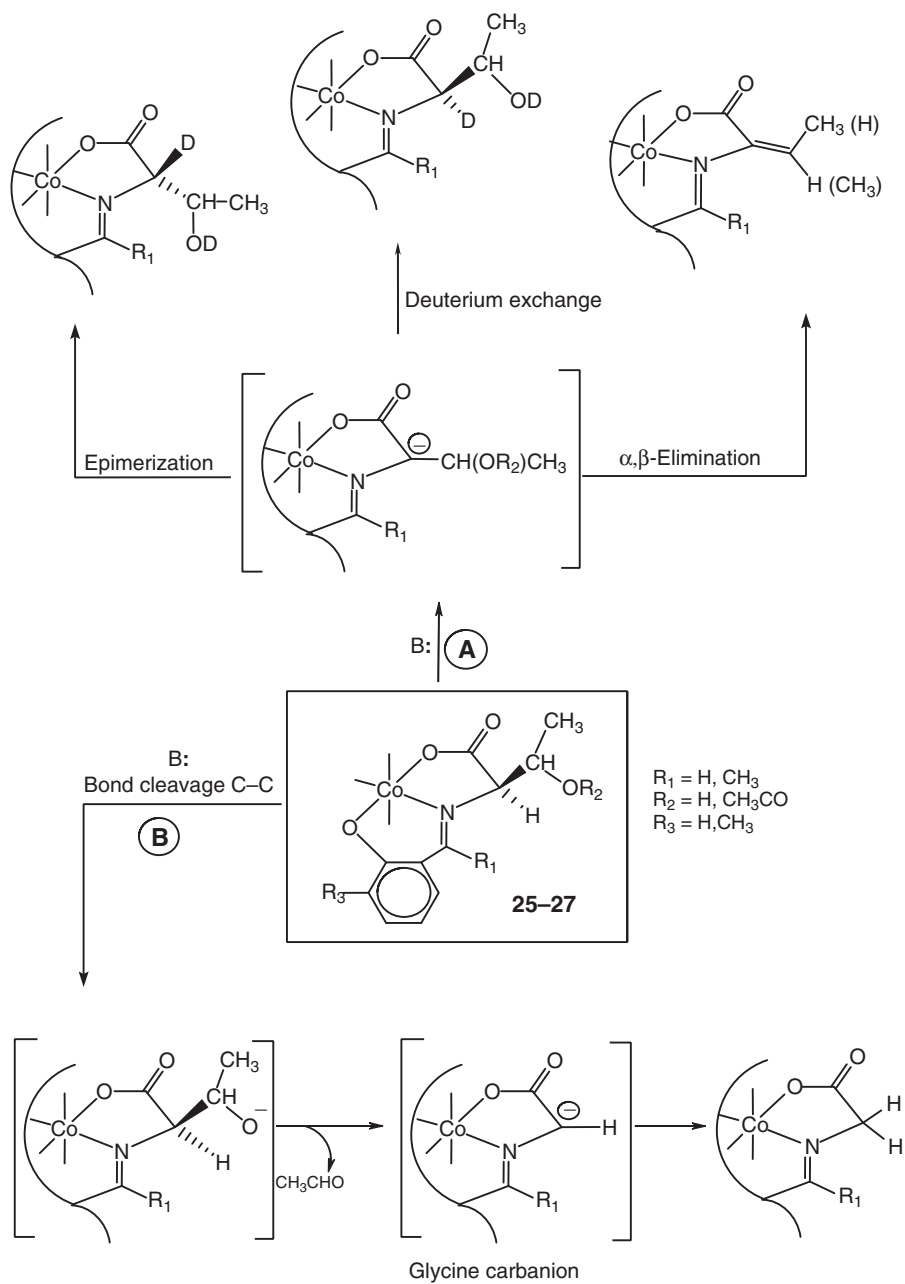
Figure 4.2 ORD curves in H_2O at $25\text{ }^\circ\text{C}$: (1) Δ -27; (2) Λ -27; (3) configuration component of ORD curve Λ -27; and (4) Λ -bis-[*N*-salicylidene-glycinate]sodium cobaltate(III) [7].

However, from both diastereoisomers, after decomposition of complexes by electrochemical reduction of Co^{III} to Co^{II} , threonine with (*S*)-absolute configuration was isolated. This proves the difference in configurations of the complexes ("configuration" component) and entical configuration of their amino acid fragments ("vicinal" component), namely Λ -(*S,S*)- and Δ -(*S,S*)-configuration of diastereomeric complexes **25–27**.

As a criterion for the evaluation of steric effects in these complexes, the ratio of cleavage rates of the $C_\alpha-C_\beta$ and $C_\alpha-H$ bonds was compared. For this, the isotherms of α,β -elimination, deuterium exchange, and epimerization as well as retroaldol decomposition with cleavage of the $C-C$ bond were investigated (see Scheme 4.2).

One would expect that the introduction of a methyl group in position 3 of the salicylaldehyde moiety in the case of complex **26** leads to shielding of base attack on α -proton of amino acid fragment in the diastereomer of Λ -configuration and difficulty in oxyethyl group leaving in diastereomer with Δ -configuration (see Figure 4.3).

Another possible way for steric control is the following – the hydrophobic shielding of a base attack on α -proton of threonine in the studied systems cannot provide changes to the relative rates of $C_\alpha-C_\beta$ and $C_\alpha-H$ bonds cleavage. For example, in a diastereomer of Λ -bis-[*N*-3-methylsalicylidene-(*S*)-threoninate]sodium cobaltate (III) (Λ -**26**) a methyl group in position 3 of the



Scheme 4.2

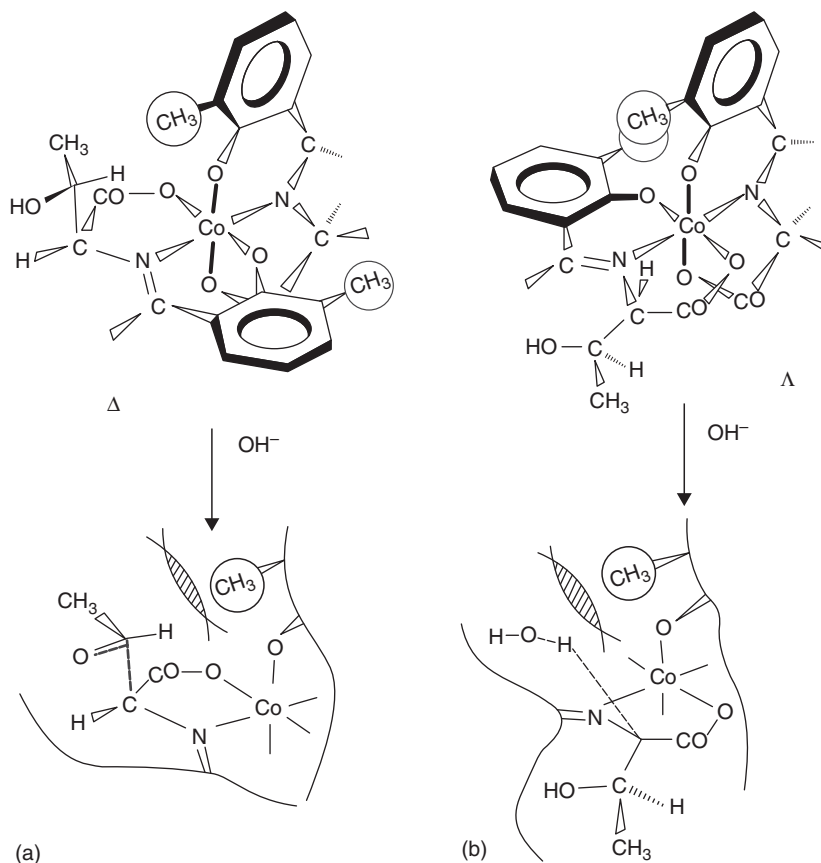


Figure 4.3 (a) Sterically hindered leaving of oxyethyl group in Δ -26 complex and (b) steric shielding of base attack on α -proton of threonine moiety in complex Λ -26.

salicylaldehyde shields the attack of base on α -proton of threonine fragment of the adjacent ligand (see Figure 4.3). However, cleavage of the $C_\alpha-C_\beta$ and $C_\alpha-H$ bonds in Λ -26 diastereomeric complex slows down to the same extent as in the case of complex Λ -25 where in position 3 of salicylaldehyde is hydrogen.

On the other hand, the introduction of a methyl group into position 7 of salicylaldehyde moiety in bis-[*N*-7-methylsalicylidene-(*S*)-threonine]sodium cobaltate (III) complex (**27**) causes the oxyethyl group of the amino acid moiety to adopt an axial position as both in case for Δ and for Λ isomers, which corresponds to the conformation shown in Figure 4.4. A large difference in the rates of exchange and cleavage would indicate, in accordance with the Danatan's hypothesis, stereoelectronic control of the reaction direction.

In D_2O under the action of a base, the threonine fragment in all diastereomeric complexes derived from salicylaldehyde and Co^{III} (**25**, **26**) is involved in α -proton exchange reactions accompanied by epimerization forming *allo*-threonine.

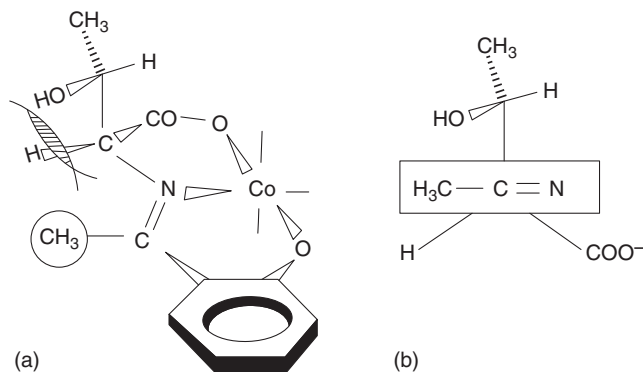


Figure 4.4 (a) Axial location of oxyethyl side group of threonine in Δ - and Λ -27 diastereomers and (b) projection from the benzene ring side.

Simultaneously, there is disintegration of threonine fragment with the formation of acetaldehyde and glycine, and the resulting *allo*-threonine has only (*R*)-configuration, but threonine retains its (*S*)-configuration. Thus, the entire process is depicted in Scheme 4.2.

Kinetic studies of the deuterium exchange reaction showed that in all diastereomeric complexes **25** and **26** α hydrogen exchange occurred with a partial retention of configuration and its rate was approximately three times more than the rate of C_{α} - C_{β} cleavage.

In this regard, fundamentally different behavior is observed in case of complexes based on *o*-hydroxyacetophenone (**27**). Thus, the analysis of amino acids formed during treatment of Δ - and Λ -27 with base in D₂O, indicates the presence of only the starting glycine and threonine and the complete absence of *allo*-threonine. In this case, the process of C_{α} - C_{β} bond cleavage is not accompanied by racemization on the metal ion, as evidenced by isorotational point of ORD curves not lying on the zero line during the decay of threonine fragment (see Figure 4.5).

By XRD analysis, it was found that in metal complexes of Schiff bases of salicylaldehyde or pyridoxal with amino acids, the lateral group of the amino acid moiety occupies pseudo-axial orientation due to steric interactions of the aldimine hydrogen with that group. Replacing aldimine hydrogen by methyl group should cause even more pronounced axial orientation of the oxyethyl group due to the increased steric interactions. The same factors lead to the fact that the transition state of C_{α} -H bond, apparently resembling flat carbanion, is sterically more difficult for hydroxyacetophenone complexes due to steric nonbinding interactions of hydroxyethyl and methyl groups than for salicylaldehyde complexes where hydroxyethyl group interacts with aldimine hydrogen (Scheme 4.2, path A). The transition state of C_{α} - C_{β} bond cleavage (see Scheme 4.2, path B), also resembling flat carbanion with interaction of α -hydrogen with the aldimine hydrogen or CH₃ group at C=N-bond, by energy almost does not differ for the acetophenone and

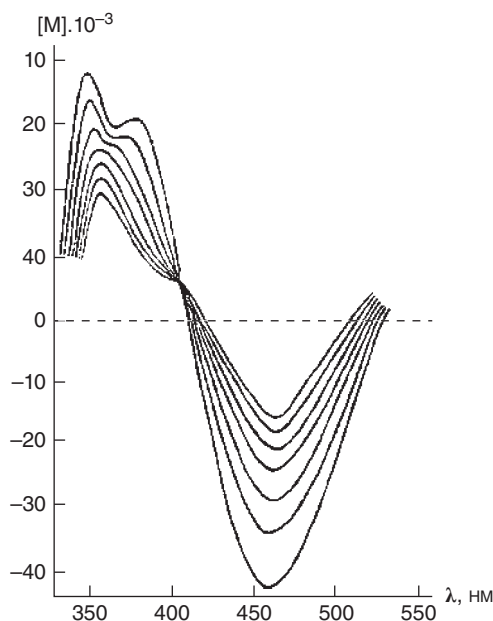


Figure 4.5 Change of ORD curve of Δ -27 in carbonate buffer in D_2O .

salicylaldehyde complexes. Therefore, the cleavage of $C_\alpha=C_\beta$ bond occurs with approximately the same rate for the Δ - and Δ -25 and Δ - and Δ -27, while the cleavage of $C_\alpha=H$ bond in complexes 27 selectively slows down [8].

It is possible that the cause for the identical slowdown of $C_\alpha-H$ and $C_\alpha-C_\beta$ bond cleavage in 3-methylsalicylic aldehyde complex Δ -26 is that the steric shielding of the attack on α -proton of the fragment of threonine moiety (see Figure 4.3) and solvation of the intermediate carbanion formed during $C_\alpha-C_\beta$ cleavage (see Figure 4.6.) experience similar steric hindrances.

If the mechanism of the threonine $C_\alpha-C_\beta$ bond cleavage is close to the S_E2 , as observed in the case of retroaldol cleavage with the formation of unstable carbanions [9], such steric hindrance can fully explain the observed slowdown (approximately five times) of $C_\alpha-C_\beta$ bond cleavage.

In other words, the predictions of the relative reactivity of $C_\alpha-H$ and $C_\alpha-C_\beta$ bonds based on Danatan's model are fully realized.

Thus, of the two possible ways to sterically control the direction of the reaction, namely rigid fixation of orientation of breaking bonds relative to the π -system of the Schiff base and steric hindrance for the base to approach either of the leaving group, the first way is more effective and allows to direct the reaction in one way. The obtained results directly correlate with the concepts put forward to explain the stereochemistry of pyridoxal phosphate (PP)-enzyme effects.

Now, we can directly pass to the study of the stereochemistry and mechanism of dehydration of the threonine moiety in octahedral Co^{III} complexes of Schiff

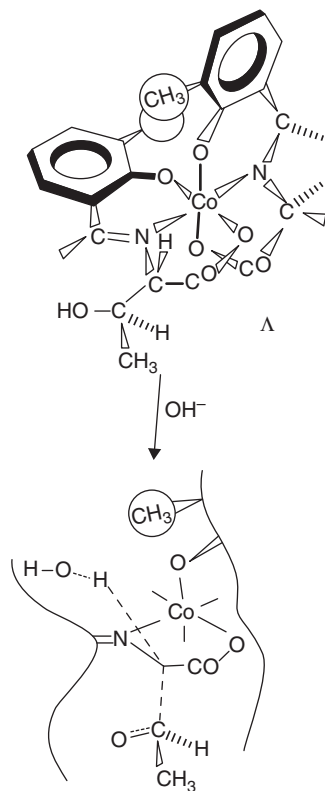


Figure 4.6 Steric shielding of solvation of carbanion intermediately formed during cleavage of $C\alpha-C\beta$ bond in Λ -26 complex.

base of threonine with salicylic, 3-methylsalicylic, and 7-methylsalicylic aldehydes (25–27).

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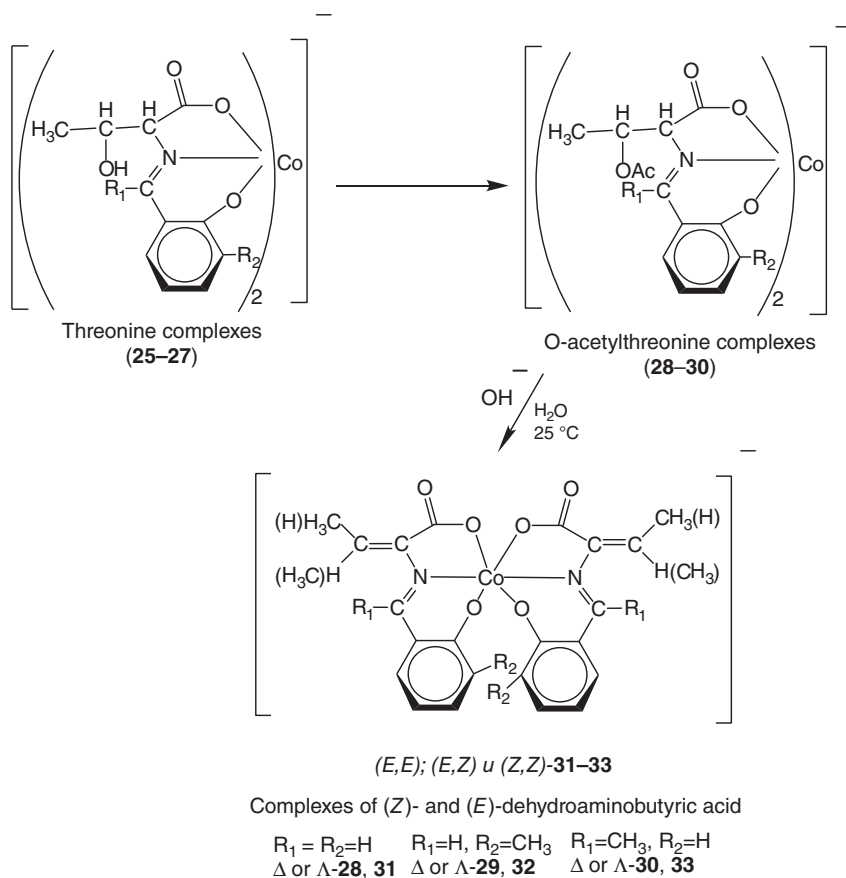
Modeling of α,β -Elimination Processes of PP-Catalysis, Kinetics, and Stereochemistry

By analogy with the natural mechanism of dehydration of β -hydroxy- α -amino acids in model studies, the threonine hydroxyl moiety can also be activated by its replacement with the easily leaving acetoxy group. Threonine fragments of diastereomeric complexes **25–27** are readily O-acetylated by acetic anhydride in acetonitrile in the presence of catalytic amounts of pyridine [1] (see Scheme 5.1). During the isolation of acetylated complexes partial elimination of acetoxy ion from O-acetylthreonine complexes occurs and products containing dehydroaminobutyric acid fragment are formed.

Comparison of optical rotatory dispersion (ORD) curves of the initial threonine and acetylthreonine complexes indicates that during acetylation, no change in the absolute configuration of the complexes occurs. The threonine, extracted from acetylated complexes after their electrochemical reduction and acid hydrolysis, does not contain traces of *allo*-threonine, which proves a lack of epimerization of amino acid fragment during acetylation of complexes.

Elimination of acetic acid in acetylated complexes of Δ - and Λ -**28**, and Δ and Λ -**29**, under the action of aqueous bases gives a set of diastereomeric complexes of Co^{III} ion, containing Schiff bases of (*Z*)- and (*E*)-dehydroaminobutyric acid (see Scheme 5.1). From a pure acetylated diastereomer **28** or **29**, a set of all three isomers with (*EE*), (*EZ*), and (*ZZ*)-configuration is obtained. Diastereomers are easily separated by preparative TLC on Al_2O_3 and differ from the starting complex parameters by electronic and ^1H NMR spectra and ORD curves.

After electrochemical reduction of the obtained dehydroaminobutyric acid complexes, the mixture did not contain any amino acid traces, which indicated the completeness of elimination reaction (free dehydroaminobutyric acid is unstable and is rapidly converted to keto acid). The structures of the obtained unsaturated compounds and their geometrical isomers were determined by ^1H NMR spectra. Since (*ZZ*)- and (*EE*)-isomers have the same C_2 symmetry, in these compounds the proton signals of both ligands have the same chemical shifts, but the (*ZE*) isomer has a double set of signals, as expected for the complex with C_1 symmetry. To determine the (*Z*)- and (*E*)-configuration of dehydroaminobutyric acid fragments of **31–33** complexes, the absolute method of classification using the Overhauser's effect was employed. Thus, irradiation of the methyl group having a large chemical shift increases the intensity of aldimine hydrogen



Scheme 5.1

signal by 15–20%, as it should be in the case of (Z)-isomer. Furthermore, no increase in intensity is observed when irradiating the methyl group, having signal in strong fields, which could be expected in the case of (E)-configuration. Additional confirmation of the correctness of this configuration classification is the relative broadening of the β -hydrogen signals of dehydroaminobutyric acid fragment in the isomers that are attributed to have a (Z)-configuration. The same broadening was observed previously for substituted acrylic esters with *trans*-location of β -hydrogen and N-atoms [2]. The shift of β -hydrogen signals of the dehydroaminobutyric acid fragment in isomers of (E)-configuration and hydrogen signals of CH_3 -group in (Z)-configuration isomers to the weak fields is apparently due to deshielding of these hydrogens by magnetic anisotropy of $\text{C}=\text{N}$ bond.

In the course of elimination of acetic acid from O-acetylthreonine fragment of 28 and 29 complexes, no changes in the complexes configuration is observed. This

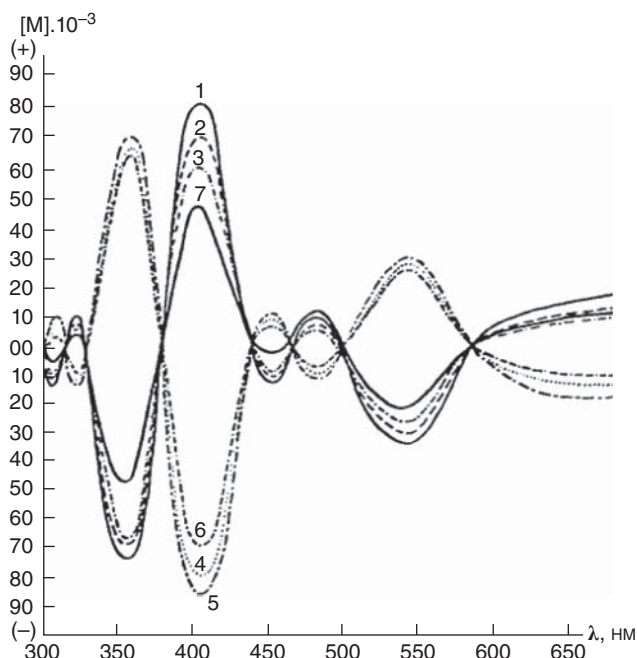


Figure 5.1 ORD curves of Δ - and Λ -**31** isomers in H_2O at 25°C (1) Δ -(ZZ), (2) Δ -(ZE), (3) Δ -(EE), (4) Λ -(ZZ), (5) Λ -(ZE), (6) Λ -(EE), and (7) the configuration component of Δ -**28**.

is evidenced by the iso-rotational points not lying on the zero line on the ORD curves during elimination, as well as by the ORD curves obtained for **31** and **32** unsaturated diastereomers (see Figure 5.1).

Due to the loss of asymmetric centers of amino acids during the elimination, “vicinal” contribution of amino acid fragment to the observed rotation disappears, that is why the ORD curve of deacetoxyated diastereomers practically coincides with the configuration component of ORD curves of starting acetylated diastereomers (see Figure 5.1).

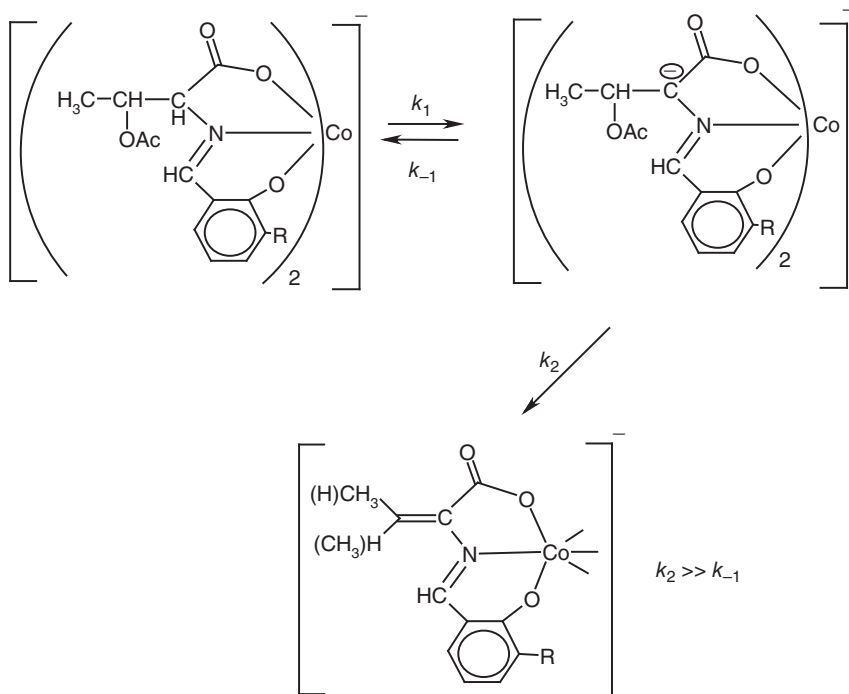
Water and methanol are not attached to the double bond of dehydroaminobutyric acid complexes in pH 7.0–12.0 range, and under acidic conditions (0.01 N HCl) the interconversion process of (*E*)- and (*Z*)-isomers is not observed. Experimentally, it was shown that only strong nucleophiles (thiophenolate ion, nitromethane, etc.) were able to bind under these conditions to the double $\text{C}=\text{C}$ bond of the dehydroaminobutyric acid moiety resulting in the formation of saturated α -amino acids (based on electronic and ^1H NMR spectra).

Thus, **28** and **29** complexes are convenient objects for studying the kinetics and stereochemistry of β -elimination of acetic acid from *O*-acetylthreonine fragment for the correlation of modeling study results with the laws of action of α,β -eliminating PP-enzymes.

To measure the reaction rate, the spectrophotometric, polarimetric, and pH-stat techniques were used. In all cases, the elimination is described by

pseudo-first-order patterns of kinetics until 80% conversion for all the diastereomers of **28** and **29**.

Kinetic studies showed [3] that the rate of elimination of acetic acid from **28** and **29** increased with the increase of base concentration in a solution. The process is not accompanied by side reactions and is faster than the epimerization of an amino acid moiety, as evidenced by the absence of *allo*-form in threonine isolated from the remainder of the acetylated starting complex **28** after 50% of the reaction flow and by the lack of α -hydrogen exchange of the threonine moiety in the reaction conducted in D_2O . This corresponds to $k_2 \gg k_{-1}$ in Scheme 5.2.



Scheme 5.2

The ratio of obtained (*EE*)-, (*EZ*)-, and (*ZZ*)-isomers of dehydroaminobutyric acid complexes **31** and **32** depends on the nature of the base catalyzing the process. Table 5.1 shows the ratio of the diastereomers obtained in different experimental conditions. Along with the OH^- ions, *Dabco* (diazabicyclooctane) was used as an organic base in elimination process.

In all cases, there was a linear dependence of the elimination rate constants on the base concentration. The rate constant values determined by spectrophotometric or polarimetric methods clearly coincided with the values determined by pH-stat method.

Table 5.1 The ratio of (Z)- and (E)-dehydroaminobutyric acid diastereomeric complexes during elimination of acetic acid in O-acetylthreonine complexes in H₂O under the action of OH⁻.^{a)}

No.	Substrate	(EE)/(EZ)/(ZZ)	The total content (%)	
			(E)	(Z)
1	Δ -28	1/3.3/2.2	40.6	59.6
2	Δ -28	1/1.1/0.4	65	35
3 ^{b)}	Δ -28	1/7.1/10.1	25	75
4 ^{c)}	Δ -28	1/4.2/6.8	26	74
5 ^{d)}	Λ -28	1/7.1/9.7	25.5	74.5
6	Δ -29	1/8.8/13.2	23.5	76.5
7	Λ -29	1/5.7/8.3	26	74

a) At pH = 10.8, 25 °C and pH-stat mode.

b) Under action of buffer Dabco: Dabco HCl = 0.5 M : 0.2 M.

c) Under action of buffer NaHCO₃: Na₂CO₃ = 0.83 M : 0.167 M (pH = 9.15).

d) Equilibrium ratio of diastereomers obtained by epimerization of Δ -(ZZ)-31 and Δ -(EE)-31.

The absence of noticeable formation of dehydroaminobutyric acid complexes in water at pH < 4.0, the linear increase of process rate with an increase in buffer capacity and the activity of OH⁻ ions, and the absence of deuterium exchange of α -hydrogen in the process and epimerization of the threonine moiety allow to attribute the elimination mechanism to class E₂ or (E1cB)₁.

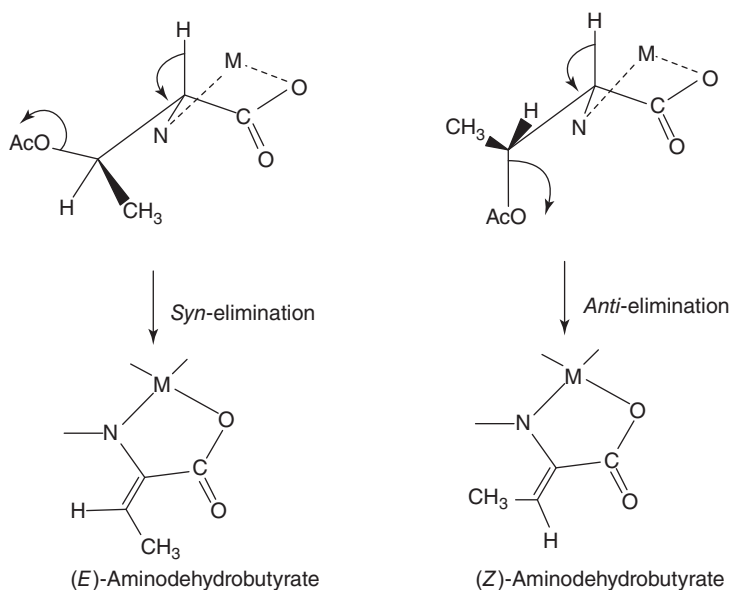
This is also confirmed by the absence of reverse isotope effect of the solvent during the process in D₂O in the buffer solution of Dabco. The argument in favor of a E1cB mechanism with the rate-limiting step of α -proton cleavage from amino acid (E1cB)₁ is the proximity of the second-order rate constants of deacetoxylation of acetylated Λ -28 and Λ -29 complexes under the action of OH⁻ ion and the rate constants of α -proton cleavage of (S)-threonine fragment in Λ -25 and Λ -26 complexes calculated as double rate of inversion of amino acid fragment under the action of the hydroxyl ion.

The reduction of the process rate constants in transition from Λ -28 to Λ -29 is similar to the decrease of the rate constant of deuterium exchange of (S)-valine fragment in transition from Λ -bis-[N-salicylidene-(S)-valinate]cobaltate (III) to Λ -bis-[N-3-methylsalicylidene-(S)-valinate]cobaltate (III) ion and may be explained by steric hindrance of attack of OH⁻ ion on the α -hydrogen of amino acid fragment due to shielding by the methyl group of the adjacent ligand in Λ -29 (see Figure 5.3).

The stereochemistry of the resulting unsaturated product is determined by conditions of kinetic control as the mutual conversion of (Z)- and (E)-isomers under the experimental conditions is very slow. Thus, isomerization of Δ -(ZZ)-31 and Δ -(EE)-31 complexes was not observed by the action of OH⁻ and CO₃²⁻. Isomerization occurs under Dabco, and the reaction is described by regularities of general base catalysis with the rate constant of $\sim 7 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ at 25 °C in H₂O,

which is significantly less than the rate constant for elimination of acetic acid ($\sim 1 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$). This means that the stereochemistry of the elimination product is determined by kinetic control.

Obviously, the isomers with (*Z*)-configuration are formed by *anti*-elimination, and isomers with (*E*)-configuration – by *syn*-elimination of acetic acid (see Scheme 5.3).



Scheme 5.3

The data presented in Table 5.1 demonstrate a very high degree of *syn*-elimination in the entire series of studied complexes, reaching 65% (see Table 5.1, No. 2). The highest degree of *syn*-elimination by (E1cB)_I mechanism in polar media was 15% in case of acetic acid moiety elimination in β -acetoxybutanoate in methanol [4].

The stereochemistry of elimination depends on the nature of the base tearing off α -hydrogen of the amino acid fragment. In case of using *Dabco* at pH = 9.4 (0.5 M *Dabco*/0.24 M *Dabco-HCl*), when the contribution of OH[−] ion catalysis against the background of *Dabco* catalysis can be neglected based on the rate constants, the stereochemistry of elimination in case of Λ -**28** tends to change, and the ratio of (*EE*) and (*ZZ*)-isomers varies from 1/2.2 (see Table 5.1, No. 1) to 2.5/1 (see Table 5.1, No. 2). In other words, transition to a catalyst, forming a positively charged conjugate acid, increases the fraction of *syn*-elimination to 65%.

An even greater effect is observed during transition to CO₃^{2−} ion catalysis. In soda buffer solution (pH = 9.15), where 56% of elimination takes place due to the OH[−] ion, and the remaining 44% – due to CO₃^{2−} (based on the rate constants),

the total ratio of 25% *syn*- and 75% *anti*-elimination is observed. This corresponds to 95% *Anti*-elimination by the action of CO_3^{2-} ion.

It is obvious that in the transition state of the studied reaction $(\text{E1cB})_1$ even in water the relationship between the base, leaving α -proton and the starting CH-acid, is retained. This connection can be realized by the type of ion pair formed by carbanion of the amino acid moiety and protonated form of *Dabco* or by the homoconjugate of the carbanion and carbonate ion stabilized by hydrogen bond, or, finally, by the carbanion solvated with water molecule (in the case of OH^- ion catalysis). Electrostatic interaction between a leaving negatively charged acetoxo group and the conjugate acid, tearing off α -proton of the base in the transition state of elimination, helps to explain the change in stereochemistry of the process during the transition from *Dabco* to CO_3^{2-} catalysis.

In the case of *Dabco*, such interaction provides mutual attraction of oppositely charged particles – the maximum in case of *syn*-elimination. For catalysis by CO_3^{2-} ion mutual repulsion of equally charged particles leads to preferable *anti*-elimination. During the catalysis by OH^- ion, the electrostatic effects are absent, as its conjugate acid H_2O is a neutral particle. In this case, the difference in preference of *syn*- and *anti*-elimination for diastereomers of different structure is only a consequence of steric effects. Comparison of stereochemistry of elimination by the action of OH^- ions in case of Δ -28 and Δ -29 is an illustration of the influence of the hydrophobic shielding of carbanion from the side opposite to the cleaving proton. The carbanion of the amino acid fragment in the Schiff bases is planar and achiral [5, 6]. However, the solvation of such a carbanion can be asymmetric.

Figure 5.2 presents a set of possible reactive conformations where optimal for β -elimination mutual orientation of the unshared electron pair of the carbanion and cleaving C–OCOCH₃ bond is realized. It also schematically presents different cases of this carbanion solvation.

It is obvious that in the original structure “A” or “B” (if $\text{HB} = \text{H}_2\text{O}$), where only one side of the carbanion is solvated by H_2O , formed from OH^- and α -proton of amino acid moiety, *anti*-arrangement of H_2O and leaving CH_3COO -group is sterically most advantageous for elimination, as represented by the structure “A.” In structure “B” sterically unfavorable nonbonding interaction between the leaving acetoxo group and H_2O occurs and, therefore, *syn*-elimination in an asymmetrically solvated carbanion should be more difficult than with *anti*-elimination due to steric hindrances.

From two symmetrically solvated structures “C” and “D” more advantageous is the structure “D,” where there is no unfavorable steric interaction between the CH_3 -group of the threonine moiety and the carbonyl group, apparently responsible for the thermodynamic instability of (*E*)-isomer. However, preference of “D” conformer as compared with “C” conformer (if $\text{HB} = \text{H}_2\text{O}$) is not greater than the thermodynamic difference of the (*Z*)- and (*E*)-isomers, where the orientation of groups are rigidly fixed in space by the double bond of dehydroaminobutyric acid moiety (see Table 5.1, No. 4). As a result, from the viewpoint of sterics, formation of (*Z*)-isomers in a series of salicylic aldehydes has always been advantageous.

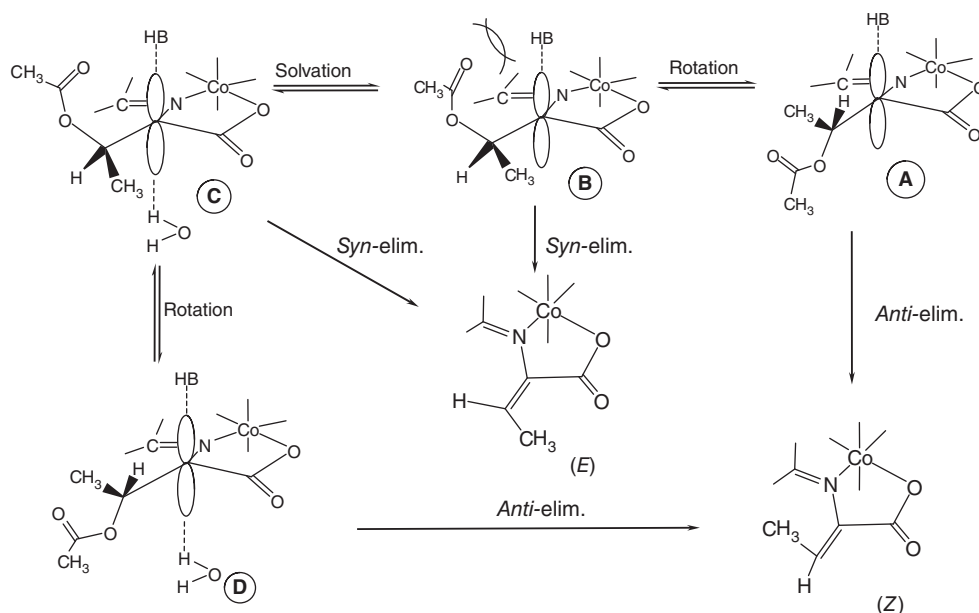


Figure 5.2 Conformation of a reactive carbanion during acetoxy-ion elimination in Δ - and Δ -28 complexes.

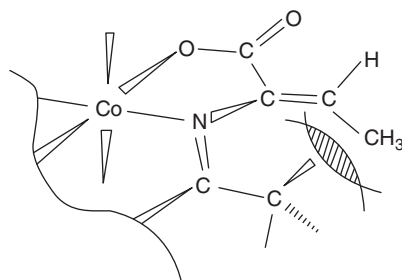


Figure 5.3 Steric nonbonding interactions of methyl groups of the C=C and C=N double bonds in Δ -(ZZ)-33 complex.

In transition from salicylaldehyde complexes to *o*-hydroxyacetophenone complexes, the aldimine hydrogen is replaced by a methyl group. In this case, sterically repulsive interaction between the methyl groups at the C=N- and C=C double bonds of the (Z)-configuration isomer should arise in the final product of elimination – Schiff base of dehydroaminobutyric acid complex **33** (see Figure 5.3). This will inevitably destabilize both this isomer and carbanions of “D” and “A” type.

It follows from the aforementioned that in elimination reaction product the isomer with (E)-configuration should prevail. And, indeed, during deacetoxylation of *o*-hydroxyacetophenone complex of *O*-acetylthreonine Δ -30, under the influence of *Dabco* acetic acid cleavage occurs within the framework of common equation of general base catalysis with the rate constant equal to $7.2 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$, which is 150 times less than in case of salicylaldehyde complexes. Taking into account

that in this case the mechanism of decomposition is E1cB, this difference corresponds to the ratio of rate constants of the tearing off of α -proton of the amino acid fragment of salicylaldehyde- and *o*-hydroxyacetophenone-based complexes. As expected, in this case while the elimination of acetic acid only (*E*)-configuration isomers are formed in a very large excess relative to the (*Z*)-configuration isomers. No isomers of (*Z*)-configuration were found in the reaction mixture by high-resolution ^1H NMR analysis.

Among the salicylaldehyde complexes, the hydrophobic steric shielding of intermediate carbanion from the opposite side of the leaving proton in case of Δ -29 (from the *si* side) increases the degree of *anti*-elimination as compared with Δ -28, where there is no such shielding (as demonstrated in the case of threonine complexes, see Figure 5.3). Thus, the ratio of the resulting (*EE*)- and (*ZZ*)-isomers of dehydroaminobutyric acid complexes varies from 1/2.2 to 1/13 at the transition from Δ -28 to Δ -29.

Obviously, in this case, approach of the second solvating water molecule from the *si* side slows down to such an extent that the elimination of acetoxo ion occurs mainly through the initially formed asymmetrically solvated carbanion "A" with preferred *anti*-elimination even in case of salicylidene complexes.

Intramolecular transfer of deuterium label from α -position of tyrosine or tryptophan on the leaving indole or phenolic moiety in the course of the pyridoxal-dependent enzyme catalysis of (tyrosinase or tryptophanase) β -elimination shows that at least in this case elimination occurs by *syn*-mechanism involving a single catalytic group of the active center of the enzyme [7]. It is known that in the active sites of many pyridoxal enzymes ε -amino group of lysine or histidine imidazole fragment are present that carry out functions of general base catalysis in the reactions of cleavage of amino acid α -proton [8]. The obtained data show that β -elimination of amino acids catalyzed by pyridoxal enzymes can occur by *syn* type due to the electrostatic stabilization of the leaving group by the positively charged protonated form of the basic groups of active center of the enzyme. Therefore, the decrease of the dielectric permeability in the active center of enzymes should increase the contribution of *syn* process [9].

Syn-elimination processes are common in nature and occur not only in the series of reactions catalyzed by pyridoxal enzymes. Thus, it is known that during dehydration and synthesis of β -hydroxycarboxylic acids enzymatically *syn*-elimination and *syn*-addition of water elements occur [10].

This type of model reactions also proceeds by E1cB mechanism, but with a predominance of *anti*-elimination products [4]. It is possible that enzymatic processes proceed by *syn* mechanism due to electrostatic interactions described above.

As noted earlier, during dehydration of (*S*)-threonine under the influence of threonine dehydratase intermediate dehydroaminobutyric acid is formed with a configuration that differs from the one formed under the action of threonine synthetase – an enzyme that produces (*S*)-threonine from homoserine via intermediate formation of dehydroaminobutyric acid [11]. It is obvious that in one of these

enzymes addition (or tearing off) of H_2O proceeds by *syn*-type, and in the other one – by *anti*-type.

The results presented in this section show that the hydrophobic shielding of one side of the carbanion and the location of a negatively charged group performing general base catalysis, in the active center of the enzyme can completely change the stereochemistry of elimination (or addition).

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6

Biomimetic Addition Reaction of Nucleophiles to Co^{III} Complexes of Dehydroaminobutyric Acid

The number of known model systems of pyridoxal phosphate (PP) enzymes catalyzing the natural reactions of α,β -addition of various nucleophilic moieties to electrophilic C=C bond of Schiff bases of dehydroamino acids is very limited. In particular, for this purpose octahedral bis-salicylidene Co^{III} ion complexes of (*E*)- and (*Z*)-dehydroaminobutyric acid **31** were investigated (see Scheme 6.1).

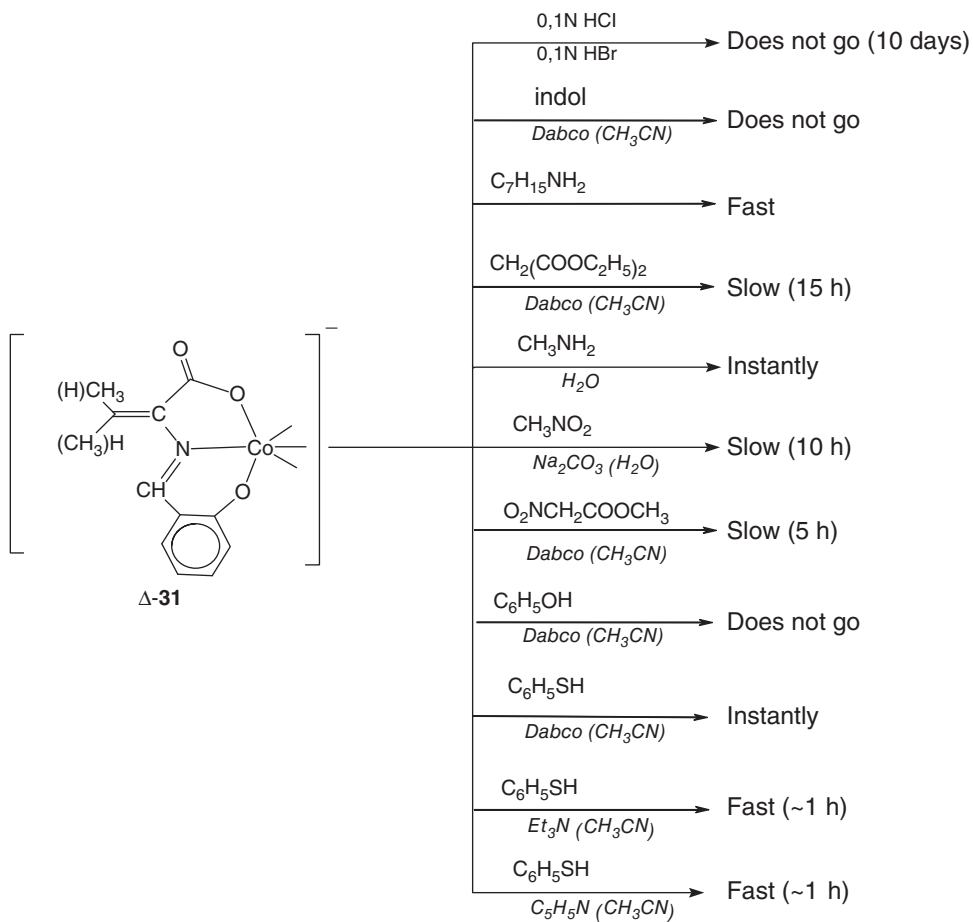
Addition reactions can be easily controlled by the spectrophotometric method following the reduction of absorption at 420 nm, accompanying the formation of saturated reaction product. As can be seen from Scheme 6.1, addition of acids including 0.1 N HCl and 0.1 N HBr to the test systems does not occur even within 5 days.

Addition of such weak nucleophiles as indole and phenol does not occur either. At the same time, there is a base-catalyzed nucleophilic addition of CH-acids to the double bond of dehydroaminobutyric acid moiety of complex Δ -**31**. Thiophenol is also added.

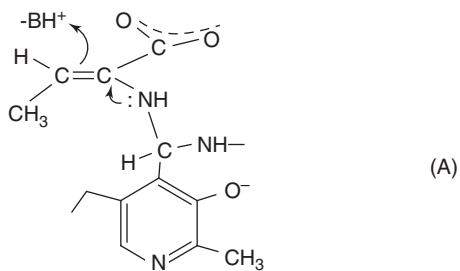
Based on these data, we can draw the following conclusions relevant to reactions catalyzed by PP-enzymes.

- 1) Nucleophilicity of the double bond of dehydroamino acid in these model systems is very small. As was shown previously, the Co^{III} ion by its electron acceptor ability is close to the proton in reactions of Schiff bases of salicylaldehyde and amino acids passing through the formation of planar carbanion [1]. Therefore, we may assume that even in pyridoxal systems (even if the nitrogen of the pyridine ring is deprotonated) the particle with the protonated imino group cannot decay with the formation of pyruvic acid through the proton attack on β -carbon atom of dehydroaminobutyric acid fragment. This is even more incredible for the systems where the nitrogen of pyridine ring is protonated.

It is possible that the true intermediate particle, through which pyruvic acid is formed, is compound A [2], formed during the attack of the ϵ -amino group of the lysine moiety on the aldimine double bond. In this compound, the nucleophilicity of the C=C bond should be sufficiently high.

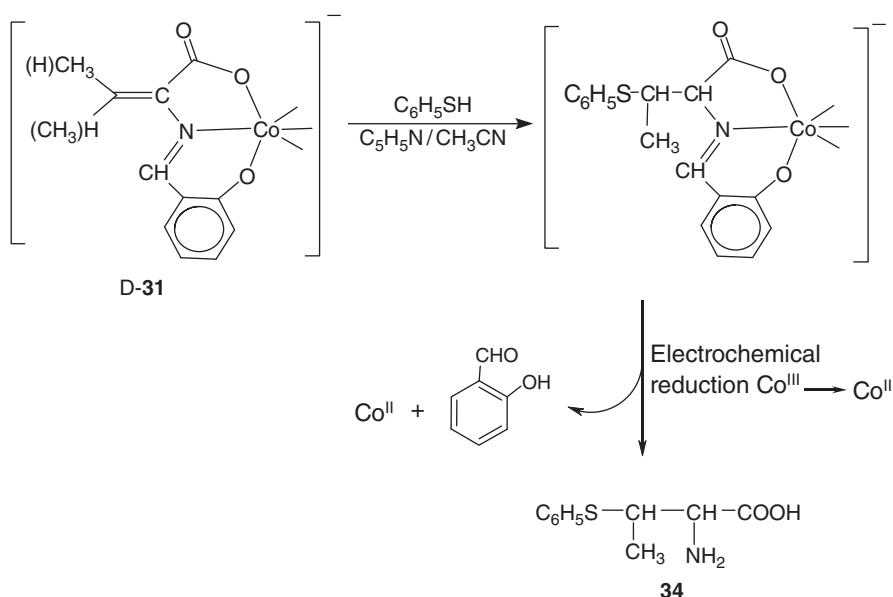


Scheme 6.1



- 2) Electrophilicity of the $\text{C}=\text{C}$ bond in the studied systems is insufficient for the synthesis of tryptophan and tyrosine from indole and phenol. This should have been expected based on published data. Besides, electrophilicity is insufficient to obtain a threonine by addition of H_2O to the double bond of dehydroaminobutyric acid moiety. From this, it follows that in the enzyme systems for the synthesis of threonine via intermediately formed dehydroaminobutyric acid the heterocyclic nitrogen atom of pyridoxal should be protonated.
- 3) Electrophilicity of the double bond is high enough for the synthesis of substituted cysteines, derivatives of ornithine, and glutamic acid by addition of thiols, nitro compounds, and malonic ester to the double bond of the Schiff base of dehydroamino acids.

To confirm the last conclusion, preparative synthesis of nonprotein amino acid *S*-phenyl- β -methylcysteine by condensation of thiophenol with Δ -bis-[*N*-salicylidene-(*E,Z*)-dehydroamino-butyrato]sodium cobaltate (III) (Δ -**31**) [3] complex was performed (see Scheme 6.2). The resulting mixture of diastereomeric complexes of adducts (without chromatography) was decomposed by the electrochemical reduction of Co^{III} to Co^{II} , and the target amino acid was isolated from the mixture by ion-exchange method.



Scheme 6.2

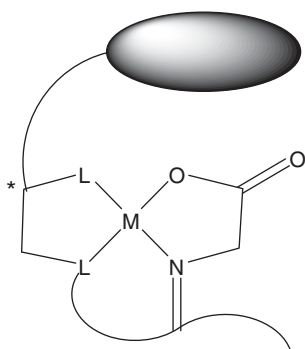
According to ^1H NMR investigation, the isolated amino acid is a mixture of two diastereomers of *S*-phenyl- β -methylcysteine (**34**). This is proved by two doublet signals typical of the methyl group protons (1.6 and 1.8 ppm) in a ratio of $\sim 65/35$

(%) with a large content of diastereomer, the methyl group doublet of which is located in the weak fields ($2L, 3L$ -*allo*-diastereomer).

Unfortunately, the observed enantioselective effects in these Co^{III} ion octahedral complexes are very low ($ee \sim 25\%$) and, therefore, they could not find further application in the preparative asymmetric synthesis of amino acids. The disadvantage of these complexes is also the technological complexity of their decomposition when isolating the desired products; complexes are decomposed by the electrochemical reduction of Co^{III} to Co^{II} .

However, these data as well as other regularities revealed by salicylidene complexes of Co^{III} ion pave the way for the asymmetric biomimetic synthesis of substituted cysteines and other β -substituted amino acids with the use of transition metal ion complexes with Schiff bases of regenerable chiral reagents.

Future effective chiral inducing systems or auxiliary reagents suitable for the asymmetric synthesis of amino acids should be resistant to racemization in the course of chemical transformations of amino acid moieties. Moreover, these systems should be easily assembled and disassembled with the release of target amino acids and the initial chiral inductors. Based on the foregoing, a hypothetical model for constructing systems for the asymmetric synthesis of amino acids can be imagined as follows:



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Part II

Asymmetric Synthesis of Nonprotein α -Amino Acids

Analysis of the literature data on biological properties of amino acids shows that these compounds are physiologically active and suitable for use in medicine, pharmacology, and other areas of economy as enantiomerically pure compounds. In most cases, they are enantiomers of natural protein L-series. It is shown that the optical antipodes of the physiologically active amino acids (of D-series) or medicinal preparations on their basis usually adversely affect the pharmacological activity or at best remain neutral. Apparently, amino acids should be made in the form of enantiomerically pure compounds.

It should be noted that while this problem is completely solved for protein amino acids, which are produced worldwide based on biotechnological (microbiological, enzymatic, and mixed enzymatic-chemical) methods, for production of nonprotein amino acids, it is highly relevant. This is due to the fact that the use of traditional methods for microbiological and enzymatic synthesis of amino acids in the production practice of nonprotein amino acids is not effective because of the unusual structure of the substrates, and the classical chemical synthesis usually gives optically inactive racemic mixtures. In this regard, to produce optically active nonprotein amino acids, recently the direction of asymmetric chemical synthesis, using various chiral inductors – catalysts or auxiliary reagents is intensively developing worldwide.

7

The Main Rules of Asymmetric Synthesis

Asymmetric synthesis is a process in which a prochiral molecule or fragment thereof is converted to a chiral one with an unequal amount of stereoisomeric products [1]. Until recently, the asymmetric synthesis was considered a quite exotic process. Today, this area of research is the center of attention for many leading scientists worldwide, and it is not amazing that the Nobel Prizes in Chemistry for 2001 were awarded to William Knowles, Barry Sharpless, and Ryoji Noyori for developing methods for the asymmetric catalysis [2, 3]. It combines all the advantages of chemical processes for the preparation of α -amino acids:

- 1) use of nonfood, low-cost raw materials;
- 2) conducting reactions in concentrated solutions;
- 3) ease of isolation of α -amino acids from the reaction medium;
- 4) reproducibility.

At the same time, this eliminates the main drawbacks of the chemical process, namely the need for separation of the obtained racemic α -amino acids into the optical antipodes and racemization of unwanted enantiomers.

The effectiveness of the asymmetric synthesis is assessed by enantiomeric purity; this value is called the *optical output* or an *enantiomeric excess* of the product (*ee*).

Currently, the following classification for the asymmetric syntheses is used (see Table 7.1).

Asymmetric syntheses are divided into partial and absolute, regardless of optical purity of the product. Absolute asymmetric synthesis (on optically active quartz, photochemical syntheses with circularly polarized light, syntheses with participation of other physical factors causing asymmetry) does not require participation of auxiliary optically active substances. In the well-known examples of absolute asymmetric synthesis, optical purity of the obtained products is very low, so this kind of asymmetric synthesis has only a theoretical value to date.

Partial asymmetric synthesis differs from an absolute one in the way that it always uses optically active auxiliary substances. Partial asymmetric synthesis in its turn has several varieties. *Diastereoselective* asymmetric synthesis is observed when the reaction results in diastereomers, which are known to differ by their

Table 7.1 Classification for the asymmetric syntheses.

Asymmetric synthesis (AS)	
Participation of optically active auxiliary substance	Participation of a natural agent causing asymmetry
Catalysis	
Auxiliary optically active group in the convertible substrate	Syntheses with participation of other physical factors causing asymmetry
Auxiliary optically active group in the reagent	
Auxiliary optically active solvent	
Homogeneous	
Heterogeneous	
	Photochemical syntheses with circularly polarized light
Diastereoselective AS	Enantioselective AS

physical properties. Among these properties, in particular, are energy reserve, and, hence, the state of thermodynamic equilibrium in a pair of diastereomers (thermodynamically controlled asymmetric synthesis (AS)), transition energies leading to diastereomers, and hence reaction rates of their formation (kinetically controlled AS). *Enantiomeric* asymmetric synthesis is observed when unequal amounts of enantiomers are directly formed during the reaction. Such reactions take place through the formation of intermediate complexes of chiral catalysts with substrates. Reactions proceed via diastereomeric transition states: different easiness of their reaching (different energy barriers on the way to enantiomers), resulting in different rates of formation of optical antipodes.

Scientists dealing with the problem of asymmetric synthesis were always interested in reaction mechanisms. The initial concepts were only of general nature. Current understanding of the mechanism of asymmetric syntheses is based entirely on conformational concepts. First attempts to predict and explain stereodifferentiation were made in early 1950s by *Prelog* [4] and *Cram and Kopecky* [5], who used a spatial model of the transition state to explain the experimental results for differentiating reactions. *Cornforth et al.* [6] also proposed an additional empirical rule. Currently, these rules are often used to explain reaction mechanisms and predict the progress of diastereo-differentiating reactions. There is no empirical rule for enantiomeric differentiating reactions, which would have been as widely used as *Prelog's* and *Krum's* rule.

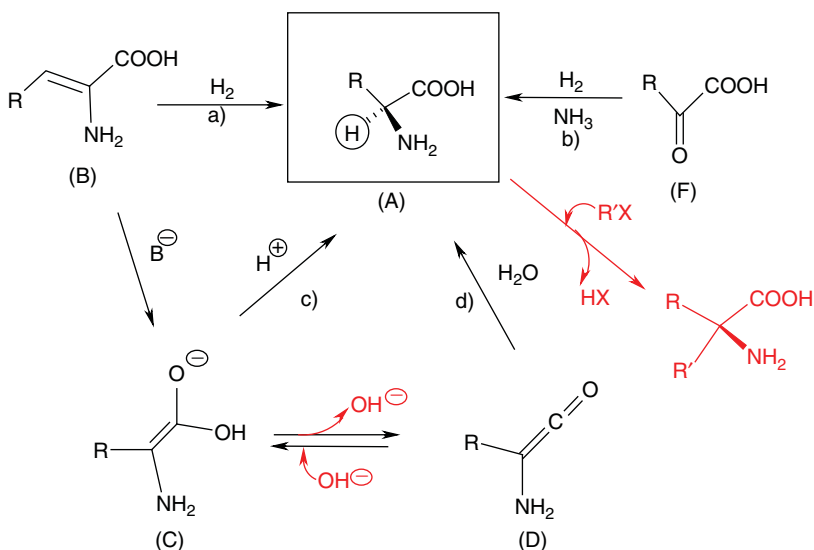
From an economic point of view, the catalytic asymmetric synthesis methods are promising [7]. Currently, considerable progress has been made in the field of asymmetric metal complex catalysis. In particular, asymmetric hydrogenation of

amino acid precursors on phosphine rhodium chiral catalysts [8] and asymmetric cyclopropanation of substituted allyl alcohols using chiral copper [9] complexes have found industrial applications. The asymmetric epoxidation of substituted allyl alcohols using chiral titanium complexes is an important synthetic method [10].

The direction of stoichiometric asymmetric synthesis based on the application of recyclable chiral inducing agents (auxiliary reagents) found a widespread use for preparative production of amino acids [11].

Interesting approaches to asymmetric synthesis of amino acids are biomimetic directions, providing establishment of simple effective systems operating by the principle of action of pyridoxal-dependent enzymes responsible for the conversion of amino acids.

General transformations leading to chiral α -amino acids (A) via conversion of sp^2 - α -carbon atom of a precursor to sp^3 - α -carbon of α -amino acid are shown in Scheme 7.1.



Scheme 7.1

These are processes of hydrogenation of derivatives of α,β -unsaturated amino acids (B) (path a), protonation of adduct of 1,4-addition of nucleophiles (C) (path c), or hydration of α -aminoketenes (D) (path d) and reductive amination of α -keto acids (F) (path b).

Depending on the nature of the chiral inductor providing stereoselective flow of the aforementioned reactions, asymmetric syntheses of amino acids are divided into catalytic and stoichiometric.

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8

Catalytic Asymmetric Synthesis

Asymmetric synthesis is considered catalytic when in the role of the chiral inducer appears a chiral catalyst, which is involved in the process in catalytic amounts (molar ratio of catalyst to substrate is 1/100–1000). To date, from a practical point of view, catalytic asymmetric synthesis methods in conditions of phase transfer are the most promising.

Phase-transfer catalysis (PTC) was launched by Makoza and Serafimowa [1], Starks and Napier [2], and Brandstrom and Gustavii [3] independently of each other in the mid- and late 1960s of the twentieth century. The formal definition of PTC is the acceleration of reactions between chemical compounds that are in different phases. Typically, they are the reactions between salts dissolved in water or available in solid state on the one hand, and the substances dissolved in organic phase, on the other hand. Such reactions in the absence of a catalyst proceed either slowly and inefficiently or do not occur at all. The primary function of the catalyst is to transfer ions of the reacting salt to the organic phase in a form of ion pairs. Most frequently onium salts or complex-forming compounds (crown ethers, cryptands) are used as catalysts in these reactions. They bind anions and alkali metal ions, respectively, thus converting them to solution.

In those cases, when anion and cation form a tight ion pair, a chiral cation of the catalyst can stimulate asymmetric induction in reactions of prochiral anions being in its environment. A necessary condition for such an effect is fairly close interaction of the anion and cation, preferably in one of several possible conformations. The high mobility of the anion relative to the cation in forming separate ion pair prevents this effect. That is why the use of quaternary ammonium salts with a chiral center in the carbon skeleton is unpromising, unless anion–cation interaction is further enhanced by an additional polar group capable of forming a hydrogen bond.

PTC has several advantages compared with conventional methods, which are as follows:

- It eliminates costly anhydrous solvents.
- It carried out reactions at temperatures close to room temperatures.
- It provides higher reaction rates and higher yields due to suppression of side reactions.

- It uses cheap alkali aqueous solutions instead of alcoholates, amides, alkali metal hydrides used for carrying out reactions in homogeneous conditions.
- It implements reactions not proceeding in other conditions.

The first works in the field of asymmetric PTC alkylation were unsuccessful, the optical purity of the obtained products was low (6–19%) [4, 5].

The breakthrough in asymmetric PTC alkylation came in 1984 with an advent of Dolling's [6] work, which revealed high efficiency of chiral quaternary ammonium salts prepared by modifying natural alkaloids of *Cinchona* family.

The most commonly used quaternary ammonium salts based on cinchonine, cinchonidine, quinine, and quinidine are shown in Figure 8.1.

The above-mentioned catalysts were prepared by alkylation of the tertiary amino group of natural alkaloids and have been widely used because of their availability and cyclic (rigidly fixed) spatial structure. Their high stereoselectivity in PTC alkylation reactions of indanone derivatives (**5**) has been revealed (see Scheme 8.1). In the presence of catalyst **1** alkylation products of **6** were prepared with 92–94% ee.

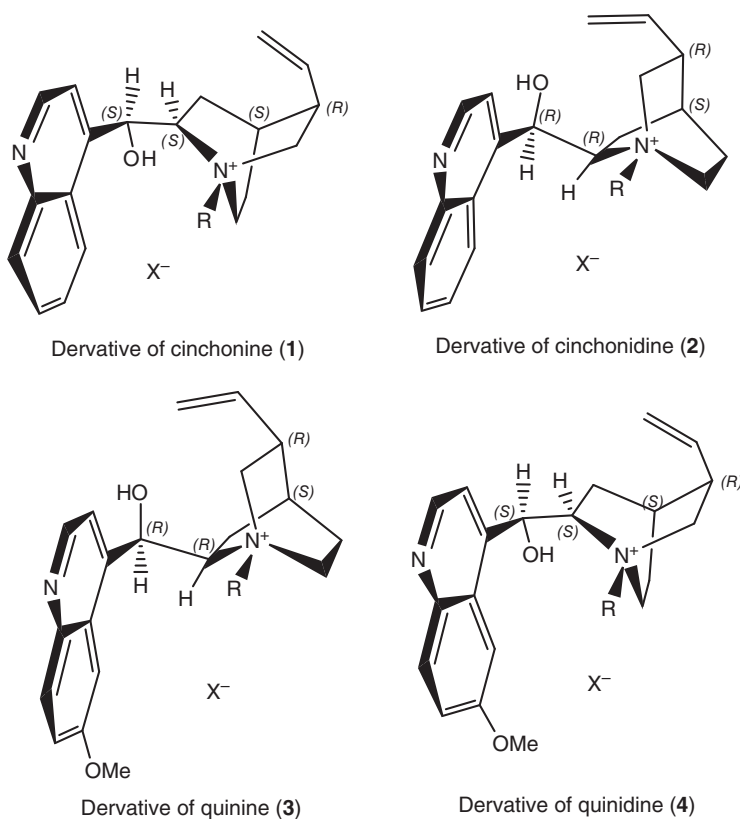
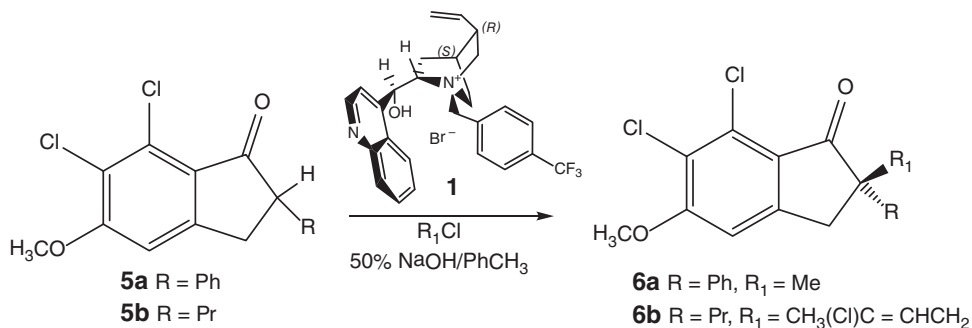
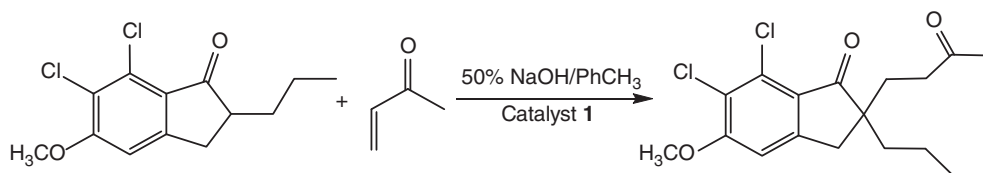


Figure 8.1 Chiral quaternary ammonium salts based on *Cinchona* alkaloid family.



Scheme 8.1

This catalyst of cinchonine type was also successfully applied in the addition reaction of 2-propylindanone with methyl vinyl ketone, which resulted in an adduct with 80% ee and 95% yield [7] (see Scheme 8.2).



Scheme 8.2

The kinetics and mechanism of the alkylation reaction of **5a** substrate with methyl chloride [8] were studied in detail. It has been found that this reaction proceeds through sequential steps of deprotonation of the substrate, extraction of the enolate into organic phase and its methylation (Scheme 8.1).

When using 50% NaOH/toluene, the deprotonation of substrate occurs at the interface of two phases, and the resulting sodium enolate precipitates as a solid salt.¹⁾ Then, Na counter ion is exchanged for the quaternary ammonium ion of the catalyst that facilitates the transfer of enolate to an organic phase. It was shown that the catalyst itself exists as dimer **7** in the organic phase (see Figure 8.2).

The final stage of alkylation already proceeds in organic phase and because of the chirality in the resulting tight ion pair asymmetric methylation is ensured. The stereochemical model that authors proposed to explain the observed stereoselectivity (ee >90%) assumes the formation of a tight ion pair between the cation of the chiral catalyst and substrate's anion generated during the reaction. Enolate is preferably alkylated from one side of the carbanion plane because of steric control of the catalyst's chiral cation and through effective shielding of one side of the carbanion plane. Along with this, additional interaction through the formation of intermolecular hydrogen bonding in the resulting tight ion pair is postulated.

1) When using a 30% aqueous NaOH solution, a precipitate as enolate salt is not formed.

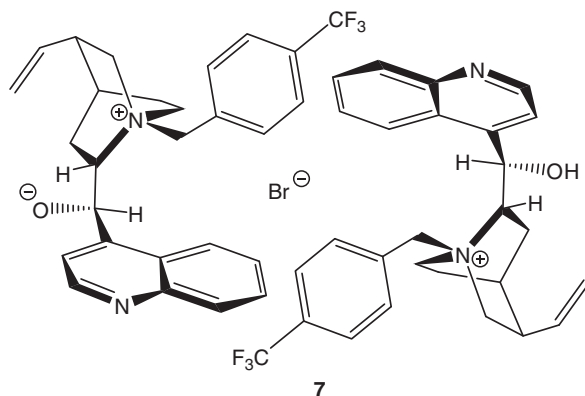


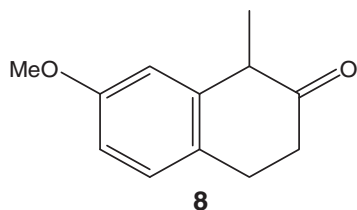
Figure 8.2 Dimeric structure of catalyst **1**.

Interestingly, the use of another diastereomer of cinchonidine-based catalyst (**2**) affords the product of alkylation with only 76% ee. Considering the spatial patterns of catalysts used, it becomes clear that cinchonine conformation is preferred, wherein the vinyl group shields the hydroxyl group of the catalyst leaving it available to form hydrogen bonds from only one side.

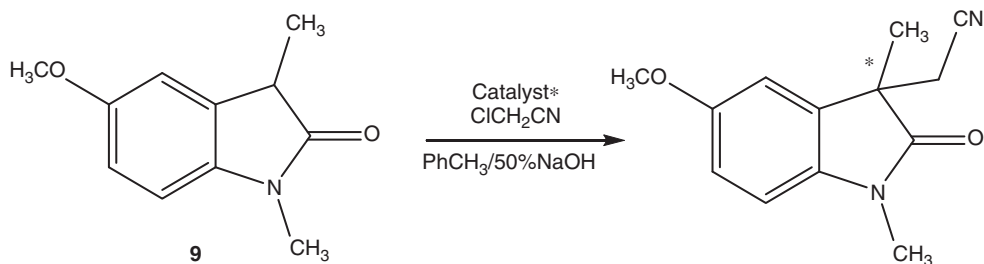
The study of changes in enantioselectivity in reactions catalyzed by various benzyl-cinchonines differing only by substituents in the benzyl moiety showed that the catalysts with electron-withdrawing substituents increased the enantioselectivity of the alkylation.

Thus, a detailed study of the mechanism of asymmetric PTC alkylation of different substrates in the presence of various cinchonine series catalysts revealed some very important features of the mechanism of alkylation. Manifestation of high stereo differentiating ability by catalysts of a cinchonine type in alkylation reactions stimulated further development in the field of asymmetric PTC.

Asymmetric alkylation of other cyclic substrates was carried out in the presence of a phase-transfer catalyst **1**. Thus, Nerincks and Vandewale alkylated 7-methoxy-1-methyl-3,4-dihydro-1*H*-naphthalen-2-one (**8**) by 1,5-dibromopentane in two-phase system (benzol/50% NaOH) [9]. The yield of the target product was 74% and ee >70%.



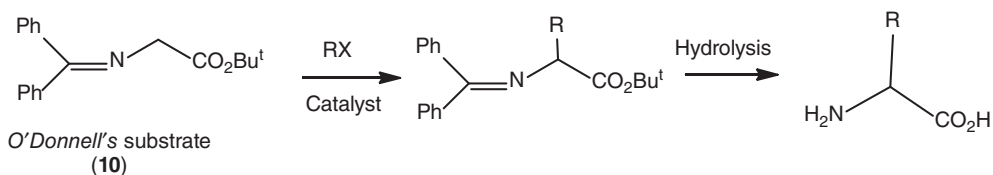
Catalyst **1** was also used in the cyanomethylation reaction of 5-methoxy-1,3-dimethyl-1,3-dihydroindol-2-one **9** (see Scheme 8.3) [10]. High stereoselectivity



Scheme 8.3

of the reaction (ee 72–77%) was observed only when cinchonine type catalysts with electron-withdrawing substituents in the aromatic ring of the benzyl moiety were used. Benzylcinchonidine under these conditions provides a product with 10% ee.

The turning point in the field of PTC asymmetric alkylation came in 1989, when *O'Donnell* and coworkers proposed the use of acyclic Schiff base of *tert*-butyl ester of 2,2-diphenylethyl-idenaminoacetic acid (*O'Donnell's* substrate) as a substrate [11] (see Scheme 8.4).



Scheme 8.4

Currently *O'Donnell's* substrate is a “reference” compound and has been successfully used worldwide as a starting synthon in many research groups to evaluate the effectiveness of the catalysts in phase-transfer asymmetric alkylation.

Initially, asymmetric induction in alkylation reactions of substrate **10** catalyzed by cinchonine derivatives (**1**) did not exceed 66%. However, thereafter, optimization of the reaction conditions using $\text{PhCH}_3/\text{CH}_2\text{Cl}_2/50\% \text{ NaOH}$ system at a ratio of 18/12/10 allowed to increase the enantioselectivity to 81% [12].

The two special features in this work are as follows:

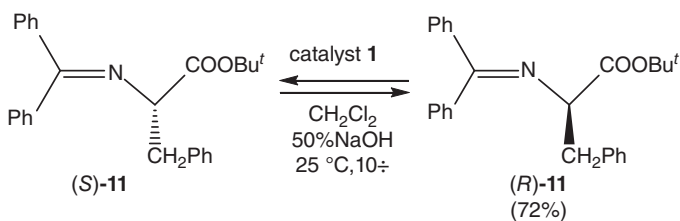
- 1) The use of cinchonine and cinchonidine derivatives leads to amino acids with close ee values but with different absolute configurations.
- 2) As opposed to the Dolling's work, introduction of acceptor substituents in the benzyl group of the catalyst did not cause any change in stereoselectivity of the catalysis.

The general scheme of the mechanism proposed by *O'Donnell* and coworkers includes the same three basic steps: deprotonation of the substrate, transfer of

carbanion into the organic phase in the form of an ion pair with a catalyst's chiral quaternary ammonium cation and direct alkylation [13].

Theoretically undesirable side processes associated with repeated alkylation of monoalkylated product and racemization of the *O'Donnell's* substrate as CH-acid were possible. However, due to the lower acidity of the monoalkylated product ($pK_{\text{substrate}} = 18.7$, $pK_{\text{product}} = 22.8$ for $R = \text{Me}$ and 23.2 for $R = \text{Bn}$ in dimethyl sulfoxide (DMSO)) [14], none of these processes occurred.

For detailed examination of the racemization process, enantiomerically pure Schiff base of *tert*-butyl ether of (*S*)-phenylalanine [(*S*)-**11**] was synthesized and its racemization investigated under the reaction conditions. It was found that in CH_2Cl_2 /50% NaOH in the presence of a catalyst and an alkylating agent racemization of substrate (*S*)-**11** did not occur; however, up to 72% racemization was observed in the absence of alkyl halide. Racemization was complete after about 2 h, and no further loss of optical activity was detected (see Scheme 8.5).



Scheme 8.5

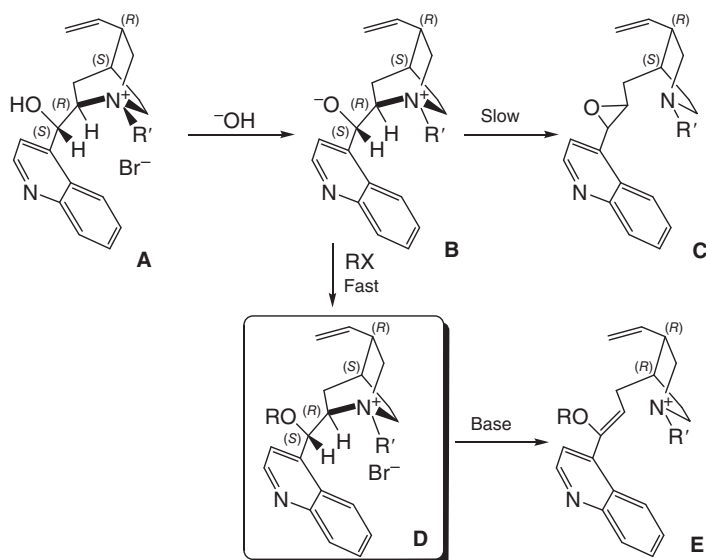
These results indicate that the catalyst in the reaction does not remain unchanged. Starting catalyst (**A**) under the action of hydroxyl ions is deprotonated to zwitterionic alcoholate (**B**), which can serve as a lipophilic base capable of deprotonating (*S*)-**11** and cause racemization (Scheme 8.6).

At the same time, the formation of a zwitterion **B** is exactly responsible for the process of “poisoning” of the catalyst, which is possible in two ways:

- 1) the slow formation of the epoxide **C**;
- 2) prompt O-alkylation in **D** followed by Hofmann elimination.

O-alkylation does not take place in the absence of alkyl halide, but slow formation of the epoxide occurs, which explains stopping of racemization process after 2 h when all of the catalyst is converted to epoxide **C**. In the presence of alkyl halide, prompt O-alkylation of the zwitterionic catalyst occurs resulting in product **D**. Since alkylating agent is always present in excess in this reaction condition, this step proceeds rapidly and the amount of the zwitterionic form of the catalyst **B** in the reaction mixture is maintained at the possibly minimum level, so no racemization of the alkylation product occurs.

By these studies, it was shown that the active catalyst in PTC alkylation is the salt of *N*-alkyl-*O*-alkylcinchonine **D**, which is generated during the reaction. The identical results obtained by the authors during alkylation with *N,O*-dibenzylcinchonine and *N*-benzyl-cinchonidine as catalysts were a further



Scheme 8.6

confirmation of the reaction progress. Only 7 years after O'Donnell's publication, there appeared other publications, in which the authors suggested the use of modified alkaloids of *Cinchona* family as catalysts.

Corey and coworkers performed a model alkylation reaction of O'Donnell's substrate, catalyzed by bromide of O(9)-allyl-N-(9-anthracenylmethyl)cinchonidine **12** and the crystal structure of the catalyst was studied (see Figure 8.3) [15].

According to X-ray data of the catalyst **12**, C(21) atom and, accordingly, the whole anthracenylmethyl group are located antiperiplanar toward C(11) atom and

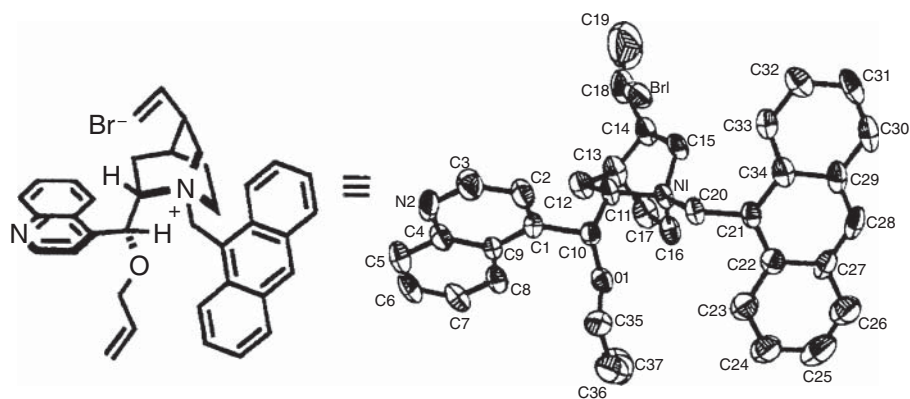


Figure 8.3 Structure of bromide of O(9)-allyl-N-(9-anthracenylmethyl)cinchonidine (catalyst **12**).

Br^- counter ion is fairly close to a charged nitrogen atom from the uncovered side of tetrahedron (opposite to C(16), distance of Br^- to N(1) is 4.06 Å). The expected structure of this ion pair is shown in Figure 8.4.

As a base in alkylation reaction of the *O'Donnell's* substrate a solid cesium hydroxide was used, thus minimizing the probability of transition of water into organic phase, which allowed lowering the reaction temperature to -78°C . A number of alkylating agents was used, and the results of these experiments are presented in Table 8.1.

Lygo almost simultaneously and independently of Corey's work performed the reaction of phase-transfer alkylation of *O'Donnell's* substrate catalyzed by salts of *N*-(9-anthracenylmethyl) substituted cinchonidine and cinchonine. The main difference in the work of these authors was that Corey used O,N-bisalkylated catalyst and Lygo only N-alkylated. Asymmetric benzylation of *O'Donnell's* substrate catalyzed by *N*-(9-anthracenylmethyl) dihydrocinchonidine in a biphasic system (50% aqueous KOH/toluene) at room temperature provides 85% chemical yield and 94% enantioselectivity [16].

In Lygo's subsequent studies different analogs of *O'Donnell's* substrate [17] and various alkylating agents [18] were used, thereby expanding the number of synthesized amino acids. Thus α,α -disubstituted optically active amino acids with ee

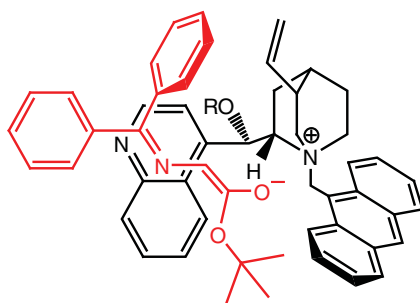
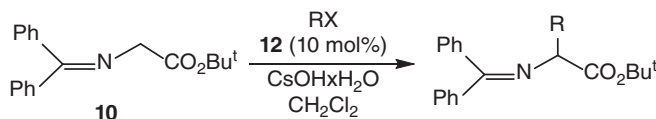


Figure 8.4 The tentative structure of the carbanion-catalyst ion pair.

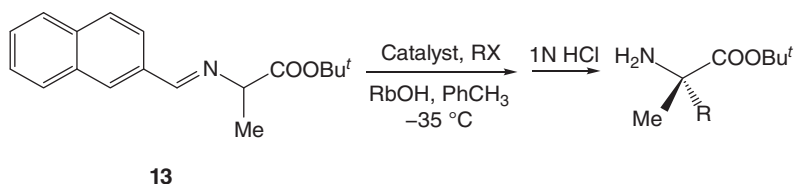
Table 8.1 The enantioselectivity in the alkylation reactions of substrate **10** catalyzed by **12**.



No.	RX	Temperature ($^\circ\text{C}$)	Time (h)	Yield (%)	ee (%)
1	CH_3I	-60	28	71	97
2	EtI	-60	30	82	98
3	AlI_3	-78	22	89	97
4	BnBr	-78	23	87	94
5	Ph_2CHBr	-78	22	73	99.5

80–95% [19] were synthesized when substrates with Schiff bases derived from alanine esters and substituted benzaldehydes were used. At the same time, bis-amino acids with diastereoselectivity of $de > 70\%$ ($ee \geq 95\%$) [18] were synthesized using different alkyl dihalides in the alkylation reaction of *O'Donnell's* substrate. A number of cinchonine-like catalysts have been studied by authors and the effect of introduction of various substituents into cinchonine molecule on the stereoselectivity of the reaction of phase-transfer alkylation was investigated.

Jew and Park performed systematic studies on the choice of substrate for an effective method for the synthesis of α -alkylalanines by PTC alkylation [20]. A number of different aldimines of alanine ester in a reaction catalyzed by bromide of *O*(9)-allyl-*N*-2',3',4'-trifluorobenzylhydro-cinchonidine were used from which *tert*-butyl ester of [2-(naphthalen-2-yl-methylene)amino]-propionic acid **13** was chosen (see Scheme 8.7).



Scheme 8.7

Optimization of the reaction conditions revealed that the best results were obtained when solid RbOH was used as a base and the reaction was performed in toluene at $-35\text{ }^{\circ}\text{C}$. Alkylation with benzyl bromide in the chosen conditions proceeds for 10 h with high enantioselectivity ($ee\ 95\%$) in 95% yield.

Jew and Park [21] and later Najera [22] expanded the number of *Cinchona* alkaloid-based catalysts used (see Figure 8.5). Authors synthesized catalysts with dimeric (**14**, **15**, **17**) and trimeric (**16**) structures that exhibited high stereoselectivity in the reaction of phase-transfer alkylation of *O'Donnell's* substrate even with substrate to catalyst ratio of 100/1.

Nájera and van Koten [23] proposed cinchonidine catalysts of original structure containing 3,5-dialkoxybenzyl group. When reaction catalysis is performed with 3,5-dihydroxy-benzyl- and 3,5-dimethoxybenzyl substituted cinchonidine salts (see Figure 8.5, **18** and **19**, respectively) and KOH is used as a base, the (*S*)-configuration product with $ee > 70\%$ is formed, and in case of NaOH – the (*R*)-configuration product is obtained with low ee .

Among catalysts synthesized by authors, 3,5-dibenzyloxybenzyl derivative of cinchonidine **20** exhibits different selectivity in the reaction conducted in $\text{PhCH}_3/\text{CHCl}_3/50\%$ aqueous KOH and NaOH system, but in both cases the isolated product has (*S*)-configuration.

A new approach to asymmetric PTC alkylation was proposed by Maruoka who used purely synthetic C_2 -symmetric binaphthyl spirobicyclic ammonium salts **22a**, **23b**, and **24c** [24] as chiral phase-transfer catalysts (see Scheme 8.8). Catalysts **22a** and **22b** were used in monoalkylation reaction of *O'Donnell's*

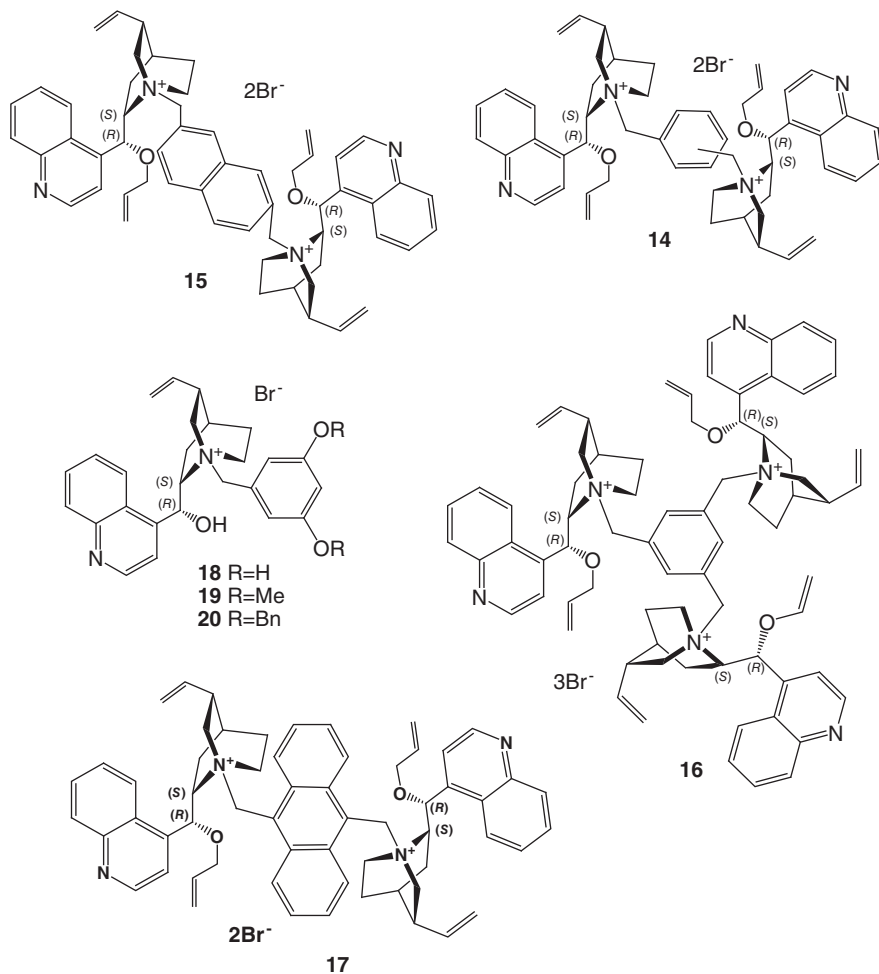
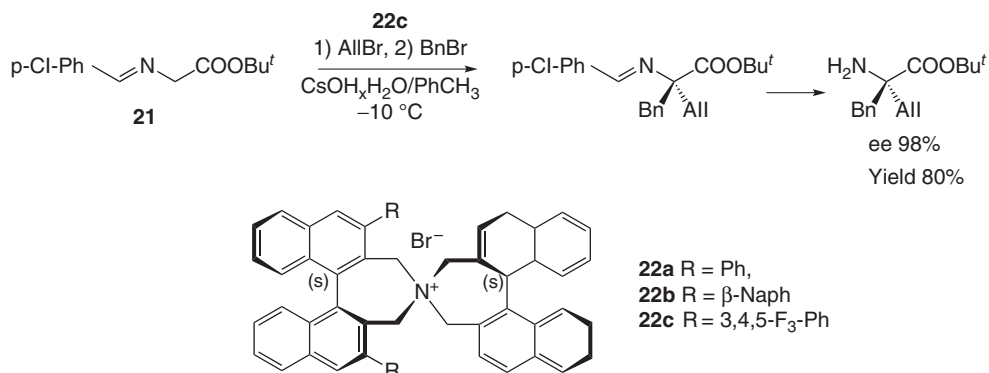


Figure 8.5 Cinchonidine-based phase-transfer catalysts.



Scheme 8.8

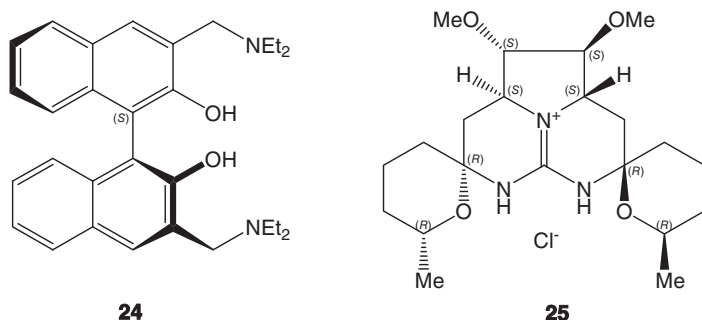


Figure 8.6 The structures of (S)-BINOLAM (**24**) and the guanidine (**25**) derivative catalysts.

substrate by benzylbromide and allylbromide. With 1 mol% the catalyst, the enantioselectivity in the system toluol/50% aqueous KOH at 0 °C was 90–96% and the chemical yields were 60 and 95%, respectively.

For the synthesis of α,α -disubstituted amino acids, double sequential alkylation using aldimine Schiff base of *tert*-butyl ether of glycine **21** as a substrate and **22c** as a catalyst was performed. It was shown that the chemo- and stereoselectivity of the reaction were quite high [25].

As catalysts in alkylation reaction of substrates **21** (see Scheme 8.8) and **23** (see Figure 8.10), specially synthesized (S)-bisaminomethyl binaphthols were used [26] (see Figure 8.6).

The alkylation product (S)- α -methylphenylalanine was isolated in 85% chemical yield and 68% ee catalyzed by (S)-3,3'-bis[(dimethylamino)methyl]-2,2'-dihydroxy-1,1'-binaphthalene (BINOLAM, **24**) in toluene/solid NaOH system at room temperature. In the case of catalyst **25**, ee did not exceed 45% (see Figure 8.6).

Nagasawa used C₂-asymmetric chiral guanidine derivative (**25**) as a phase-transfer catalyst for alkylation of O'Donnell's substrate [27].

Initially, alkylation was conducted in a biphasic system of CH₂Cl₂/1 M aq. KOH at room temperature in the presence of 10 mol% of **25**, which led to the product of (R)-configuration with 70% yield and 75% ee. The use of 30 mol% of **25** at 0 °C increased the ee of the product to 90%.

Following O'Donnell's work, several other authors proposed the use of modified alkaloids of *Cinchona* family as catalysts.

A number of synthetic catalysts for the asymmetric PTC reactions were synthesized by Dehmlow's group by quaternization of analogs of *Cinchona* family alkaloids with naphthyl radical instead of quinoline substituent [28]. As a model reaction, the authors chose the alkylation of *tert*-butyl ester of 2-oxocyclopentanecarboxylic acid of BnBr (see Scheme 8.10).

Deaza-analog of benzylcinchonine **26** (ee 52%) proved to be the best catalyst among those proposed in this work. It should be noted that the catalysts based on the corresponding natural alkaloids of *Cinchona* family in the same reaction proved to be less effective (ee up to 39%).

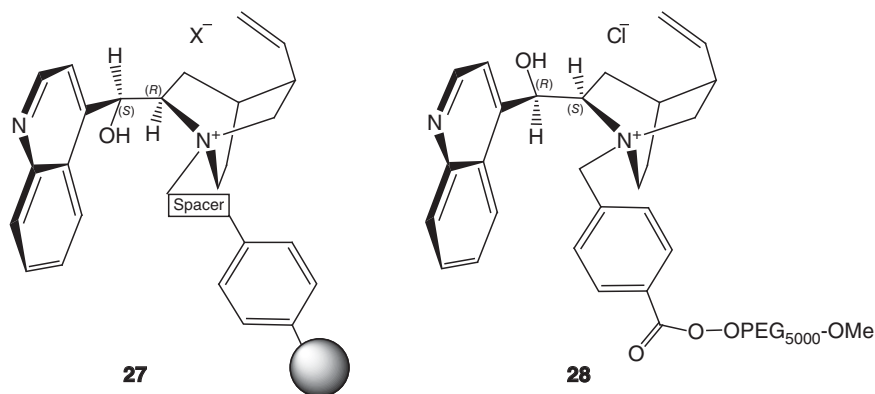


Figure 8.7 Polymer grafted alkaloids of a *Cinchona* family.

The *Cinchona* alkaloids embedded in Merrifield's resin [29] could be added to the family of semi-synthetic catalysts. Enantioselective alkylation of *O'Donnell's* substrate catalyzed by polymer grafted onium salts proceeds with 58% enantioselectivity. When using isopropyl ether of benzylidene glycine the observed asymmetric induction increases to 90%.

Continuing research in this area, Cahard synthesized alkaloids of *Cinchona* series grafted on to polystyrene through the hydrocarbon chains (spacers) of different lengths (**27**; see Figure 8.7) [30]. The optimum catalyst in this series was cinchonine-based catalyst containing a chain with four carbon atoms linking it to polymer matrix. In the reaction of *O'Donnell's* substrate alkylation, catalyzed by it, the asymmetric induction was 81%. Alkaloids of *Cinchona* family grafted onto a polyethylene glycol matrix [31] is another modification of polymeric catalysts. Maximum asymmetric induction (ee 81%) and yield (84%) of a product in a model alkylation reaction of *O'Donnell's* substrate by benzyl bromide is observed using a homogeneous cinchonidine-based catalyst **28**.

Maruoka in his subsequent work reported the use of modified spirobicyclic symmetric 4,4',6,6'-tetraaryl substituted binaphthyl ammonium salts **29** as phase-transfer alkylation catalysts. Benzylation reaction of *O'Donnell's* substrate catalyzed by **29** (see Figure 8.8) proceeds with 97% ee and 87% yield [32].

The other catalyst containing a quaternary nitrogen atom (**30**) (see Figure 8.9) was used by Lygo in a model alkylation reaction of *O'Donnell's* substrate by BnBr in toluene/KOH system, which resulted in the formation of alkylation product with 97% ee and 89% yield [33].

The chiral phosphonium salts containing hydroxyl and amide groups (**31**, **32**) were specifically synthesized for use as phase-transfer alkylation catalysts [34].

The effectiveness of this type of catalysts was tested in alkylation reaction of β -ketoesters, particularly on *tert*-butyl esters of 2-oxocyclopentanecarboxylic acid by benzyl bromide (see Scheme 8.10) in toluene/sat. aq. K_2CO_3 system. Stereoselectivity at 0 °C with 1 mol% of **31** (see Figure 8.10) was 50%.

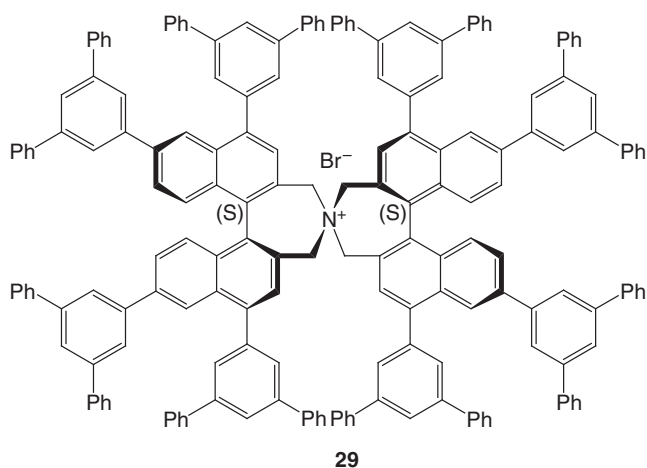


Figure 8.8 Maruoka's catalyst for asymmetric phase-transfer alkylation.

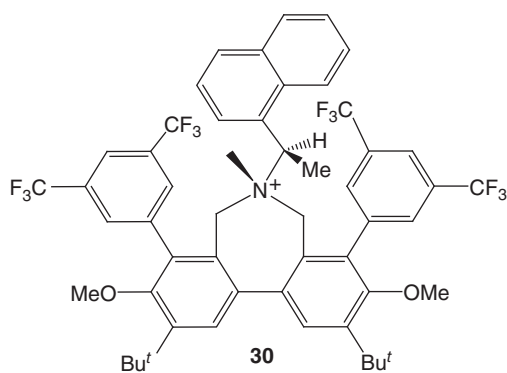


Figure 8.9 Lygo's catalyst for asymmetric phase-transfer alkylation.

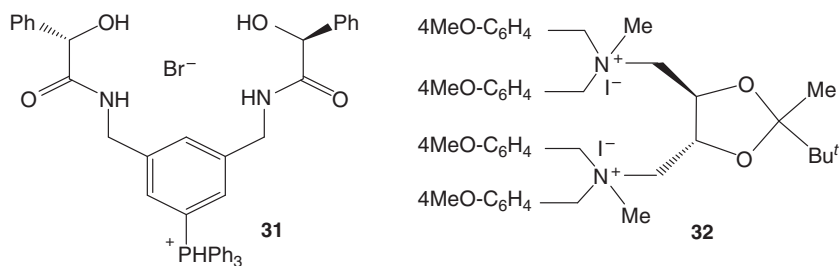
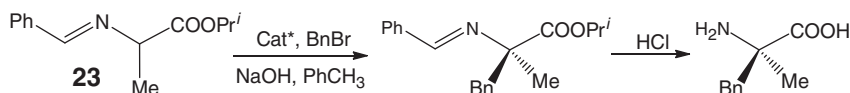


Figure 8.10 Phase-transfer catalysts 31 and 32.

New diammonium catalysts **32** (Figure 8.10) with two cationic centers, able to fix and activate the substrate, were synthesized and used by Shibasaki in asymmetric phase-transfer alkylation and Michael addition reactions [35]. The enantioselectivity in alkylation of *O'Donnell's* substrate by BnBr catalyzed by 10 mol% of **32** in the $\text{PhCH}_3\text{--CH}_2\text{Cl}_2$ (7/3)/ $\text{CsOH} \times \text{H}_2\text{O}$ system was 93% at -70°C .

Belokon' and coworkers as a catalyst for the asymmetric phase-transfer alkylation of substrate **23** (the imine prepared from isopropyl ether of (*R,S*)-Ala and benzaldehyde) used the (*R,R*)-2,2-dimethyl-1,3-dioxolane-4,5-bis(diphenylmethanol) (**TADDOL**) (**33**) [36] (see Scheme 8.9, Figure 8.11). Conducting the reaction at room temperature with catalysis by 10 mol% **TADDOL** leads to (*R*)-amino acid with 82% ee and 81% yield.



Scheme 8.9

In the same reaction, (*S*)-2-hydroxy-2'-amino-1,1'-binaphthyl (**NOBIN**) (**34**) and its derivatives [37] were also used as catalysts. However, the latter showed lower selectivity (maximum ee did not exceed 68%) than (*R,R*)-**TADDOL** (Scheme 8.10).

We should also mention the methods for the asymmetric synthesis of α -amino acids, based on the stereoselective hydrogenation of dehydroamino acid derivatives (**35**) in the presence of complexes of transition metal ions with different chiral phosphine ligands as chiral catalysts described in detail in a review article of Najera and Sansano (Scheme 8.11).

Monodentate ligands containing P–C bonds (**37** [38], **38** [39], etc.), monodentate phosphoramidites (**39** [40], **40** [41], etc.), monodentate phosphites (**41** [42], **42** [43], etc.), 1,1-, 1,2-, 1,3-, 1,4-diphosphinoalkanes (**43** [44], **44** [45], **45** [46], **46** [47], etc.), aromatic 1,2-diphosphines (**47** [48], **48** [49], etc.), metal connected diphosphines with planar chirality (**49** [50], **50** [51], etc.), homobidentate (**51** [52], **52** [53], etc.), and heterobidentate (**53** [54], **54** [55], etc.) ligands and others were used as chiral ligands (see Figure 8.12).

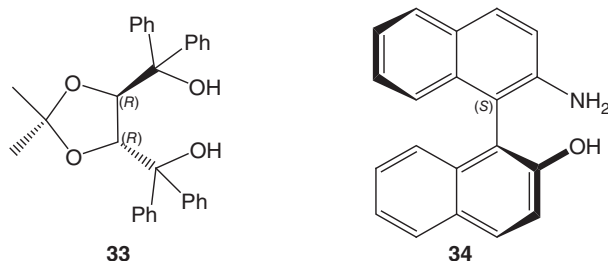
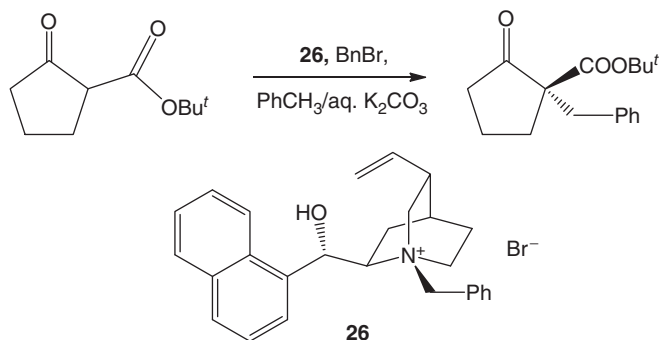
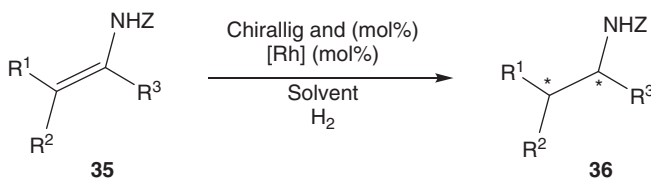


Figure 8.11 Structures of catalysts (*R,R*)-**TADDOL** (**33**) and (*S*)-**NOBIN** (**34**).



Scheme 8.10



Scheme 8.11

As a result of hydrogenation, the optical purity of the obtained chiral amino acids (valine, leucine, phenylalanine, phenylglycine, homophenylalanine, β,β -difluoroglutaminic acid, etc.) is in the range of 63–99%.

As can be seen from the reviewed material, the area of asymmetric phase-transfer alkylation is a relatively new trend in modern organic synthesis, which interests many research groups. Practically, all of the proposed phase-transfer catalysts comprise onium groups. The mechanism of their action is based on the formation of ionic pairs and the preferential formation of one of the diastereomeric forms of the ionic pair is controlled by occurring hydrophobic interactions.

The synthesis and biological properties of α -amino acids containing a cyclopropyl group were reported in Brackman's and de Meijere's review article [56]. The authors describe in detail the methods for the synthesis of 1-aminocyclopropanecarboxylic acid (ACC) and its optically active deuterated analogs, and the ways of their use in the synthesis of biologically active compounds. Particularly, synthesis of pure enantiomers of 1-amino-2,2-dideuterocyclopropanecarboxylic acid ($[2,2\text{-}^2\text{H}_2]$ -**57**) by gradual cyclodialkylation of enantiomerically pure chiral ether of bislactim (*R*)-**55** by 2-bromoethyltosylate and subsequent hydrolysis of compound **56–57** with 44% ee [57] is given (see Scheme 8.12).

Asymmetric synthesis of stereospecifically monodeuterated methyl-1-aminocyclopropane carboxylate (1*S*,2*S*)- $[2\text{-}^2\text{H}]$ -**62** was performed by adding deuterium to the $\text{C}=\text{C}$ bond of compound **58** in the presence of $\text{Rh}(\text{R,R})$ -*dipamp* complex as hydrogenation chiral catalyst [58]. Further hydrolysis gives

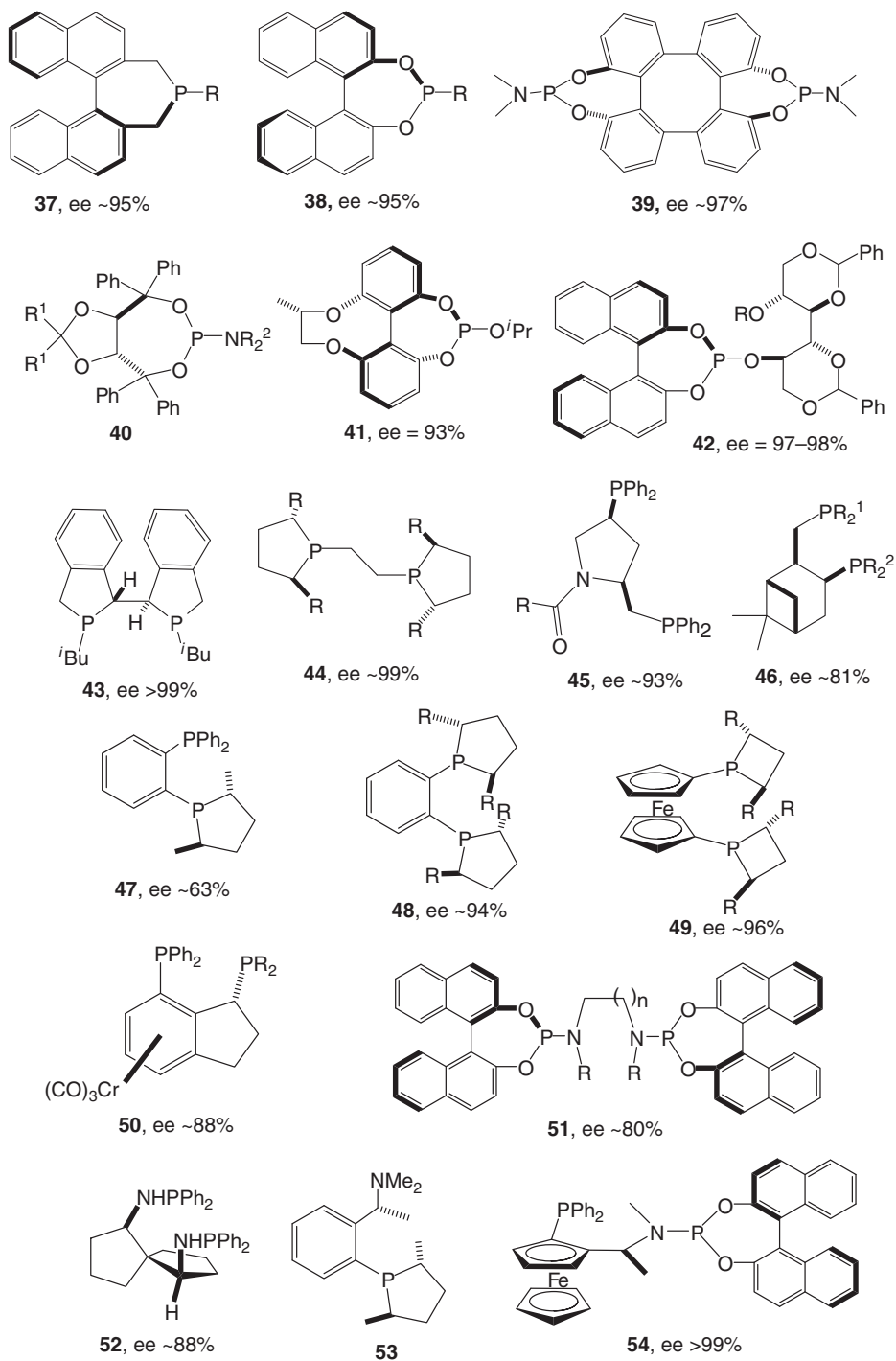
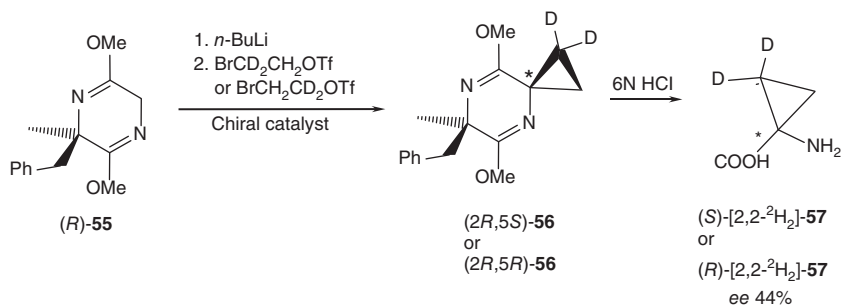
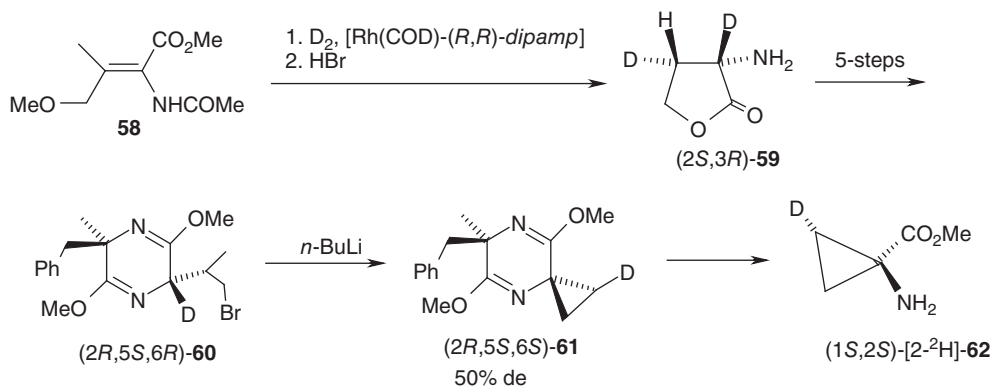


Figure 8.12 Structures of chiral phosphine ligands (37–54).



Scheme 8.12

the corresponding homoserine lactone, which binds to a chiral auxiliary reagent and is subjected to four-step transformation to bislactim ether $(2S,5S,6R)$ -**60**. The cyclization of **60** by intramolecular nucleophilic substitution gives bislactim ether **61** with 50% de. The final hydrolysis leads to the formation of monodeuterated ACC $(1S,2S)$ -[2- ^2H]-**62** (see Scheme 8.13). When (S,S) -*chiraphos* was used as chiral ligand in asymmetric deuteration of compound **58**, the $(1R,3S)$ -enantiomer of compound **59** was obtained, which can be similarly converted to $(1R,2R)$ -[2- ^2H]-**62**.



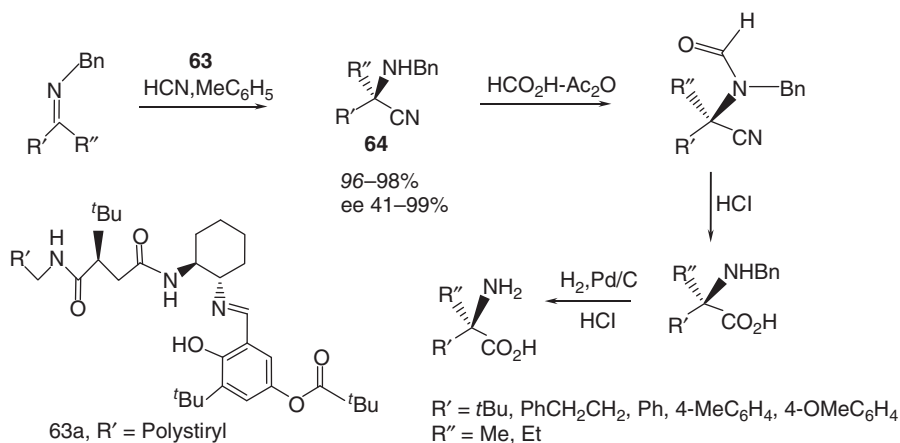
Scheme 8.13

The Strecker reaction is one of the most attractive methods for the synthesis of α -amino acids and other bioactive compounds including natural products. The asymmetric Strecker reaction represents a simple and efficient method for the synthesis of optically pure α -amino acid derivatives, nucleic acids, various nitrogen and sulfur containing heterocycles and pharmaceuticals. In general, two approaches have been used to achieve successful asymmetric Strecker reactions and obtain optically active α -amino nitriles. The first is the addition of cyanide to chiral non-racemic imines, and the second is the enantioselective catalytic cyanation of achiral imines. The catalytic asymmetric Strecker reaction has proved

to be a simple and efficient method for the synthesis of optically pure α -amino acid derivatives. Over the past several decades, great strides have been made in the asymmetric hydrocyanation of imines, in particular, in the field of catalytic asymmetric Strecker reactions. Some highly efficient asymmetric methods with excellent enantioselectivities, low catalyst loading and new cyanide sources used are also developed.

All the best-known methods for the asymmetric synthesis of α -amino acids by the Strecker reactions may be grouped into the following types: diastereoselective Strecker reactions, enantioselective Strecker reaction using metal catalysts, enantioselective Strecker reactions using organocatalysts [59].

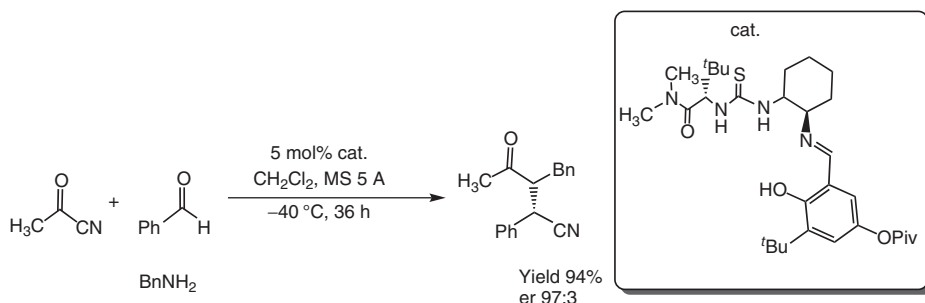
The first non-metal catalyzed asymmetric Strecker synthesis, reported by Lipton and coworkers, used a cyclic dipeptide catalyst to achieve high yields and enantiomeric excess [60]. In particular, phenylglycine and *p*-methoxyphenylglycine were synthesized in >99% and 96% ee, respectively. This work was soon followed by Jacobsen and co-workers who in 2000 reported on another chiral, non-metal catalyst for the asymmetric Strecker synthesis [61, 62]. It was the first application of chiral thiourea organocatalysts for enantioselective Strecker reaction. They demonstrated that thiourea-based derivative could stereoselectively catalyze the Strecker reaction. Various α -methyl- α -arylglycine derivatives in significantly high yields and 88–95% ee were prepared by the reaction of *N*-protected ketimines with hydrocyanic acid under the action of resin-bound or soluble catalyst of Schiff base (**63a** and **63b**, respectively) (see Scheme 8.14).



Scheme 8.14

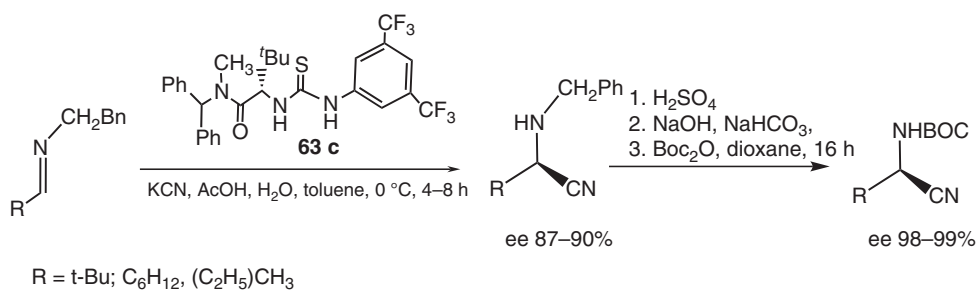
The authors observed a decrease in stereoselectivity in the case of ketimines with nonaromatic substituents. On the other hand, aryl substituents substituted in *ortho*-position destabilized the formed aminonitriles **64**. The hydrolysis of **64** was only possible after formylation of the amine as nonformylated samples were subjected to *retro*-Strecker's reaction.

In 2007, Pan and List developed the organocatalytic asymmetric three-component Strecker reaction, the urea-catalyzed acylcyanation of in situ generated imines [63]. Different α -amido nitriles were formed in excellent yields and enantioselectivities from aldehydes, amines, and acyl cyanides in the presence of Jacobsen's thiourea catalyst (Scheme 8.15).



Scheme 8.15

Then in 2009, Jacobsen *et al.* offered an improved method for the Strecker reaction using thiourea to obtain enantiomerically enriched α -amino acids. They reported a new catalytic asymmetric method for the syntheses of highly enantiomerically enriched non-natural amino acids using a simple chiral amido-thiourea catalyst to control the key hydrocyanation step. This catalyst is robust, without sensitive functional groups, so it is compatible with aqueous cyanide salts, which are safer and easier to handle than other cyanide sources; this makes the method adaptable to large-scale synthesis. They had used this new method to obtain enantiopure amino acids that are not readily prepared by enzymatic methods or by chemical hydrogenation. In this case, the efficiency of this reaction is relatively insensitive to small changes in reagent and catalyst concentration: using an optimized protocol, hydrocyanation experiments using 0.5 mol% catalyst were executed reproducibly and safely at the 25–100 mmol scale for the preparation of protected amino acid derivatives [64] (Scheme 8.16).



Scheme 8.16

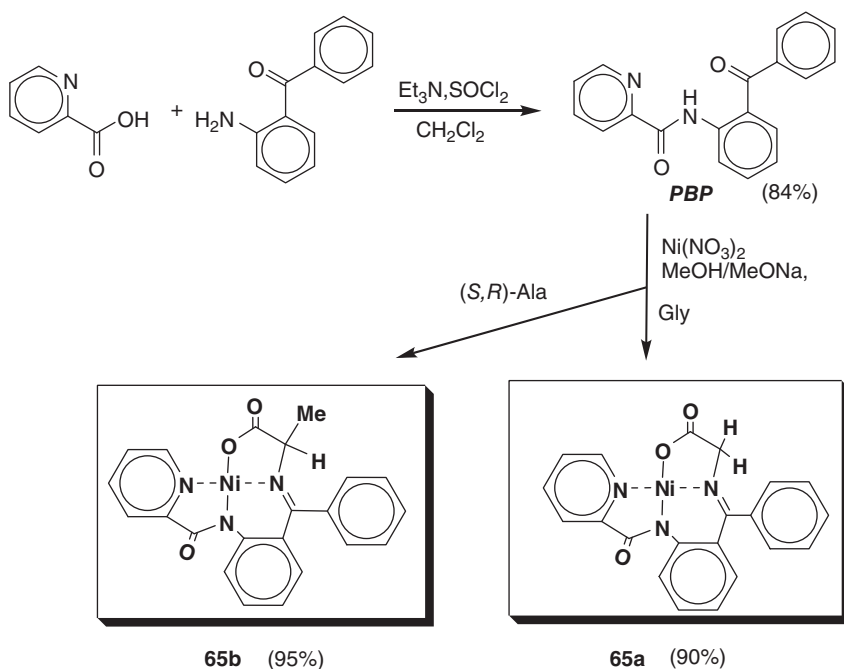
Other methods for catalytic asymmetric synthesis based on other substrates of α -amino acids are also described in the literature. The most famous of them are listed in this section.

8.1

Achiral Ni^{II} Complexes of Schiff Bases of Amino Acids

This section describes the results of studies in catalytic asymmetric synthesis of (*S*)- and (*R*)- α -amino acids and their precursors using chiral metal complexes as catalysts [65]. A number of asymmetric alkylation reactions of achiral amino acid precursors were carried out under phase-transfer catalysis.

A suitable substrate in the alkylation of amino acids in PTC conditions is a synthetic equivalent of glycine synthon **65a**, an achiral square-planar complex of Ni^{II} ion with Schiff base of (2-benzoylphenyl)amidopyridyl-2-carboxylic acid (*PBP*) and glycine, which was synthesized according to Scheme 8.17.



Scheme 8.17

The initial *PBP* ligand was obtained in one-step reaction by the condensation of 2-amino-benzophenone and 2-pyridyl-carboxylic acid in dichloromethane in 85% chemical yield. With the condensation of *PBP* with glycine and $\text{Ni}(\text{NO}_3)_2$ in MeOH in the presence of sodium methylate was prepared complex **65a** in 94% chemical yield, which was purified by crystallization from chloroform.

According to X-ray data, crystal structure of Ni^{II} complex **65a** is a centrosymmetrical dimer, wherein enantiomeric conformers are in a very short distance due to weak interactions of Ni(1)···N(1) with Ni(1A)···N(3A) and N(3) of one conformer with pyridine's π -system of another [N(3)···C(2A) 3.319] Å (see Figure 8.13). Therefore, the chiral catalyst that is able to coordinate with the complex and replace one of the conformers in such a structure can provide high stereodifferentiation at the stage of C–C bond formation and thereby provide high enantioselectivity of the reaction.

Radiographic structure of Ni^{II} complex **65b** of alanine derivative (see Figure 8.13) synthesized in a similar way (see Scheme 8.17) also has a centrosymmetric dimeric structure, but differs from the structure of **65a**.

These changes are associated with the steric repulsion between phenyl and alkyl groups, whereby the intradimeric interaction of complex **65b** is

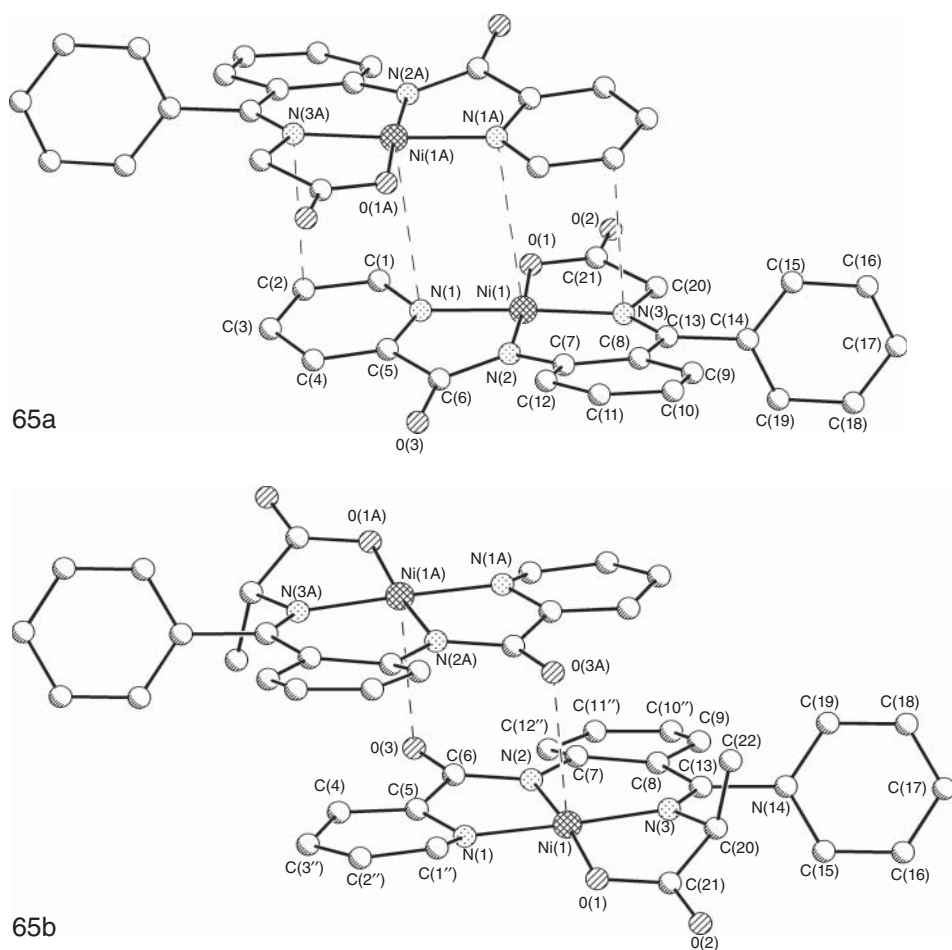
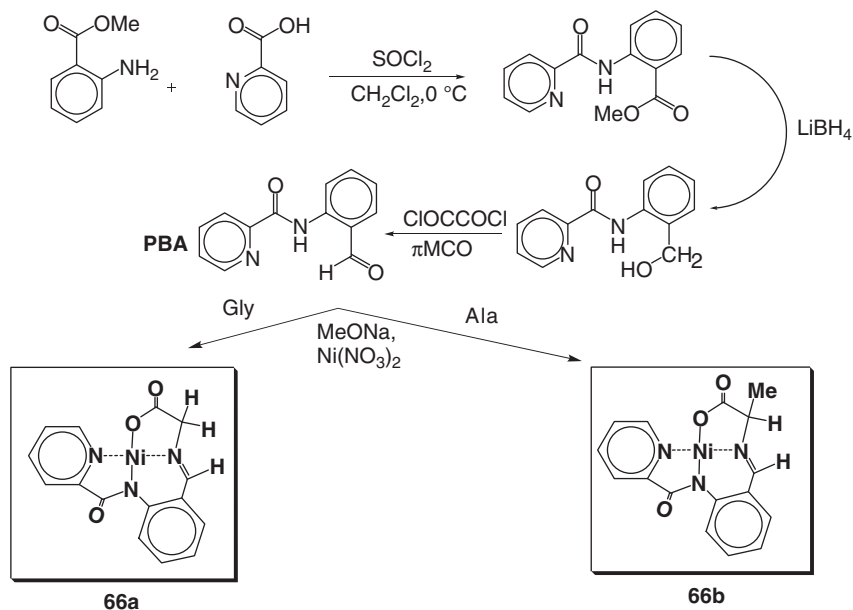


Figure 8.13 Crystallographic structures of complexes **65a** and **65b**.

only due to weak interaction between the nickel atom and the carbonyl group ($\text{Ni}(1) \cdots \text{O}(3\text{A}) = 3.287 \text{ \AA}$). The dihedral angle between the plane $\text{Ni}(1)\text{O}(1)\text{N}(1)\text{N}(2)\text{N}(3)$ and benzene ring in structures **65a** and **65b** differs and is 90.8° and 108.8° , respectively. This difference is also due to steric repulsion between the alkyl and phenyl groups in the structure of **65b**.

Spatially less hindered complexes **66a** and **66b** were synthesized from (2-formylphenyl) amidopyridyl-2-carboxylic acid (PBA), $\text{Ni}(\text{NO}_3)_2$, and corresponding amino acids in MeOH/MeONa medium in similar manner described for **65a,b** substrates (Scheme 8.18).



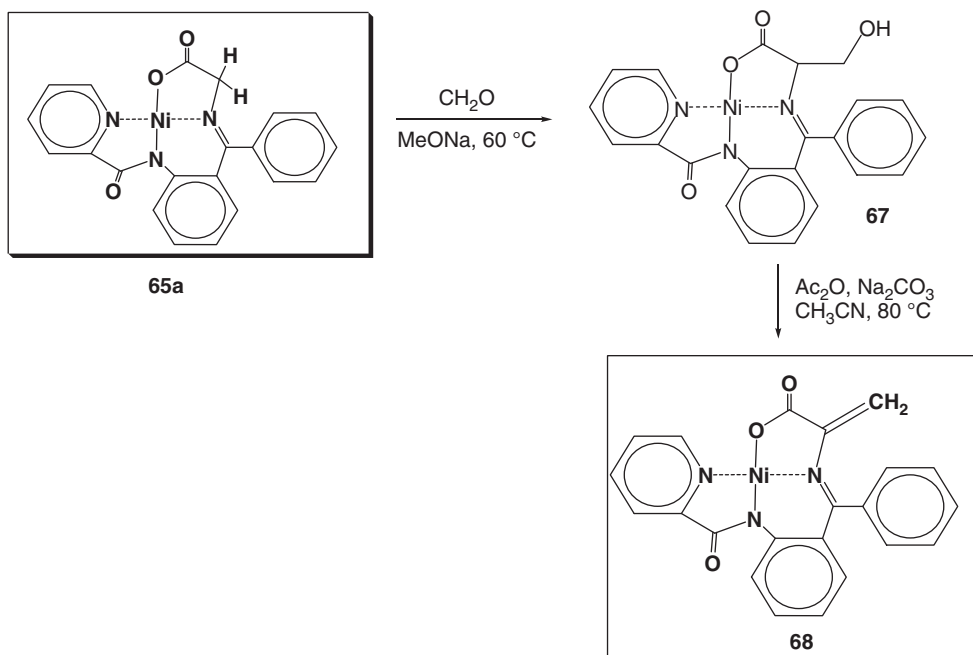
Scheme 8.18

The starting PBA ligand was obtained by the condensation of picolinic acid with methyl ester of anthranilic acid, followed by the reduction of the condensation product and oxidation of the resulting alcohol according to the Shvern's method. The resulting square-planar Ni^{II} ion complexes are air stable, diamagnetic, red crystalline compounds, easily chromatographed on SiO_2 , and very poorly soluble in most organic solvents. Preferred solvents are chloroform and methylene chloride. These complexes may be further purified either by chromatography or crystallization.

Based on the research on the synthesis of enantiomerically pure β -substituted α -amino acids using a chiral complex of Ni^{II} ion with Schiff base of dehydroalanine [66, 67], attempts were made to obtain an achiral analog of this compound to be

used in catalytic asymmetric synthesis reactions of optically active β -substituted α -amino acids and synthesis of their racemic analogs [68].

The achiral Ni^{II} complex of dehydroalanine **68** was prepared from complex **65a** according to Scheme 8.19 (without preliminary purification) with a total yield of 84%. Condensation of complex **65a** with formaldehyde affords complex **67**, which is a Schiff base of racemic serine and PBP (see Scheme 8.19). The subsequent O-acetylation of complex **67** by acetic anhydride in CH₃CN and simultaneous deacetoxylation by Na₂CO₃ provides final substrate **68**, containing a dehydroalanine moiety with an unsaturated double bond.



Scheme 8.19

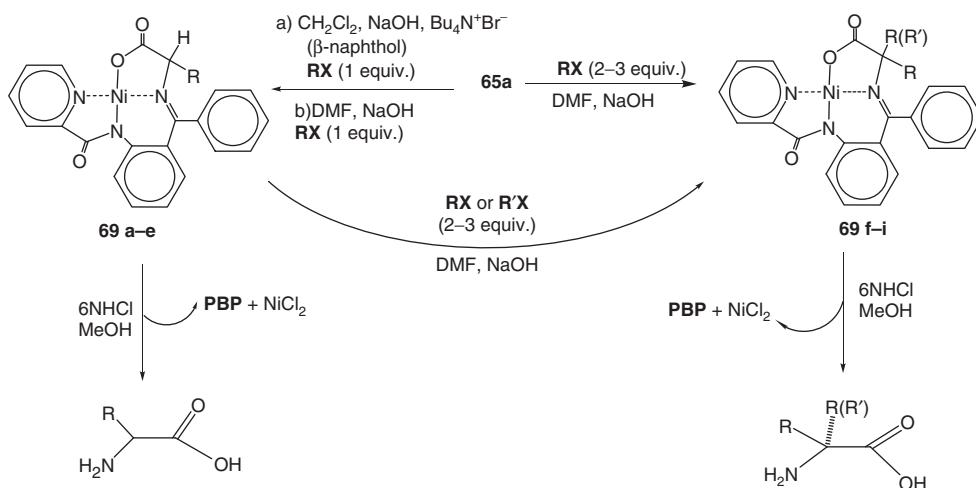
This product unlike other known dehydroalanines [69–72] reactive derivatives has a number of advantages; it has crystalline structure and is brightly colored, which makes it convenient for usage; moreover, it is stable and the method for its synthesis is fairly simple [65].

The acidity of the proton at α -carbon atom in complexes of **65a** and **65b** type is quite high (~ 18 pK_a in DMSO) [73]. This allows to perform easily the alkylation of a glycine moiety of the complex at α -carbon atom with various electrophiles. The presence of the benzene ring in the imine part of the complex causes additional steric hindrances and difficulties to introduce the second alkyl group, thus minimizing the possibility of bisalkylation.

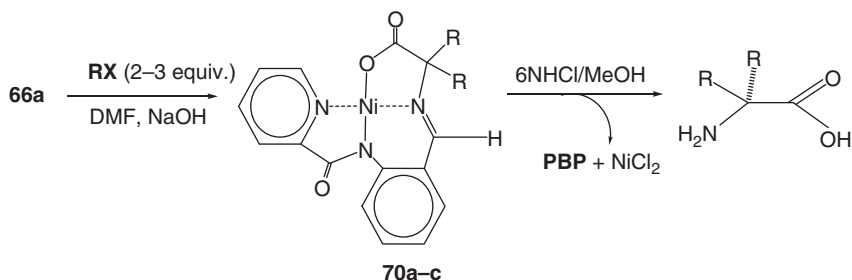
8.1.1

The Alkylation of Achiral Ni^{II} Complexes Under Phase-Transfer Catalysis

Alkylation of **65a** and **65b** substrates with alkyl halides was carried out according to Schemes 8.20 and 8.21 under PTC [65]. As phase-transfer catalysts, achiral quaternary ammonium salts of triethylbenzylammonium bromide (TEBA-Br), tetrabutylammonium bromide (TBA-Br), and β -naphthol were used. Depending on the desired product (mono- or bis-) reactions were carried out either in dimethylformamide (DMF) or in CH_2Cl_2 using NaOH as a base. If the reaction is carried out in DMF, there is no need of using PTC.



Scheme 8.20



Scheme 8.21

The reaction progress was conveniently monitored by thin-layer chromatography (TLC) (SiO_2 , CHCl_3 /acetone) as R_f of the alkylated product was higher than the R_f of the starting complex due to higher lipophilicity. The product was

purified by chromatography or crystallization, but in most cases it was not needed due to a very high conversion degree (>95%). The alkylated complex was easily decomposed by boiling in MeOH/6NHCl mixture until the disappearance of red characteristic color of the complexes. Thus, the starting PBP or PBA ligands were easily regenerated as hydrochlorides in quantitative yields and the target amino acid was isolated from the aqueous solution by ion-exchange chromatography.

Table 8.2 summarizes experimental results of alkylation of achiral complexes **65a** and **66a** by a variety of alkyl halides at room temperature under the action of bases in a series of solvents.

Monoalkylation reaction of substrate **65a** proceeds in CH₂Cl₂ in a quantitative yield using 1 equiv. of alkylating agent in the presence of NaOH in PTC conditions (see Scheme 8.20, Table 8.2, No. 1, 2, 4). It was found that the efficiency of catalysis of these reactions by β-naphthol was comparable with the conventionally used quaternary ammonium salts in PTC. An optimum reaction condition for bulkier alkylating agents is DMF in the presence of alkali (Table 8.2, No. 3, 5). Bis-alkylation products of substrate **65a** can be readily synthesized by performing the reaction in DMF using 2–3 equiv. of an alkylating agent (see Table 8.2, No. 6, 7).

As alkylating agent α,α'-dibromo-*o*-xylene can also be used to form a corresponding complex of 2-amino-2'-carboxyindan **69f**, a substitution product of both protons of substrate **65a** (Table 8.2, No. 8), from which cyclic amino acid **71** can be obtained (see Figure 8.14).

Table 8.2 The alkylation reactions of **65a** and **66a** by alkyl halides under PTC.

No.	Substrate ^{a)}	Alkylating reagent ^{b)}	Solvent/base	Catalyst ^{c)} (10–15%)	Time (h)	Yield ^{d)} (%)
1	65a	PhCH ₂ Br	CH ₂ Cl ₂ /NaOH	TEBA-Br	1	69a />95
2	65a	EtI	CH ₂ Cl ₂ /NaOH	TEBA-Br	15	69b />95
3	65a	Ph ₂ CHCl	DMF/NaOH	-	0.5	69c />83
4	65a	AllylBr	CH ₂ Cl ₂ /NaOH	TBAB	1	69d />95
5	65a	<i>i</i> -PrI (3 equiv.)	DMF//NaH	-	1	69e />95
6	65a	PhCH ₂ Br (2 equiv.)	DMF//NaOH	-	1	69f />81
7	65a	AllylBr (3 equiv.)	DMF//NaH	-	1	69g />59
8	65a	<i>o</i> -C ₆ H ₄ (CH ₂ Br) ₂ (1 equiv.)	DMF//NaH	-	1	69h />32 ^{e)}
9	65a	EtI	CH ₂ Cl ₂ /NaOH	TEBA-Br	15	69b />95
		PhCH ₂ Br	DMF//NaOH		0.5	69i />95
10	66a	EtI (2.5 equiv.)	DMF//NaOH ^{e)}	-	0.5	70a />95
11	66a	<i>i</i> -PrI (3 equiv.)	DMF//NaH	-	1	70b />78
12	66a	<i>o</i> -C ₆ H ₄ (CH ₂ Br) ₂ (1 equiv.)	DMF//NaOH	-	1	70c />48 ^{f)}

a) 0.1–0.4 M.

b) In those cases where it is not specified, 1.1 equiv. was used.

c) β-Naphthol (No. 1–5) can also be used.

d) The chemical yield is calculated by weight of the pure product.

e) Starting substrate was regenerated with 40% yield.

f) NaH can be also used as a base.

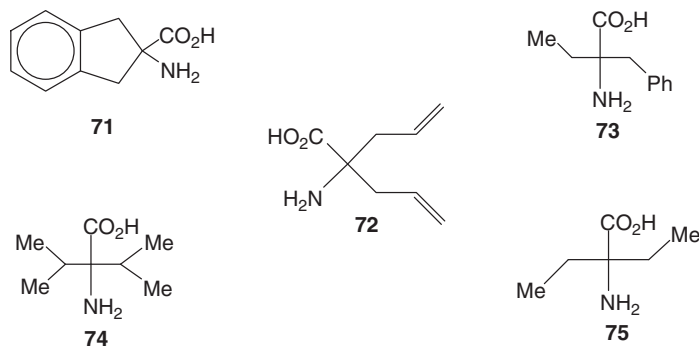


Figure 8.14 Structures of alkylation products.

A convenient method for sequential double alkylation of substrate **65a** was designed. First, a monoalkylation product is obtained with one alkylating agent in CH_2Cl_2 under PTC, which is then subjected to the secondary alkylation by other alkyl halide in DMF (see Scheme 8.20). This method was used to synthesize α -ethylphenylalanine **74**, which was isolated by the decomposition of complex **69i**, which is a product of gradual alkylation of substrate **65a**, alkylated first with EtBr, and then BnBr (see Table 8.2, No. 9).

However, attempts to obtain bisalkylation product of substrate **65a** by bulkier isopropyl iodide were unsuccessful even by using triplicate amount of *i*-PrI. To solve this problem, substrate **66a** was used, the benzophenone moiety of which was substituted by benzaldehyde (see Scheme 8.21). Due to the absence of the phenyl group, the methylene moiety of such a substrate is spatially less shielded. An advantage of this structure is the ability to selectively form only bisalkylation product even when the reaction is performed in CH_2Cl_2 in a substrate/alkylating agent ratio of 1/1 in PTC. However, maximum yield of bisadduct is achieved when the reaction is performed in DMF in the presence of NaOH.

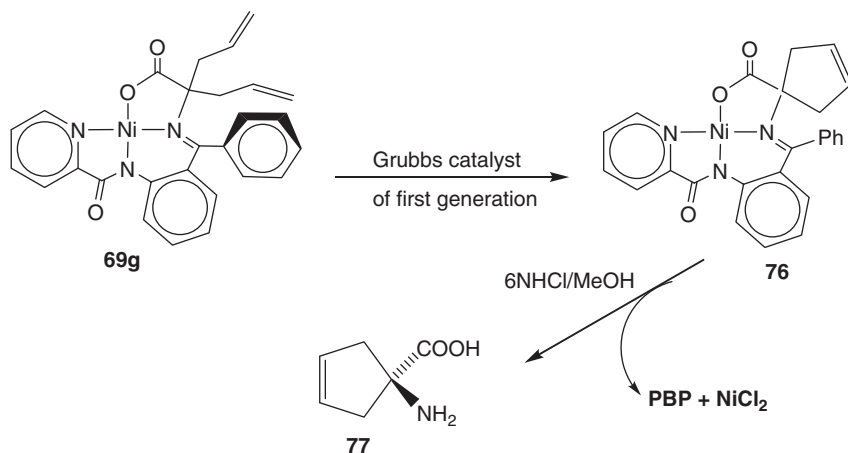
Even bulky *i*-PrI reacts with substrate **66a**, forming only bisalkylation product **70b** (see Table 8.2, No. 11); hydrolysis of **70b** allows to obtain α,α -diisopropylglycine (**74**) in high chemical yield (see Figure 8.14).

The other valuable amino acid α,α -diethylglycine (**75**) was synthesized in the same way, under the same conditions by hydrolysis of complex **74a** (see Table 8.2, No. 10, Figure 8.14).

The structure of Ni^{II} ion complexes allows to modify the lateral fragment of amino acid, without affecting its functional carboxyl and amino groups. Thus, the reaction of metathesis of diallyl fragment of complex **69g** afforded complex **76**, hydrolysis of which resulted in cyclic amino acid **77** (see Scheme 8.22).

Thus, complex **65a** is a very convenient substrate for the synthesis of racemic α -amino acids containing α -proton in the initial glycine moiety.

Simple alkylation of **65a** in PTC by alkyl halides leads to monoalkylated products, and therefore to synthesis of a whole series of racemic amino acids. As we expected, unlike spatially less hindered complex **66a**, the steric load due to the



Scheme 8.22

presence of the phenyl group next to the C=N bond in complex **65a** contributes to monoalkylation. This difference in behavior of benzophenone and benzaldehyde Schiff bases of glycine ethers has been discussed in detail in O'Donnell's work [74].

The interaction of the methyl substituent of alanine moiety with the phenyl group of benzophenone moiety can be clearly seen when crystallographic structures of complexes **65a** and **65b** are compared. A consequence of this interaction is the additional compression of chelate chain and some rotation of the phenyl group relative to the coordination plane of the complex; thereby the methyl group is in pseudo-axial position and α -proton – in equatorial position.

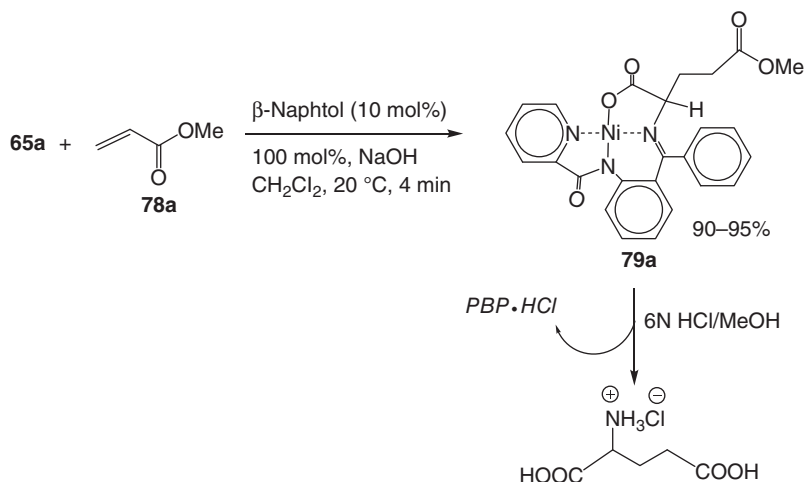
Thus, predominant monoalkylation of substrate **65a** is due to CH-acidity decrease in monoalkylated complex **69** compared with the original glycine complex and the additional spatial shielding of the reactive center in it for the approach of the second molecule of the alkylating agent. Spatially less hindered complex **66a**, free of such complicated intramolecular interactions, is an excellent substrate for the synthesis of achiral amino acids with a quaternary carbon atom.

8.1.2

Reactions of 1,4-Michael Addition to Achiral Glycine and Dehydroalanine Complexes

Substrate **69a** can also be used as electron donor compound in Michael reaction. Scheme 8.23 illustrates the coupling reaction of complex **65a** to various Michael acceptors on the example of acrylic acid methyl ester. Reaction was carried out in CH₂Cl₂ in the presence of a base and a phase-transfer catalyst. As a phase-transfer catalyst β -naphthol was selected to be used in this case.

It is found that β -naphthol, as in the case of alkylation reaction, is a highly effective catalyst for the Michael addition reaction (reaction proceeds in a few minutes). Meanwhile, in the absence of a catalyst, the reaction practically does not proceed even when heated in the presence of a large excess of alkali. It should



Scheme 8.23

be noted that the addition reaction catalyzed by β -naphthol, runs exceptionally smooth and without formation of any by-products including bis-addition products.

The effectiveness of substrate **65a** in Michael reaction is shown by the example of synthesis of racemic glutamic acid and its derivatives (see Table 8.3). In all cases, the reaction proceeds at room temperature for a few minutes with a quantitative yield of the final Michael adduct. When *Dabco* (diazabicyclooctane) is used as a base, the coupling reaction of the substrate practically does not proceed (Table 8.3, No. 1–3).

Table 8.3 The addition reaction of substrate **65a** to Michael acceptors in CH_2Cl_2 ^{a)}

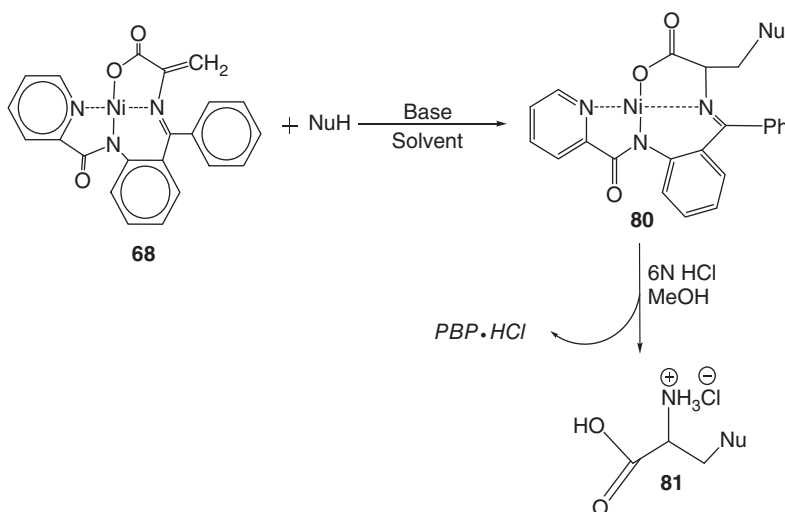
No.	Base	Michael acceptor 78	Product 79	Time (min)	Yield (%) ^{b)}
1	NaH	$\text{CH}_2=\text{CH}-\text{CO}_2\text{Me}$	a	4	90
2	KOH	$\text{CH}_2=\text{CH}-\text{CO}_2\text{Me}$	a	5	88
3	Dabco	$\text{CH}_2=\text{CH}-\text{CO}_2\text{Me}$	a	60	—
4	NaOH	$\text{CH}_2=\text{CH}-\text{C}(=\text{O})\text{NH}_2$	e	4	85
5	NaOH	$\text{CH}_2=\text{CH}-\text{C}(=\text{O})\text{N}(\text{cyclohexyl})$	d	4	84

a) Reaction conditions: 0.1–0.4 M substrate, 1 equiv. base, 0.1 equiv. β -naphthol, $T = 20^\circ\text{C}$.

b) Yield was determined by the weight of the product.

Another interesting possibility of synthesis of α -amino acids is the use of 2-aminoacrylic acid derivatives in various reactions. However, methods known in the literature are limited and have a number of drawbacks [70–72]. The final deprotection requires harsh reaction conditions – an extended time and use of concentrated acids and bases, which hinder the selectivity of the process. Besides, aminoacrylic substrates themselves are unstable since they are partially subjected to dimerization.

Modification of methylene moiety of substrate **65a** to dehydroalanine derivative **68** allowed the use of Ni^{II} complex not only as a proton donor but also as Michael acceptor in addition reactions with various nucleophiles (see Scheme 8.24).



Scheme 8.24

The progress of the reaction was monitored by TLC. After disappearance of traces of starting complex **68**, the reaction mixture was neutralized followed by decomposition of complex **80** and isolation of target amino acid **81** and PBP ligand. Thus, PBP can be regenerated and reused in the synthesis of original complex **68**.

The obtained amino acids depending on the hydrophobicity are isolated either by ion-exchange chromatography or by using EDTA. Michael attachment of complex **68** to electron-donor compounds occurs in different solvents depending on the nature of the nucleophile. The reaction could be carried out just in the presence of a base without the additional use of a catalyst (see Scheme 8.24). The results are presented in Table 8.4.

Attachment of complex **68** to SH- and CH-acids, particularly to thiophenol and derivatives of diethyl ester of malonic acid proceeds in CH₂Cl₂ for several minutes under NaH catalysis in a quantitative yield of final product **80** (see Table 8.4, No. 1, 3). It should be noted that Michael addition reaction rate is not correlated with

Table 8.4 Results of addition of nucleophiles to complex **68**.

No.	NuH (pK_a) ^{a)}	Solvent ^{b)} /T (°C)	Time (min)	Base ^{c)}	(±)- 80	Yield 80%
1	PhSH (10.3)	CH ₂ Cl ₂ /20	25	NaH	A	75 ^{d)}
2	CH ₂ (CN) ₂ (11.1)	CH ₂ Cl ₂ /20	12 h	NaH	b	79 ^{d)}
3	CH ₂ (CO ₂ Et) ₂ (16.4)	CH ₂ Cl ₂ /20	10	NaH	c	85 ^{d)}
4	CH ₃ NO ₂ (17.2)	CH ₂ Cl ₂ /20		NaH	d	—
5	CH ₃ NO ₂	CH ₃ CN/80	120	NaH	d	—
6	CH ₃ NO ₂	<i>t</i> BuOH		<i>t</i> -BuOK	d	60
7	PhOH (18)	CH ₃ CN/80	60	<i>t</i> -BuOK	f	40 ^{e)}
8	β-Naphthol (17.1)	CH ₃ CN/80	180	NaH	g	84 ^{f),g)}
9	Benzylamine	CH ₂ Cl ₂ /20	60	NaH	h	68 ^{d)}
10	Benzylamine	<i>t</i> BuOH/60	10	-	h	72
11	Imidazole	CH ₃ CN/80	90	NaH	i	86 ^{d)}
12	Indole (24.7)	CH ₃ CN/80	180	NaH	j	80 ^{d)}

a) pK_a values determined in DMSO, based on Borduelli's review.

b) Substrate concentration 0.23 M.

c) Concentration of NaH 10–50 mol%.

d) Ratio of Nu/**68** = 3.0.

e) In this case, product does not correspond to the Michael adduct, phenol is not attached (see text).

f) Ratio Nu/**69** = 1.2.

g) Addition based on Scheme 8.25.

the pK_a values of nucleophiles [75]. Thus, despite high CH-acidity of malononitrile compared with malonic ester, its attachment to substrate **68** proceeds quite slow and reaches maximum conversion in 12 h (see Table 8.4, No. 2). According to the X-ray diffraction (XRD) analysis there are no intramolecular interactions in addition product of malonic ester to **68** (see Figure 8.15). The same refers to the addition product of nitromethane.

Despite the relatively close pK_a values of the malonic ester and nitromethane, adduct of the nitromethane with substrate **68** could not be obtained in methylene chloride, or even in a more polar solvent – acetonitrile by heating the reaction mixture to 80 °C (see Table 8.4, No. 4,5).

However, in transition to a protic solvent, particularly *tert*-butanol, nitromethane adduct is obtained in a quantitative yield (Table 8.4, No. 6). This difference in the behavior of adducts with malonic ester and nitromethane apparently is due to a less stable carbanion intermediate in the first case, stabilized by protonation in *tert*-butanol. Apparently, the resulting carbanion intermediate in the case of nitromethane is less stable than the malonate anion.

Alcohols were also involved in Michael reaction. Interaction of the substrate with sodium methylate resulted in a complex mixture of unidentified products. Attachment of β-naphthol and phenol to substrate **68** requires harsher reaction conditions, particularly long boiling in acetonitrile in the presence of a base, and in methylene chloride these reactions do not proceed at all (see Table 8.4, No. 7, 8).

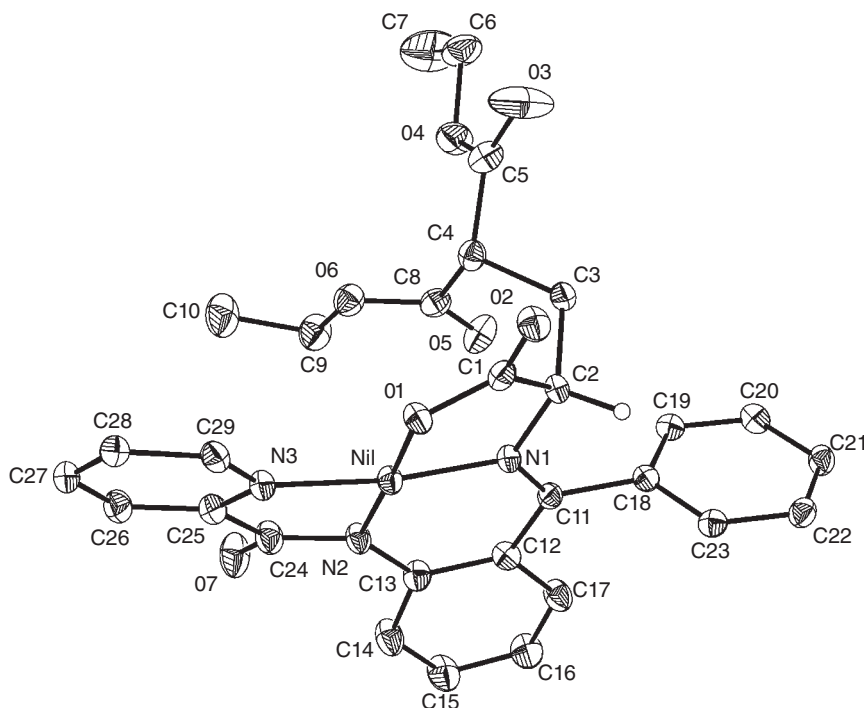
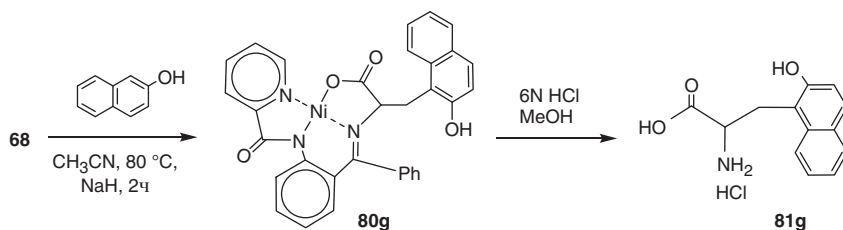


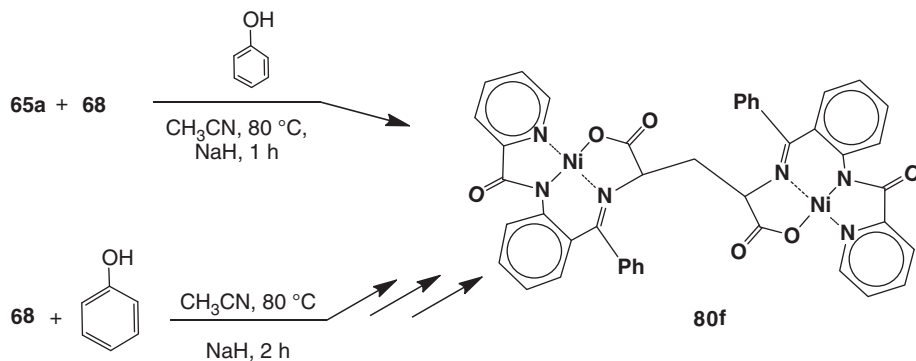
Figure 8.15 The crystallographic structure of Michael adduct **80c**.



Scheme 8.25

During the reaction of β -naphthol with substrate **68**, C-alkylation was observed (see Scheme 8.25) [20]. This was evidenced by the presence of hydroxyl signal in the IR spectrum, and the absence of the characteristic aromatic proton in ^1H NMR spectrum of product **80g**. Target amino acid **81g** was isolated by hydrolysis of complex **80g**.

Since the obtained amino acid **81g** is not soluble in water, after decomposition of the complex and evaporation of the hydrolysate, water was added to the reaction mixture and pH of the solution was adjusted to 8 and the original ligand was extracted with chloroform. The precipitate (amino acid) was filtered off and crystallized from 3N HCl.



Scheme 8.26

An attempt to attach phenol to substrate **68** under the same conditions failed. Phenol itself does not react, but catalyzes the formation of adduct **80f** (addition product of complexes **68** and **65a**), generated by the reversible addition of water to complex **68** and subsequent decay of the serine product to **65a** and formaldehyde (Table 8.4, No. 7, Scheme 8.26). In addition, a large amount of the oxidized product was found in the reaction mixture. An attempt to attach complexes **68** and **65a** in acetonitrile in the presence of NaH failed; however, the reaction in the presence of 1 equiv. of Na phenolate afforded the same product as during an attempt to attach phenol to complex **68**, but in a higher chemical yield.

Nitrogenous nucleophiles such as benzylamine, imidazole, and indole were also involved in Michael reaction with complex **68** (see Table 8.4, No. 9–12). Benzylamine reacts most easily. The addition reaction of benzylamine does not proceed in methylene chloride without a base; however, with the addition of Na hydride the reaction proceeds for an hour (see Table 8.4, No. 9). Along with this, the reaction in *tert*-butanol proceeds without a base for 10 min at 60°C (see Table 8.4, No. 10). The addition product of benzylamine **80h** can be purified either by crystallization or chromatography, but in the case of chromatography to prevent decomposition of the product to the original compounds, it must be acylated.

The optimal conditions for the addition of imidazole to complex **68** are conducting the reaction in acetonitrile at 80°C in the presence of NaH (see Table 8.4, No. 11). In this case, the reaction proceeds for 90 min in a high chemical yield. The reaction with imidazole also proceeds in methylene chloride but in lower chemical yield. Imidazole is attached to complex **68** by the nitrogen atom. This is confirmed by the presence of the typical β -proton signal in ^1H NMR spectrum in the field of aromatic protons, the absence of NH -group signal in IR spectrum, and the discrepancy of chromatograms of isolated amino acid and histidine.

It was also possible to perform the addition of indole to dehydroalanine complex **68**. Addition reaction of indole proceeds under the same conditions as in the case of imidazole, but with longer boiling (see Table 8.4, No. 12). As with other amines,

indol is also attached by the nitrogen atom. This is verified by IR and ¹H NMR spectra.

Addition reactions of cyclopentadienyllithium, naphthylamine, phenylenediamine, and diiso-propylamine to complex **68** in acetonitrile do not proceed even when boiled for several hours.

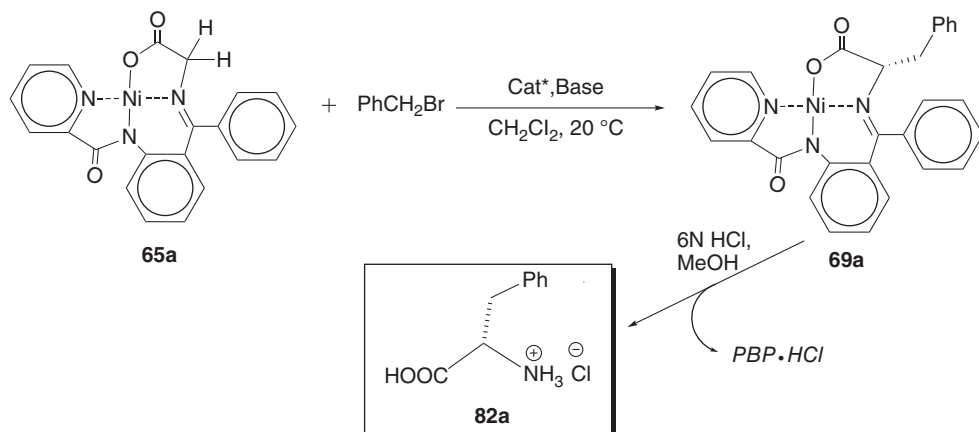
8.1.3

Synthesis of Enantiomerically Enriched α -Amino Acids

As shown earlier, the achiral Ni^{II} ion complexes are universal substrates for the Michael reactions and C-alkylation. The peculiarities of chemical structure of these complexes allow their use as templates for the synthesis of the whole series of α -amino acids. Naturally, the actual problem is to implement an asymmetric catalytic version of these reactions in order to obtain optically pure α -amino acids. The fact that the β -naphthol in the presence of a base is an effective catalyst in both Michael reactions and alkylation involving Ni^{II} complexes prompted the idea to use chiral chelating compounds of similar to the naphthol structure as catalysts for generation of the C–C bond.

8.1.3.1 The Asymmetric Alkylation of Substrate **65a** by Alkyl Halides Under Phase-Transfer Catalysis

As a model reaction of asymmetric catalytic alkylation of achiral glycine complexes by alkyl halides the reaction of benzyl bromide with substrate **65a** was selected (see Scheme 8.27) [65, 76]. As noted above, in the presence of a base, but in the absence of a catalyst, the reaction does not proceed even in 5 h. Chiral alcohols and aminoalcohols capable of chelating the cation of the base and coordination with Ni-substrate **65a** were selected as catalysts.



Scheme 8.27

Alkylation results of chiral PTC are presented in Table 8.5. The chiral ligand **83** traditionally used in asymmetric PTC (see Figure 8.16) proved to be ineffective in alkylation reaction of **65a**, providing only 50% yield in an hour and low ee (see Table 8.5, No.1).

Another ligand – a chiral diol TADDOL **33a**, being a very effective catalyst for the alkylation of the Schiff base of benzaldehyde and alanine ester, in this case

Table 8.5 Results of alkylation of **65a** by alkyl halides promoted by derivatives of chiral aminobinaphthols.

No.	Solvent ^{a)}	Catalyst	Base	Time (min)	Yield 79a (%) ^{b)}	ee Phe 82a (%) ^{c)}
1	CH ₂ Cl ₂	83	NaOH	60	50	16(<i>R</i>)
2	CH ₂ Cl ₂	(<i>R,R</i>)- 33	NaOH	10	10	12(<i>R</i>)
3	CH ₂ Cl ₂	(<i>R</i>)- 34a	NaOH	8	90	97(<i>R</i>)
4 ^{d)}	CH ₂ Cl ₂	(<i>R</i>)- 34a	NaOH	15	85	87
5 ^{e)}	CH ₂ Cl ₂	(<i>R</i>)- 34a	NaOH	3	13	74
6	C ₆ H ₅ CH ₃	(<i>R</i>)- 34a	NaOH	45	50	89(<i>R</i>)
7	CH ₂ Cl ₂	(<i>S</i>)- 34a	NaOH	8	88	96(<i>S</i>)
8	MeCN	(<i>R</i>)- 34a	NaOH	20	80	17(<i>R</i>)
9 ^{f)}	(CH ₂) ₂ Cl ₂	(<i>R</i>)- 34a	NaOH	5	92	93(<i>R</i>)
10	CH ₂ Cl ₂	(<i>R</i>)- 34a	KOH	7	80	16(<i>R</i>)
11	CH ₂ Cl ₂	(<i>R</i>)- 34a	CsOHxH ₂ O	15	25	10(<i>R</i>)
12	CH ₂ Cl ₂	(<i>R</i>)- 34a	50% aqueous NaOH	60	5	55(<i>R</i>)
13	CH ₂ Cl ₂	(<i>R</i>)- 34a	NaH	11	50	97(<i>R</i>)

a) Reaction conditions: Concentration of **65a** is 1.5 M, PhCH₂Br/substrate ratio = 5, (*R*)-**34a**/substrate = 0.1, MOH/substrate = 10. Room temperature unless otherwise indicated, under Ar.

b) Yield of **79a** determined after its isolation from the reaction mixture.

c) Determined by chiral GLC of amino acid.

d) (*R*)-**34a**/substrate = 0.05.

e) (*R*)-**34a**/substrate = 0.025.

f) Experiment conducted at 70 °C.

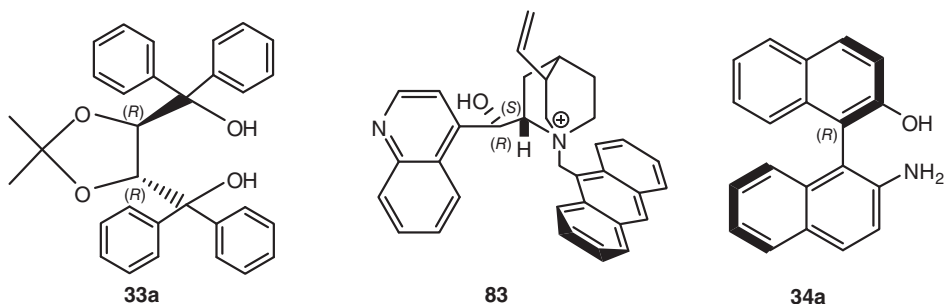


Figure 8.16 The catalysts of the asymmetric alkylation reaction.

proved to be inappropriate in terms of the chemical yield and enantioselectivity of the reaction (Table 8.5, No. 2).

A chiral aminobinaphthol – (*R*)-NOBIN **34a** [76] (see Figure 8.16) proved to be an optimal catalyst for alkylation reaction of substrate **65a** by alkyl halides, which at 10 mol% concentration provides high chemical yield and 97% enantiomeric purity of the final product (see Table 8.5, No. 3). This reaction proceeds at room temperature with 100% conversion within 8 min.

Reducing the amount of catalyst from 10 to 2.5 mol% causes insignificant reduction of the reaction enantioselectivity and a significant reduction of the chemical yield in 3–15 min (see Table 8.5, No. 3–5).

When the reaction is conducted in toluene, the reaction time increases – in 45 min the chemical yield reaches only 50%. As expected, increase in polarity of the solvent reduces ee of the alkylation reaction. Thus, in acetonitrile, the reaction proceeds for 20 min in 80% chemical yield and 17% enantiomeric purity of the product (see Table 8.5, No. 7).

As follows from the analysis of numerous literature data, variation of the reaction temperature leads to dramatic changes in the selectivity of the reaction. It is shown that in most cases the temperature increase leads to a significant decrease of enantioselectivity. A rare example of the reaction proceeding even at 70 °C with high enantioselectivity at regular increase of the chemical yield was detected (see Table 8.5, No. 8).

The reaction is very sensitive to the nature of the base used. In transition from NaOH to KOH, and further to CsOH, the enantioselectivity of the reaction drops from 97% to 10%, suggesting a possible cation chelation in the transition state of the reaction, the effectiveness of which essentially depends on its size (see Table 8.5, No. 5, 10, 11). Using sodium hydride instead of solid NaOH does not affect the enantiomeric purity of the product (see Table 8.5, No. 13).

When 50% aqueous alkali is used instead of solid freshly ground NaOH, sharp reduction in the product chemical yield (as low as 5%) and ee (as low as 55%) is observed (see Table 8.6, No. 12), which is explained apparently by the competitive binding of water with the catalyst by hydrogen bonds. This causes the inhibition of catalytic activity of **34a**. The use of 2,2'-dihydroxy-1,1'-binaphthyl – **34b** and 2,2'-diamino-1,1'-binaphthyl – **34c** (see Figure 8.17) as catalysts in alkylation reaction of substrate **65a** by benzylbromide leads to a dramatic reduction in both chemical yield and ee of the final product (see Table 8.6, No. 2, 3).

The role of unsubstituted amino- and hydroxy groups of the catalyst is crucial for the rate and enantioselectivity of the alkylation reaction. Modification of the catalyst by substituting the NH₂ group with NHPh or NMe₂ groups (see Figure 8.17) leads to a reduction of chemical yield and ee of the end product (see Table 8.6, No. 1, 4, 5). It is also shown that the *O*-benzyl derivative of NOBIN is catalytically inactive.

N-Formyl derivative of NOBIN **34f** also proved to be an ineffective catalyst for alkylation reaction (see Figure 8.17) affording only a tiny amount of the product in 35 min (see Table 8.6, No. 6). The use of (*R*)-*N*-acetyl-NOBIN **34g** leads to a low chemical yield of the product with 28% ee (see Table 8.6, No. 7). However, with

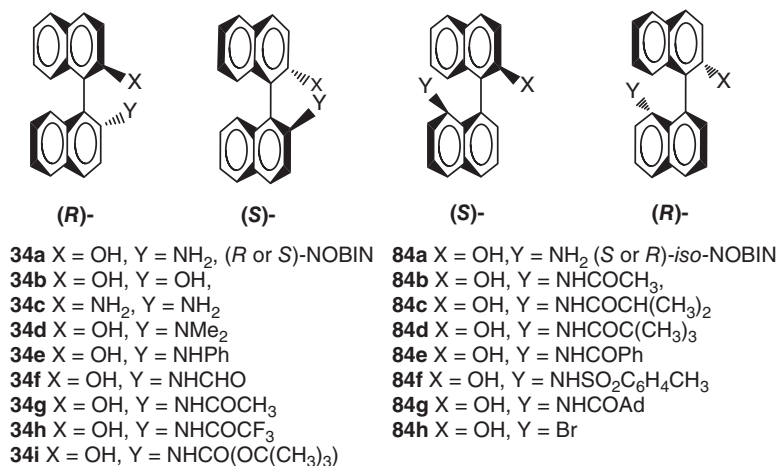
Table 8.6 Results of alkylation of substrate **65a** in CH_2Cl_2 catalyzed by derivatives of NOBIN and *iso*-NOBIN in the presence of NaOH.^{a)}

No.	Catalyst	Time (min)	Yield 69a (%) ^{b)}	ee Phe 82a (%) ^{c)}
1	(<i>R</i>)- 34a	8	90	97 (<i>R</i>)
2	(<i>S</i>)- 34b	60	14	17 (<i>S</i>)
3	(<i>R</i>)- 34c	30	16	18 (<i>S</i>)
4	(<i>R</i>)- 34d	15	15	5 (<i>R</i>)
5	(<i>R</i>)- 34e	60	10	3 (<i>R</i>)
6	(<i>R</i>)- 34f	35	Traces	Not determined
7	(<i>R</i>)- 34g	30	30	28 (<i>S</i>)
8	(<i>R</i>)- 34h	20	Traces	Not determined
9	(<i>S</i>)- 84a	13	36	87.5 (<i>S</i>)
10	(<i>R</i>)- 84b	6	90	71(<i>S</i>)
11	(<i>S</i>)- 84c	7	60	90 (<i>R</i>)
12	(<i>S</i>)- 84d	9	70	92 (<i>R</i>)
13	(<i>S</i>)- 84e	10	10	88 (<i>R</i>)
14	(<i>S</i>)- 84f	30	Traces	Not determined

a) Reaction conditions: Concentration of **65a** is 1.5 M, PhCH_2Br /substrate ratio = 5, catalyst/substrate = 0.1, NaOH/substrate = 10, $T = 25^\circ\text{C}$, under Ar.

b) Yield of (*R*)- or (*S*)-**69a** was determined after its isolation from the reaction mixture.

c) Determined by chiral GLC.

**Figure 8.17** Chiral catalysts based on aminobinaphthols.

catalyst **34g**, there occurs a conversion of the final amino acid configuration as compared with the configuration observed in (*R*)-NOBIN catalysis. Substitution of the methyl group of the catalyst with trifluoromethyl group **34h** actually inhibits catalytic activity (see Table 8.6, No. 8).

When isomer NOBIN **34a**, namely (*R*)-2-hydroxy-8'-amino-1,1'-binaphthyles (*iso*-NOBIN) **84a**, is used as a catalyst, the chemical yield of the reaction sharply decreases, the enantioselectivity of the reaction reaches 87% (see Table 8.6, No. 9), and yet there is no conversion of amino acid configuration [76].

For acylated derivatives of *iso*-NOBIN, the configuration conversion of amino acid is also typical as compared with unsubstituted *iso*-NOBIN (see Table 8.6, No. 10–13). It is important to note that unlike the acylated derivatives of NOBIN, in reactions catalyzed by acylated derivatives of *iso*-NOBIN the obtained product has high chemical yield and enantiomeric purity. For example, in the case of catalysis of (*R*)-*N*-acetyl-*iso*-NOBIN **84b** the reaction is complete in 6 min in 90% chemical yield and 71% ee of the final product of (*S*)-configuration (see Table 8.6, No. 10).

Furthermore, an interesting tendency is observed with acylated derivatives of *iso*-NOBIN. With the increase of the acyl substituent volume in the amino group of the catalyst simultaneous increase of the reaction enantioselectivity and reduction of the chemical yield of the final product is observed (see Table 8.6, No. 10–13). Thus, under catalysis of (*R*)-*N*-pivaloyl-*iso*-NOBIN **84d** the alkylation reaction was complete within 9 min in 70% chemical yield and 92% ee (see Table 8.7, No. 12). Benzoyl derivative of *iso*-NOBIN also provides high stereoselectivity of the alkylation reaction of substrate **84e** but chemical yield reaches only 10% in 10 min. Introduction of the tosyl substituent in the amino group of *iso*-NOBIN leads to the inhibition of the catalytic activity of **84f** (see Table 8.6, No. 14).

Other Ni^{II} ion complexes were also used as substrates for the asymmetric alkylation (see Scheme 8.28). The results of alkylation of Ni^{II}-substrates **65b** and **66a,b** in PTC catalyzed by NOBIN are presented in Table 8.7.

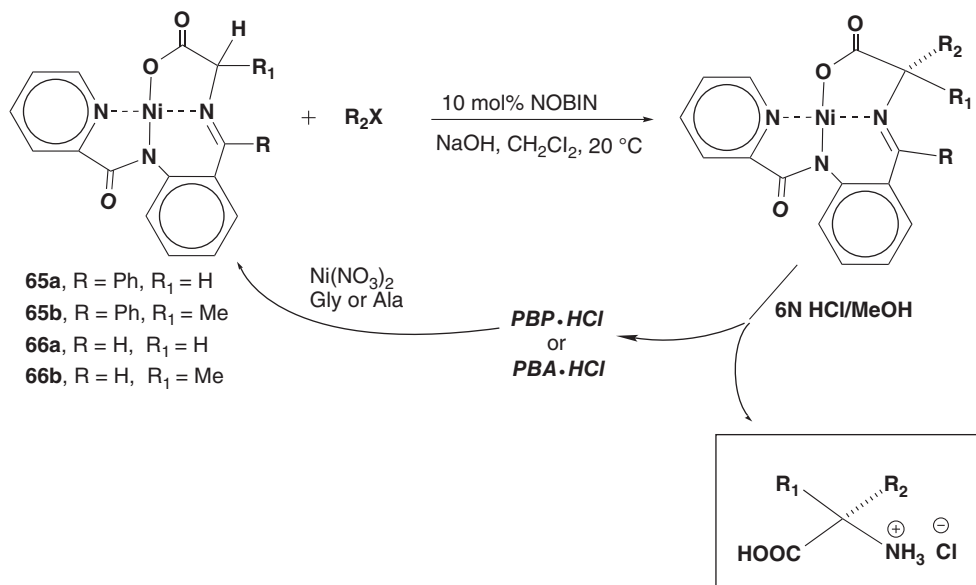
Table 8.7 Results of PTC alkylation of Ni^{II} complexes in CH₂Cl₂ catalyzed by (*R*)-NOBIN in the presence of NaOH.^{a)}

No.	Substrate	Time	Alkylating agent	Chemical yield of alkylated complex (%) ^{b)}	ee (<i>R</i>) amino acid (%) ^{c)}
1	65b	18 h	PhCH ₂ Br	95	43.6
2	65b	1 h	AlIBr	70	20
3	66a	1 h	PhCH ₂ Br	mono-(30), bis-(38)	0
4	66b	40 min	PhCH ₂ Br	100	20
5	66b	Does not go	<i>i</i> -PrOH	—	—

a) Reaction conditions: substrate concentration 1.5 M, the ratio of alkylating agent/substrate = 5, the catalyst/substrate = 0.1, NaOH/substrate = 10, RT, under Ar.

b) Yield determined after its isolation from the reaction mixture.

c) Determined by chiral GLC.



Scheme 8.28

Alkylation of alanine substrate **65b** by benzyl bromide (see Scheme 8.28) occurs over a longer period of time (18 h) with 43% reaction enantioselectivity (see Table 8.7, No. 1). Low stereoselectivity is also observed in the case of substrate **65b** allylation (see Table 8.7, No. 2).

During alkylation of spatially less hindered complex **66a**, the reaction proceeds rather fast, but with the formation of both mono- and bis-products (see Table 8.7, No. 3).

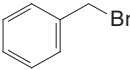
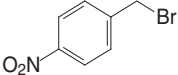
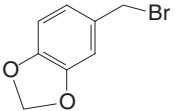
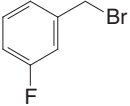
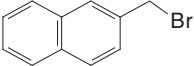
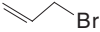
Alanine substrate **66b**, as opposed to **65b**, is characterized by higher rate of alkylation but nevertheless fairly low stereoselectivity (see Table 8.7, No. 4).

Accordingly, it could be concluded that the optimal conditions for highly stereoselective asymmetric alkylation of **65a** in the PTC are

- 1) the use of unsubstituted chiral aminobinaphthol NOBIN **34a** at 10 mol% concentration as a catalyst;
- 2) conducting the reaction in CH₂Cl₂ at room temperature in the presence of solid powder-like NaOH.

After determining the optimal conditions for alkylation reaction catalyzed by NOBIN, the latter was used for alkylation of substrate **65a** by various alkyl halides for the synthesis of the whole series of optically active α -amino acids. The results of alkylation of **65a** with various alkyl halides are presented in Table 8.8. As follows from the table, alkylation reaction of **65a** proceeds most effectively with activated alkyl halides at room temperature for 4–30 min, affording reaction products in quantitative chemical yields and stereoselectivity of 92–98.5% (Table 8.8, No. 1–7). Such a high rate of reaction and the enantiomeric purity of the products

Table 8.8 Results of asymmetric PTC alkylation of substrate **65a** by a variety of alkyl halides, promoted by (*R*)-NOBIN (**34a**) at RT.^{a)}

No.	Alkylating agent	Time (min)	Yield (%) ^{b)}	ee (<i>R</i>)-amino acid (%) ^{c)d)}
1		8	90	97 (>99.8% ^{e)})
2		4	92	93
3		6	70	98.5
4		7	80	94
5		6	62	98.5
6		30	68	90
7		4	75	90
8		5	2	93
9		30	15(70) ^{f)}	93
10	<i>n</i> -C ₆ H ₁₃ I	60	10	91
11	BrCH ₂ COO <i>t</i> Bu	4	22	49
12	BrCH ₂ COO <i>t</i> Bu	8	53	40
13	BrCH ₂ COO <i>t</i> Bu	20	100	25

a) Reaction Conditions: in CH₂Cl₂, concentration of **65a** is 1.5 M, the ratio of substrate **65a**/RX = 1/1.2, (*R*)-NOBIN/**65a** = 1/10, NaOH/**65a** = 10–20/1, RT, under Argon.

b) Chemical yield of alkylated complex was determined after its isolation from the reaction mixture.

c) ee determined by chiral GLC and HPLC analyses.

d) Enantiomerically pure amino acids can be recrystallized from a mixture of alcohol–water.

e) Amino acid is isolated from a preliminary recrystallized complex.

f) Used 50 mol% of catalyst **34a**.

make the process very convenient for the synthesis of short-lived isotope labeled α -amino acids.

At the same time, the reactions with aliphatic alkyl halides for the same time period have lower chemical yields; however, the enantiomeric purity of the obtained products is 90% (see Table 8.8, No. 8–13). The yields of products of substrate **65a** alkylation by aliphatic halides can be increased by increasing the amount of NOBIN **34a** in the reaction mixture (see Table 8.8, No. 9). Introduction of electron-withdrawing substituents in the side chain of the amino acid accelerates racemization of the product, which is clearly illustrated by alkylation by *tert*-butyl bromoacetate (see Table 8.8, No. 11–13).

The alkylated complex before isolating the amino acid can be easily purified either by chromatography or crystallization. Due to high values of specific rotation of this type of complexes ($>2000^\circ$, CHCl_3), the enantiomeric purity of amino acid moiety is easily estimated by the value of $[\alpha]_D$, since the structure of the side moiety of amino acid actually does not affect the specific rotation value of the enantiomerically pure specimen.

The same arguments are applicable for the circular dichroism (CD) spectra. Figure 8.18 depicts positive Cotton effect spectra. Figure 8.18 depicts positive Cotton effect for the amino acid complexes of (*S*)-configuration and negative Cotton effect for the amino acid complexes of (*R*)-configuration. Despite the difference in the structures of amino acid side fragments (Phe and Glu), the CD spectra are almost mirror images. Consequently, absolute configuration of any amino acid

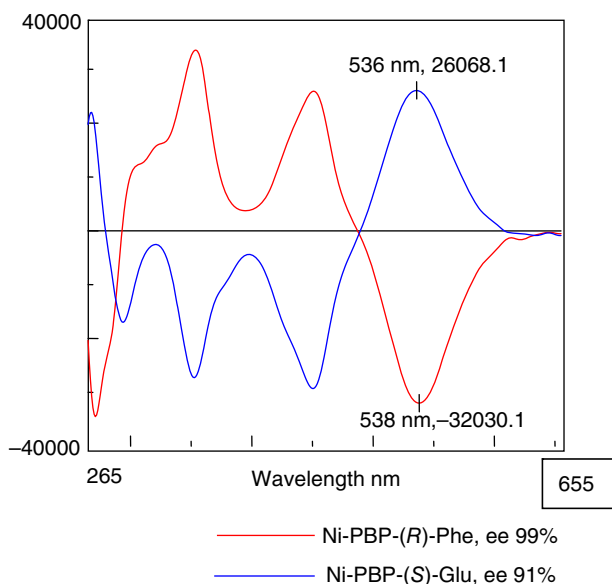


Figure 8.18 CD spectra for (*R*)-**69a** with ee 99%, negative Cotton effect at 538 nm for complex (*R*)-Phe, and positive Cotton effect at 536 nm for complex (*S*)-Glu with ee 91%.

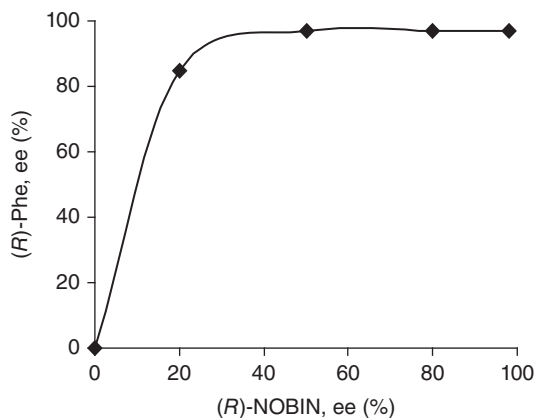


Figure 8.19 (+)-NLE in alkylation reaction of **65a** by benzylbromide under catalysis of **34a**.

fragment can be readily determined by comparing the direction of the Cotton sign of corresponding complexes.

After decomposition of the alkylated complex and the isolation of amino acid, the PBP achiral ligand can be easily regenerated and reused for the synthesis of substrate **65a**, similar to the case of synthesis of racemic amino acids. Catalyst **34a** can also be regenerated by column chromatography (SiO₂), but only in 20% yield. Low chemical yield of regenerated catalyst is due to the fact that a significant portion of NOBIN during the reaction becomes modified to an alkylated derivative of an unidentified structure.

Another interesting feature of NOBIN catalysis is the observed rather substantial positive nonlinear effect ((+)-NLE) of the dependence of the enantiomeric purity of the benzylation reaction product on enantiomeric purity of NOBIN (see Figure 8.19).

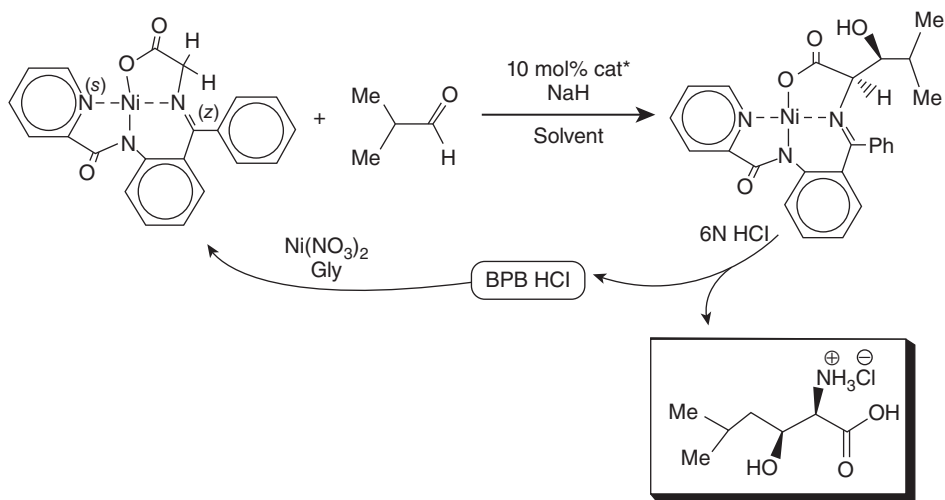
In practical terms, this means that for obtaining an amino acid with 90–95% enantioselectivity, a catalyst with 40% enantiomeric purity can be used, which allows the use of catalyst that is not enantiomerically pure but enantiomerically enriched.

8.1.3.2 Asymmetric Aldol Condensation of Achiral Ni^{II} Complexes of Amino Acids

β -Hydroxy- α -amino acids of various structures are important components of physiologically active peptides, cyclic peptides (vancomycin, cyclosporine, etc.) [77], enzyme inhibitors [78], and so on. They are also convenient intermediate compounds in the synthesis of β -halogen- α -amino acids, β -lactams, and other important compounds [79, 80]. Therefore, development of methods for the synthesis of optically active stereoisomers of these amino acids is essential.

Before starting the implementation of the catalytic asymmetric reaction with substrate **65a**, conditions for aldol condensation of chiral analog of Ni^{II} glycine complex had been preliminarily worked out for subsequent transfer of the results to the achiral glycine complex.

As a model reaction for aldol condensation using achiral Ni^{II} complex **65a**, a reaction with isobutyraldehyde was selected. Condensation was carried out in tetrahydrofuran (THF) at room temperature in the presence of NaH and with various derivatives of NOBIN and *iso*-NOBIN [65, 81] (see Scheme 8.29).



Scheme 8.29

Unsubstituted NOBIN **34a** catalyzes the reaction, but the asymmetric induction is significantly lower compared with results obtained for alkylation reaction. Thus, in THF at room temperature the reaction proceeds with 21% of ee and its chemical yield after 40 min is 60% (see Table 8.9, No. 1). In aldol condensation reaction, the catalyst with (*R*)-configuration, in the same manner as in alkylation reaction catalyzed by NOBIN, ensures the formation of an amino acid with (*R*)-configuration. Conducting the reaction at higher temperature leads to the formation of a large amount of oxidized product, whereby the yield of the aldol product is no more than 10% (see Table 8.9, No. 2). When CH_2Cl_2 is used as a solvent, the yield of the product is further reduced. Attempts to increase the yield by increasing the amount of base were unsuccessful. During catalysis with other derivatives of NOBIN, in particular with formyl (**34f**), the reaction product is obtained with fairly high chemical yield; however, its enantioselectivity is only 9% (see Table 8.9, No. 9).

Other derivatives of chiral aminobinaphthols proved to be less effective. The greatest yield and highest enantioselectivity of the product can be achieved using stoichiometric quantities of the catalyst.

Thus, when condensation reaction is conducted in methylene chloride in the presence of 1 equiv. NaH and 1 equiv. catalyst the reaction is complete in 20 min at room temperature with 42% ee and 65% chemical yield of the product (see Table 8.9, No. 6). The condensation reaction of **65a** with pivaloyl aldehyde catalyzed by NOBIN sodium alcoholate does not progress.

Table 8.9 Results of aldol condensation of isobutyraldehyde with achiral substrate **65a** catalyzed by 10 mol% chiral aminobinaphthols in the presence of NaH.^{a)}

No.	Catalyst	Solvent	Time (min)	Yield (%) ^{b)}	ee, amino acid (%) ^{c)}
1 ^{d)}	(<i>R</i>)- 34a	THF	40	60	(<i>R</i>) 21
2 ^{e)}	(<i>R</i>)- 34a	THF	40	10	(<i>R</i>) 13
3 ^{f)}	(<i>R</i>)- 34a	CH ₂ Cl ₂	20	17	(<i>R</i>) 25
4 ^{g)}	(<i>R</i>)- 34a	CH ₂ Cl ₂	60	—	—
5 ^{g)}	(<i>R</i>)- 34a	C ₂ H ₄ Cl ₂	20	12	(<i>R</i>) 25
6 ^{h)}	(<i>R</i>)- 34a	CH ₂ Cl ₂	20	65	(<i>R</i>) 40
7 ⁱ⁾	(<i>R</i>)- 34a	CH ₂ Cl ₂	30	25	(<i>R</i>) 22
8	(<i>R</i>)- 34g	CH ₂ Cl ₂	10	35	(<i>R</i>) 9
9	(<i>R</i>)- 34f	CH ₂ Cl ₂	15	68	(<i>R</i>) 9
10	(<i>R</i>)- 84a	CH ₂ Cl ₂	10	15	(<i>R</i>) 10

a) Concentration of **65a** in THF and CH₂Cl₂ is 0.12 M.

b) Yield was determined by mass of pure complex.

c) Determined by chiral GLC analysis.

d) Molar ratio of substrate/NaH = 1/1.

e) Molar ratio of substrate/NaH = 1/5.

f) Molar ratio of substrate/NaH = 1/0.1.

g) Condensation was carried out with pivaloyl aldehyde.

h) Molar ratio of substrate/catalyst = 1 : 1.

i) Reaction temperature 40 °C.

Thus, for the synthesis of β-hydroxy-α-amino acids using an achiral Ni^{II} substrate **65a**, it is necessary to use stoichiometric amounts of catalyst **34a**, while the maximum enantioselectivity reaches 42%. Consequently, the most effective approach for the preparative production of optically active β-hydroxy-α-amino acids is the stoichiometric asymmetric synthesis using chiral auxiliary reagents (see later chapters).

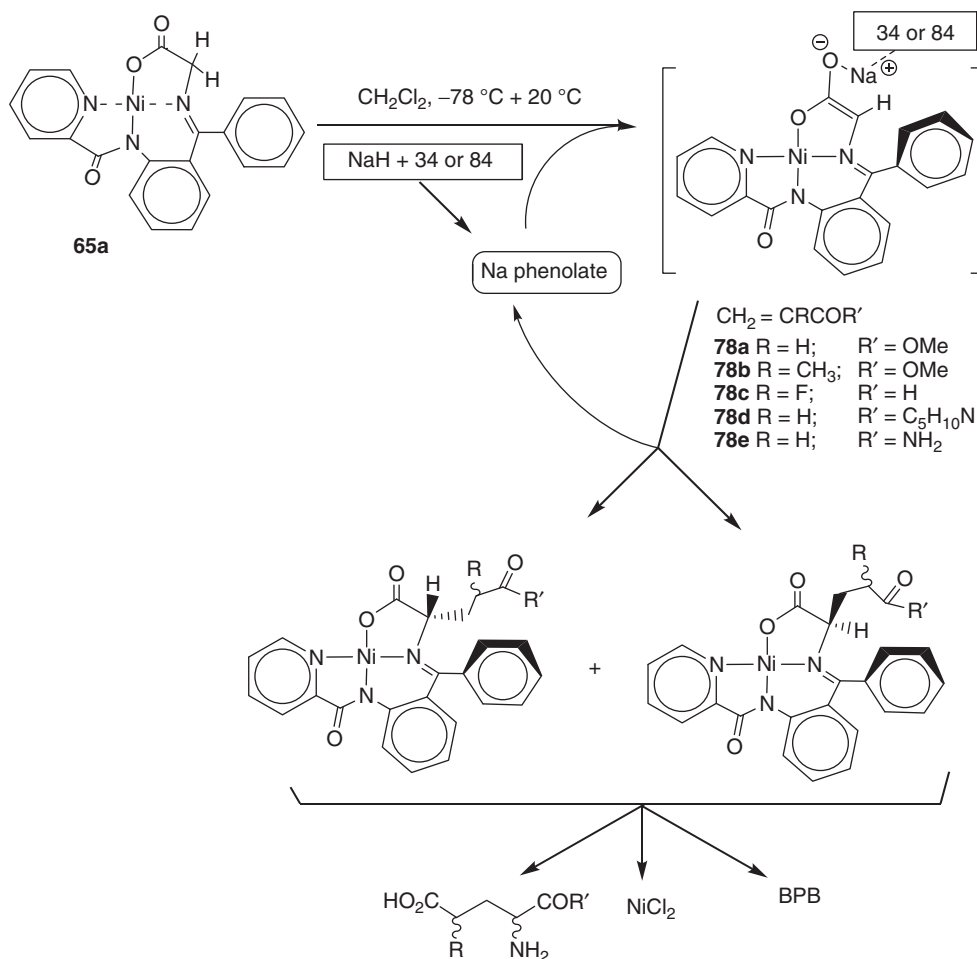
8.1.3.3 The Asymmetric Michael Addition of Achiral Ni^{II} Substrates to Electron-Withdrawing Compounds

As mentioned earlier in the example of synthesis of racemic amino acids, achiral substrate **65a** is ideal for use as donor in Michael reaction. Naturally, the next task is to implement an asymmetric version of this reaction promoted by chiral catalysts for obtaining valuable optically active glutamic acid derivatives.

To investigate the effectiveness of the catalysts, an addition reaction of **65a** to the methyl ester of acrylic acid (**78a**) was chosen as a model reaction, which led to complex **79a** [65]. The Michael addition reaction is shown in Scheme 8.30.

At room temperature in the absence of a catalyst the reaction does not proceed. As shown in the preceding section, the achiral version of this reaction is easily executed by catalysis by β-naphthol in the presence of a base.

Furthermore, Belokon' and coworkers previously showed that the asymmetric version of this reaction could be carried out by catalysis with disodium salt of TADDOL ((*S*)-**33**). However, the maximum enantioselectivity achieved in this



Scheme 8.30

reaction using stoichiometric amounts of catalyst (*S*)-**33** is 45% at 20°C [82, 83]. The authors explain low stereoselectivity by possible racemization of the condensation product due to high basicity of the catalyst.

As a catalyst for Michael reaction spatially more hindered analog of TADDOL containing naphthyl groups was used. Despite high catalytic activity, the final product appeared to be practically racemate.

According to the literature, for effectiveness of the catalyst in Michael reaction in terms of chemical yield and stereoselectivity, a hydroxyl group must be present. Based on this as well as possible racemization of the Michael product when the catalyst's basicity is high, it can be assumed that the use of catalysts, derived from chiral aminobinaphthols, having lower basicity in comparison with **33a** and necessary for catalysis functional groups, can provide high stereoselectivity.

Methylene chloride was selected as a solvent. Various bases were used. The results of addition reaction of substrate **65a** to **78a**, catalyzed by NOBIN **34a** under phase-transfer conditions, are presented in Table 8.10.

The rate of the reaction promoted by 10 mol% of sodium salt of NOBIN **34a** was quite high. After 3 min, the reaction proceeded with 30% yield and ee 26% of adduct (see Table 8.10, No. 1). The nature of a base significantly affects the course of the reaction. The most effective bases are NaH and NaOH, while KOH and *t*-BuOK reduce both enantioselectivity and the chemical yield of the reaction product (see Table 8.10, No. 6–9). When *Dabco* is used, even in a 10-fold excess, the reaction does not take place at all (see Table 8.10, No. 12). Use of a larger amount of sodium hydride dramatically increases the yield of the reaction product without substantial decrease of enantioselectivity of the reaction (see Table 8.10, No. 9).

Rise of temperature facilitates the increase of chemical yield of the product; however, its enantiomeric purity decreases (see Table 8.10, No. 3). Enantioselectivity can be increased to 45% with the use of negative (subzero) temperatures but the yield of the product in this case is insignificant (see Table 8.10, No. 10). The reaction carried out in toluene, which is less polar than CH₂Cl₂, affords Michael addition product in low chemical yield and ee (see Table 8.10, No. 5).

Adding copper salt, which is known to enhance the ee value in many Michael reactions, in this case led to its reduction (see Table 8.10, No. 4).

Catalysis of Michael reaction by (*R*)-NOBIN **34a** results in Michael product of (*S*)-configuration, whereas catalysis of the alkylation reaction of substrate **65a** with alkylhalides promoted by a catalyst of the same configuration affords the

Table 8.10 The results of the Michael addition of **65a** to methacrylate, promoted with 10 mol% of (*R*)-**34a** in CH₂Cl₂ in the presence of 10 mol% of a base.^{a)}

No.	<i>T</i> (°C)	Time (min)	Base (equiv.)	Yield 79a (%)	ee (%)
1	18	3	NaH	30	(<i>S</i>) 26
2	–5	15	NaH	15	(<i>S</i>) 33
3	40	1	NaH	55	(<i>S</i>) 10
4 ^{b)}	18	3	NaH	40	(<i>S</i>) 7
5 ^{c)}	18	24 h	NaH	15	(<i>S</i>) 4
6	18	30	NaOH	40	(<i>S</i>) 7
7	18	25	KOH	50	(<i>S</i>) 8
8	18	45	<i>t</i> -BuOK	30	0
9 ^{d)}	18	3	NaH	78	(<i>S</i>) 24
10 ^{d)}	–78	10 h	NaH	5	(<i>S</i>) 45
11 ^{d)}	18	3	NaOH	60	(<i>S</i>) 22
12 ^{e)}	18	1.5 h	<i>Dabco</i>	—	—

a) Substrate concentration 0.07–0.1 M.

b) Reaction was carried out by adding 0.1 equiv. of Cu(OAc)₂.

c) Solvent – toluene.

d) 1 equiv. of base was used.

e) Ratio of **65a**/*Dabco* = 1/10.

alkylation product of (*R*)-configuration. In addition, as noted in the previous section, in alkylation reaction catalyzed by acylated NOBIN derivatives the configuration of the final amino acid converses, that is, (*R*)-catalyst produces (*S*)-product, as in the case of the Michael reaction.

It can be assumed that the catalyst containing an extra chelating group, acyl substituent, can prove to be more effective in Michael reaction than unsubstituted NOBIN. A number of acylated derivatives were synthesized from unsubstituted NOBIN (see Figure 8.17, **34a–i**). Results of addition of **65a** to methacrylate **78a** Table 8.11.

As expected, the stereodifferentiating ability of (*R*)-*N*-acetyl-NOBIN **34g** in the Michael reaction appeared to be twice higher as compared with the unsubstituted catalyst. Michael reaction catalyzed by **34g** proceeds in 4 min in a chemical yield of 71 and 56% of ee (see Table 8.11, No. 4). Use of an equimolar amount of NaH, and subzero temperatures did not lead to the increase of the reaction enantioselectivity. Conducting the reaction in the presence of *t*-BuOK did not cause any significant changes in ee and yield of the product and use of *t*-BuLi as a base resulted in racemate (see Table 8.11, No. 6, 7).

In catalysis with BOC-derivative of NOBIN **34i**, the tendency to ee increase in comparison with unsubstituted NOBIN preserved, but its efficacy was lower than in the case of **34g** (see Table 8.11, No. 10). To achieve maximum ee value, this catalyst requires the use of 2 equiv. of base *s* compared with the substrate, since its molecule contains two hydroxyl groups (see Table 8.11, No. 12).

Table 8.11 Results of the asymmetric Michael addition of substrate **65a** to methacrylate promoted by 10 mol% of NOBIN derivatives in CH₂Cl₂ at room temperature.^{a)}

No.	Time (min)	Base ^{b)}	Catalyst	Product yield ^{c)} (%)	ee Glu ^{d)} (%)
1	3	NaH	(<i>S</i>)- 34d	70	(<i>S</i>) 8
2	3	NaH	(<i>S</i>)- 34e	67	(<i>S</i>) 11
3	6	NaH	(<i>R</i>)- 34f	65	(<i>R</i>) 2%
4	4	NaH	(<i>R</i>)- 34g	71	(<i>S</i>) 56
5 ^{e)}	12	NaH	(<i>R</i>)- 34g	22	(<i>S</i>) 55
6	4	<i>t</i> -BuOK	(<i>R</i>)- 34g	60	(<i>S</i>) 42
7	4	<i>t</i> BuLi	(<i>R</i>)- 34g	55	0
8 ^{f)}	5 h	NaOH	(<i>R</i>)- 34g	10	(<i>S</i>) 49
9	15	NaH	(<i>R</i>)- 34h	30	0
10 ^{g)}	2	NaH	(<i>R</i>)- 34i	72	(<i>S</i>) 32
11 ^{g)}	8	NaH	(<i>R</i>)- 34k	22	(<i>S</i>) 49
12 ^{g)}	8	NaH ^{h)}	(<i>R</i>)- 34k	13	(<i>S</i>) 56

a) Substrate concentration 0.07–0.01 M.

b) Ratio of **65a**/base = 1/1.

c) Yield determined by weight of pure complex.

d) Determined by enantiomeric GLC analysis.

e) Ratio of **65a**/base = 1/0.1.

f) Reaction temperature –45 °C.

g) 15 mol% catalyst was used.

h) 2 equiv. NaH was used.

The result of introducing electron-withdrawing substituents into NOBIN amino group, particularly in the case of trifluoroacetyl NOBIN derivative **34h** is inhibition of the catalytic and stereodifferentiating ability of the catalyst (see Table 8.11, No. 9.) Alkylated NOBIN derivatives **34d,e** despite high catalytic activity in Michael reaction, lead to a racemic product (see Table 8.11, No. 1, 2).

Using NOBIN derivative **34k** as a catalyst (see Figure 8.20) in Michael reaction provided enantioselectivity within 49–56% (see Table 8.11, No. 11, 12).

When searching for an optimal catalyst structure to improve the enantioselectivity in Michael reaction, it was discovered that (*R*)-*iso*-NOBIN **84a**, an isomer of NOBIN, provides a high chemical yield in some minutes but ee of the product is kept at the level of 13% (see Table 8.12, No. 1).

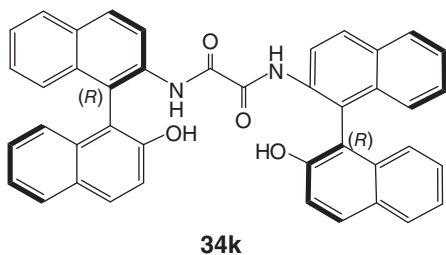


Figure 8.20 The structure of catalyst **34k**.

Table 8.12 Results of addition of **65a** to methacrylate promoted by derivatives of *iso*-NOBIN in CH₂Cl₂ at room temperature in the presence of 100 mol% NaH.^{a)}

No.	Time (min)	Catalyst (%)	Yield 79a (%) ^{b)}	ee Glu (%) ^{c)}
1	3	(<i>R</i>)- 84a	50	(<i>S</i>) 13
2	4	(<i>R</i>)- 84b	86	(<i>S</i>) 94
3	20	(<i>R</i>)- 84b	96	(<i>S</i>) 84
4	60	(<i>R</i>)- 84b	96	(<i>S</i>) 67.8
5 ^{d)}	4	(<i>R</i>)- 84b	80	(<i>S</i>) 94
6 ^{e)}	4	(<i>R</i>)- 84b	81	(<i>S</i>) 90
7 ^{f)}	5	(<i>R</i>)- 84b	62	(<i>S</i>) 72
8 ^{g)}	1	(<i>R</i>)- 84b	85	(<i>S</i>) 77
9	3	(<i>S</i>)- 84c	84	(<i>R</i>) 90
10	4	(<i>S</i>)- 84d	81	(<i>R</i>) 96
11	4	(<i>S</i>)- 84e	86	(<i>R</i>) 88
12	3	(<i>R</i>)- 84g	88	(<i>S</i>) 84
13	40	(<i>S</i>)- 84f	75	(<i>R</i>) 8
14	2.5	(<i>S</i>)- 84h	75	(<i>S</i>) 13

a) Substrate concentration 0.07–0.01 M.

b) Yield determined by weight of pure complex.

c) Determined by chiral GLC analysis.

d) Quantity of substrate **65a** 2 g.

e) Used catalyst was regenerated from No. 5.

f) 5 mol% of catalyst was used.

g) Reaction conducted in C₂H₄Cl₂ at 70 °C.

Despite the low stereoselectivity of *iso*-NOBIN **84a** catalysis, its acyl derivatives proved to be highly effective catalysts for Michael reaction, providing high enantiomeric purity of the final glutamic acid (see Table 8.12, No. 2, 9–12). Thus, *N*-acetyl-*iso*-NOBIN **84b** catalyzes the Michael reaction with 94% ee, providing a quantitative chemical yield in only 4 min at room temperature (see Table 8.12, No. 2). With scaling up, namely by carrying out the reaction with 2 g of **65a** similar values of the chemical yield and ee of the product were observed. Moreover, this catalyst can be recovered in 70% yield and reused practically without loss of activity (see Table 8.12, No. 5, 6).

On reducing the amount of the catalyst from 10–15 to 5 mol%, the reaction enantioselectivity and yield reduce (see Table 8.12, No. 7). By increasing the duration of the reaction catalyzed by **84b** from 4 to 20 and 60 min, there is a gradual reduction in an enantiomeric purity from 94% to 84% and 68%, respectively (see Table 8.12, No. 2–4). This is due to the racemization of the product under basic conditions. However, there is no need to carry out the reaction for such a long time since already in 4 min practically maximum conversion is achieved. Conducting the reaction in dichloroethane at 70 °C, in spite of very high reaction rate, negatively affects enantioselectivity of the reaction, since the value of ee falls from 94% to 77% (see Table 8.12, No. 8).

In a series of NOBIN acyl derivatives, the stereoselectivity of Michael reaction significantly depends on the amount of acyl substituent. With the increase of the substituent amount, the enantioselectivity of the reaction increases. The best phase-transfer catalyst of the Michael reaction is pivaloyl derivative of *iso*-NOBIN **84d**, promoting reaction in high chemical yield and 96% ee of amino acid only within 4 min at room temperature. This is a solution of the problem of fast synthesis of enantiomerically pure amino acids for positron emission tomography (see Table 8.12, No. 9–11). Later, it was found that catalysis with more bulky adamantyl derivative of *iso*-NOBIN **84g** decreased the enantioselectivity of the reaction to 84% (see Table 8.12, No. 12).

Introduction of tosyl substituent into the amino group of *iso*-NOBIN leads to a sharp fall in stereoselectivity of the reaction, ensuring only a 70% yield and 8% ee in 40 min (see Table 8.12, No. 13). In Michael reaction with substrate **65a** along with methacrylate, other electron-deficient compounds were involved leading to a wide range of valuable amino acids with high enantiomeric purity (see Figure 10.1). The results of Michael reaction with other acceptors catalyzed by acyl derivatives of *iso*-NOBIN in the presence of a base are shown in Table 8.13.

The reaction of substrate **65a** with methyl methacrylate **78b**, catalyzed by (*R*)-*N*-acetyl-*iso*-NOBIN **84b**, runs for 9–10 min with the formation of two diastereomers in a ratio of (*S,R*)/(*S,S*) = 7/1 and 81%/66% ee (see Table 8.13, No. 1). Similar results are obtained when the same reaction is catalyzed with **84d**. The ratio of diastereomers formed by the reaction of fluorine analog of acrylic ester **78c** with substrate **65a**, catalyzed by **84b**, was found to be 1.5/1. In contrast to the previous reaction, in this case the predominant diastereomer has (*S,S*)-configuration with 85% ee (see Table 8.13 No. 2). The use of acrylamide **78e** under the same conditions leads to low values in both chemical yield and ee of the final product (see

Table 8.13 Results of asymmetric 1,4-addition reaction of **65a** to various Michael acceptors catalyzed by 15 mol% of the acyl derivatives of *iso*-NOBIN in CH₂Cl₂ in the presence of 1 equiv. of NaH.^{a)}

No.	Michael acceptor	Catalyst (%)	Time (min)	Yield 79 (%) ^{b)}	ee amino acid (%) ^{c)}
1	78b	(<i>R</i>)- 84b	10	60	61 ^{d)}
2 ^{e)}	78c	(<i>R</i>)- 84b	10	15	85
3 ^{f)}	78e	(<i>R</i>)- 84b	5	85	(<i>S</i>) 7
4 ^{f)}	78d	(<i>R</i>)- 84b	3	70	(<i>S</i>) 80
5 ^{f)}	78d	(<i>R</i>)- 84d	3	90	(<i>S</i>) 86
6 ^{f)}	78d	(<i>R</i>)- 84g	3	85	(<i>S</i>) 75
7 ^{g)}	78a	(<i>R</i>)- 84b	240	10	(<i>S</i>) 31.4
8	78a	(<i>R</i>)- 84b	3	50	(<i>S</i>) 39
9 ^{h)} i)	78a	(<i>R</i>)- 84b	3	17	(<i>S</i>) 88

a) Substrate concentration 0.12 M, room temperature, under Ar.

b) Yield determined by weight of product.

c) Analysis by enantiomeric GLC.

d) Ratio of diastereoisomers (*S,R*)/(*SS*) = 7/1.

e) Ratio of diastereoisomers (*SS*)/(*S,R*) = 1.5/1.

f) Used 10 mol% catalyst and 10 equiv. NaOH instead of NaH.

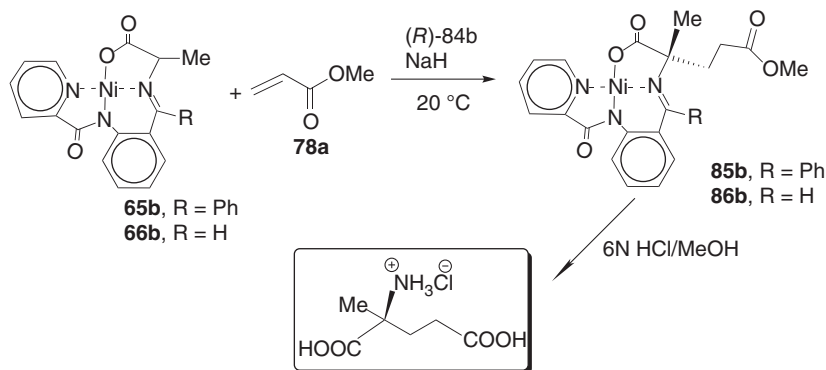
g) Substrate **65b** was used.

h) Substrate **66b** was used.

i) Reaction conducted in toluene.

Table 8.13, No. 3). The transition from acrylamide to acrylic acid piperidide in the same reaction provides high yield and high ee values (Table 8.13, No. 4–6).

Under standard conditions, the addition reaction of methacrylate **78a** to alanine substrate **65b** (see Scheme 8.31) proceeds rather slow with low stereoselectivity, providing a 10% yield and 31% ee within 4 h (see Table 8.13 No. 7). In addition to this, the use of sterically less loaded alanine substrate **66b** in this reaction made it possible to considerably accelerate the reaction, but the stereoselectivity was low again, which seems to be due to racemization (Table 8.13, No. 8). In order to



Scheme 8.31

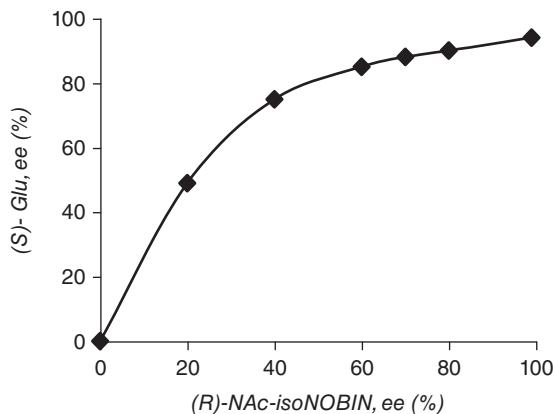


Figure 8.21 (+)-NLE in the Michael addition reaction of methacrylate to **65a** catalyzed by **84b**.

slow down the process of racemization, the reaction was carried out in a less polar toluene. The product was obtained with 88% ee (see Table 8.13, No. 9); however, the chemical yield was quite low, while increasing the reaction time reduced the enantioselectivity.

When studying the dependence of enantiomeric purity of the Michael²⁾ reaction product on enantiomeric purity of catalyst **84b**, a significant (+)-NLE was detected, which gives a possibility to use the catalyst without further purification (see Figure 8.21). The catalyst and an achiral ligand can be regenerated in a 70% chemical yield and used repeatedly without loss of activity, which makes the reaction more economical and suitable for large-scale synthesis.

Initial Ni^{II} complex **65a** is poorly soluble in almost all organic solvents, except for CH₂Cl₂. The concentration of a saturated solution of the complex therein is 8.8×10^{-3} M. It was found that during the reaction, when **65a** was added to the solution of sodium salt of (*R*)-NOBIN **34a** in CH₂Cl₂, its solubility, before adding the alkylating agent or Michael acceptor, increased considerably. This increase in the solubility of the substrate is easily observed visually because the color of the reaction mixture changes from light red to dark red to the extent of complex dissolution.

To quantify the degree of solubility of **65a**, UV spectroscopy method was used. Considering the volatility of methylene chloride, UV measurements were performed in dichloroethane, in which the concentration of a saturated solution was 2.37×10^{-3} M. The results of the UV measurements are as follows:

- 1) Increase in solubility of **65a** in the presence of (*R*)-NOBIN without adding a base is insignificant;
- 2) In the presence of NaH in equimolar quantity with (*R*)-NOBIN, the solubility of the complex increases significantly and has the form shown in Figure 8.22a
- 2) The addition reaction of substrate **65a** to the methyl ester of acrylic acid catalyzed by enantiomerically enriched **84b**.

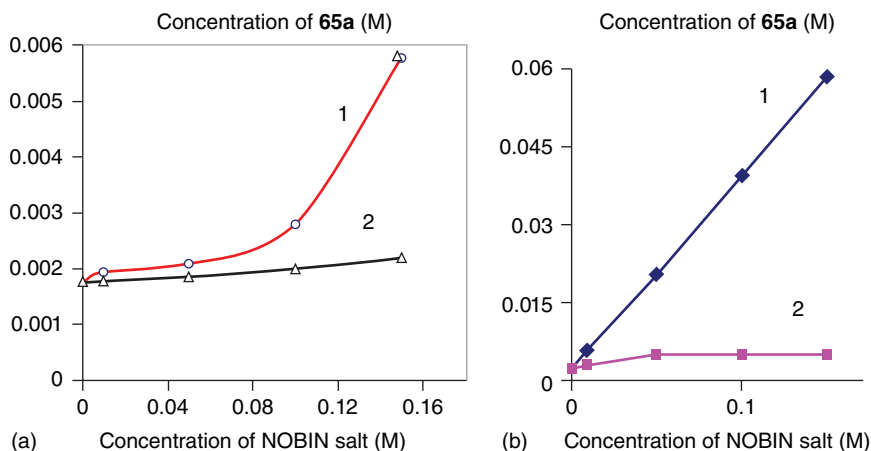


Figure 8.22 The solubility of substrate **65a** in 1,2-dichloroethane as a function of concentrations of sodium salts of (*R*)-NOBIN (curve 1) and (*R,S*)-NOBIN (curve 2) in the ratio of NOBIN/NaOH = 1/1 (a) and ratio of NOBIN/NaH = 1/100 (b).

- (curve 1). For the sodium salt of racemic (*R,S*)-NOBIN, increase in solubility is practically absent and the dependence curve substantially is a straight line (see Figure 8.22a, curve 2);
- 3) A sharp increase in solubility of **65a** is observed at a ratio of (*R*)-NOBIN/NaH = 1/100 (which corresponds to alkylation reaction conditions). Graphically, the dependence of the complex solubility on the catalyst, adjusted by the method of least squares, is a straight line (see Figure 8.22b). And in the case of the racemic catalyst at a ratio of (*R,S*)-NOBIN/NaH = 1 : 100 increase in solubility of the substrate **65a** is insignificant (see Figure 8.22b).

The difference in solubility of **65a** in the presence of sodium salts of racemic and enantiomerically pure NOBIN is consistent with the presence of a (+)-NLE in alkylation and Michael reactions, as mentioned earlier. Presence of (+)-NLE indicates that ionized aminophenolate of racemic NOBIN, probably forms heterochiral aggregates with lower reactivity than the homochiral aggregate or monomeric mixture. Herewith, the heterochiral unit is more stable than the homochiral particle and as a result, homochiral monomer remains in a solution, simultaneously dissolving the substrate. The following observation is made in support of this theory: the sodium salt of enantiomerically pure NOBIN is well soluble in CH_2Cl_2 , but with a decrease of enantiomeric purity its solubility decreases.

Thus, the differences between the solubility curves obtained for the sodium salts of enantiopure and racemic NOBIN are related to greater self-association of racemic NOBIN. This amplification effect refers to the effect of the tank according to the terminology proposed by professor Kagan.

IR spectroscopy method was used to investigate the processes occurring when complex **65a** and sodium salt of (*R*)-NOBIN were mixed in dichloroethane in different ratios.

Preliminarily IR spectra of (*R*)-NOBIN solution **34a** in CCl_4 were taken, where the absorption band characteristic of the hydroxyl group was observed in the region of 3527 cm^{-1} (in β -naphthol it is in lower frequencies, at 81 cm^{-1}) and those of the amino group were observed at 3482 and 3394 cm^{-1} regions that are identical to amino group frequencies of β -naphthylamine.

With a threefold decrease in the concentration of **34a**, no signal in the region of higher frequencies was observed that could indicate the appearance of a free hydroxy group. Shift of the hydroxy group signal to a lower frequency region and absence of concentration dependence indicate the inclusion of OH-group in intramolecular hydrogen bond. It can be assumed that the OH-group of **34a** forms a hydrogen bond with the π -system of the neighboring naphthyl group [84].

IR spectroscopy data of the sodium salt **34a** in dichloromethane indicate the presence of association by coordinating the amino group with Na cation. Two absorption bands characterizing amino group of the catalyst appear at 3406 and 3324 cm^{-1} , which, compared with frequencies of free **34a**, are lower by 42 and 63 cm^{-1} , respectively.

IR spectrum obtained for Ni^{II} complex **34a** in the region characteristic of the CO group has two signals: the band at 1645 cm^{-1} is characteristic of amide I, the second band at 1675 cm^{-1} is characteristic of ν_{as} carboxyl group and ν_{s} is at 1329 cm^{-1} . The difference between asymmetric and symmetric vibrations is 349 cm^{-1} , which is typical of monodentate coordination of ionized carboxyl group with metal cations [85–87].

The results of IR spectra of the mixture of substrate **34a** and free NOBIN in dichloroethane and methylene chloride in various ratios of substrate to the catalyst, confirmed that there were no strongly expressed interactions between them.

IR spectra of mixtures of sodium salt **34a** and substrate **65a** in dichloroethane in ratios of 1/1 and 3/1 were compared with the spectra of the starting reagents obtained in the same solvent. At the same time the occurring changes associated with some frequency shifts were clearly visible. With increasing concentration of sodium salt NOBIN **34a** relative to substrate **65a**, a gradual shift of the carboxyl group frequencies to higher frequencies was observed.

All the changes in IR spectra are reversible. When equimolar amount of weak acid (relative to the sodium salt of NOBIN) is added to the studied mixtures, a reverse recovery of carboxyl group frequencies is observed. Thus, summing up the results of IR experiments, we can draw the following conclusions:

- 1) There is no interaction between the NH_2 group of the sodium salt NOBIN and substrate **65a**.
- 2) In the presence of sodium salt NOBIN, the frequency of the carboxyl group (ν_{as}) decreases. Since the absorption bands of the solvent and the NOBIN salt cover (overlap) a fairly large portion of the spectrum, determining the position of the new band is a difficult task.
- 3) Frequency retention of CH_2 group of the substrate at 2927 and 2855 cm^{-1} indicates the absence of any interaction between the CH_2 group and sodium salt of NOBIN **34a**.

Mixtures with different ratios of **65a** and sodium salt **34a** in CD₂Cl₂ were studied by NMR. The vials with samples of 1/1 and 1/3 were prepared immediately before taking the spectra. The spectra of starting complex **65a** and sodium salt **34a** were taken in the same solvent for comparison. In the spectrum of 1/1 mixture, almost all protons of the catalyst were significantly shifted to the weak field and broadening of all the signals corresponding to the complex and NOBIN sodium salt was observed. In the spectrum of 1/3 mixture, all the changes were more pronounced.

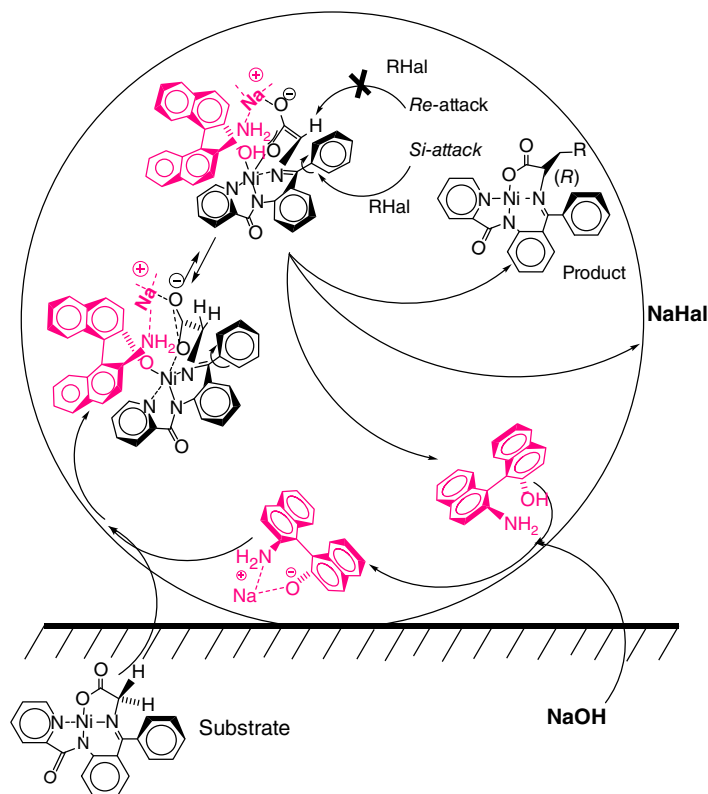
NMR spectra of mixtures of substrate **65a** with sodium salt of *N*-acetyl-NOBIN **34g** (in the ratios of 1/1, 1/3) were also taken. They also showed a similar effect of broadening of the proton signals, including their shift. However, all of the observed phenomena, as distinct from the previous case, were expressed more weakly.

These results along with the data of X-ray analysis (see Figure 8.13) can indicate the formation of a soluble complex of substrate **65a**/(*R*)-NOBIN **34a**, possibly by introducing NOBIN sodium salt into the crystal structure of Ni-complex. The catalyst is likely to replace one of the conformers in the dimeric structure of the complex through the formation of weak interactions with it. IR and NMR spectroscopy results show the interaction between the substrate and the catalyst.

Summarizing the results, we can draw some conclusions about the nature of the interaction between the substrate and the catalyst. There are fast reversible interactions between them. In NMR spectrum, the observed shift of signals of aromatic protons of the catalyst to the weak field can be attributed to location of the catalyst above the Ni ion. The broadening of the NMR signals is probably due to fast exchange between some particles, and at the same time, it can be caused by the formation of paramagnetic octahedral mixed nickel complexes with NOBIN sodium salt, which differs from square-planar arrangement of ligands around Ni ion in the initial complex.

According to IR spectroscopy, the amino group of the catalyst is not included in any coordination. How is the catalyst related then to a nickel substrate? It can be assumed that the ionized oxygen atom of a hydroxy group in coordination sphere of **65a** replaces a carboxyl group, which is thus partially or completely released and forms an ionic bond with the sodium cation with which the observed IR spectra changes may be associated. The function of the amino group of the catalyst is probably stabilization of the formed carbanion by hydrogen bonding in the next reaction step.

The key role of hydrogen bond formation is determined by a sharp drop of the process stereoselectivity when other compounds capable of competitive formation of a hydrogen bond are present in the reaction mixture, for example, the presence of water. Another argument in favor of this hypothesis is the lack of asymmetric induction in the Michael reaction when acrylamide is used as an acceptor that can form a hydrogen bond competitively with a catalyst. However, when the amino group of acrylamide is substituted by piperidyl moiety thus excluding the possibility of hydrogen bond formation, the enantioselectivity of the reaction makes up 86%. The most probable mechanism of the reaction is



Scheme 8.32

presented in Scheme 8.32. The reaction involves the formation of aminonaphtholate of NOBIN (or phenolate of β -naphthol, which is also an effective catalyst for this reaction) on the surface of solid NaOH.

Then, the sodium salt of the catalyst is coordinated with the insoluble nickel substrate and converts it to a solution of CH_2Cl_2 . The next step involves deprotonation of complex **65a** with the formation of an ion pair comprising a molecule of the catalyst, after which an alkyl halide attack takes place. The intermediate structure described here should ensure high stereodifferentiation at the stage of alkyl halide attack because the *re*-side is covered with the catalyst and the phenyl ring, and the attack can only take place from an uncovered *si*-side. In this case, the catalyst with (*S*)-configuration should provide the final product of (*S*)-configuration, which in fact is observed.

The stereochemistry and mechanism of the Michael reaction differ significantly from those of the alkylation reaction. Considering that the $\text{p}K_{\text{a}}$ of the substrate in DMSO is 18–19 and that of acetic ester is about 30, formation of the γ -carbanion intermediate, which would be stabilized only by the carbomethoxy group of the acrylic moiety is unlikely. Apparently, it is essential that the formation of the C–C

bond and protonation of the formed carbanion by the catalyst occur simultaneously. In such a case, the protonation of the carbanion will be implemented most effectively only if the attack of methacrylate happens from the side of coordination of chiral catalyst with Ni^{II} complex, where the OH-group is present. With this, there might be a difference in configurations of products derived from alkylation and Michael reactions catalyzed with chiral aminobinaphthols **34a** and **84a** of the same configuration.

The catalytic activity of *N*-acyl derivatives of NOBIN **34f–h** in alkylation reaction is almost negligible. On the other hand, *N*-acyl derivatives of *iso*-NOBIN **84b–e** and **84g** are highly efficient catalysts for the Michael reaction and provide a product of the same configuration in both Michael reaction and alkylation reaction. Apparently, the carbonyl group of the acyl moiety of these catalysts is also involved in the chelation of either Na or Ni atoms, and thus further contributes to the enantiodifferentiation process. The sharp decrease in catalytic activity during the introduction of electron-withdrawing substituents into the catalyst molecule could be due to this, resulting in the reduction of the value of the negative charge localized on the oxygen atom of the carbonyl group, which consequently reduces the effectiveness of chelation.

However, many details of the mechanism of the described processes remain unclear, and their identification is a task for the nearest future.

8.1.3.4 Catalytic Asymmetric Addition of Nucleophiles to an Achiral Dehydroalanine Substrate

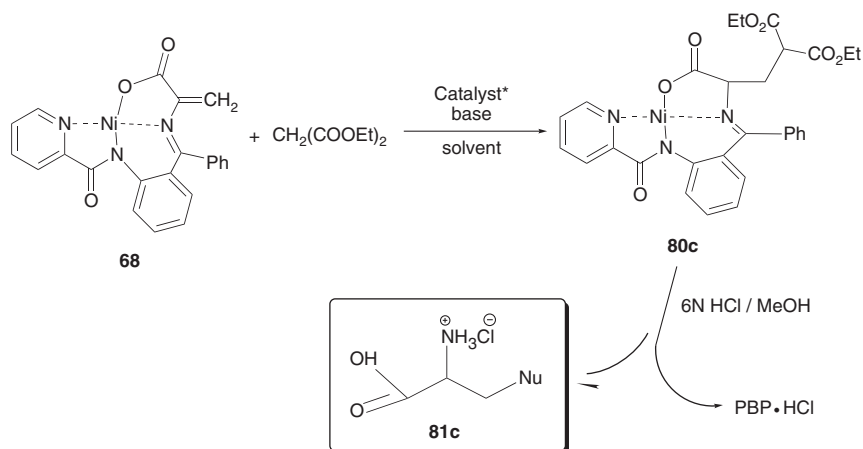
As it was shown in the previous sections, the achiral dehydroalanineNi^{II} complex **68** is an excellent substrate for the synthesis of a series of β -substituted α -amino acids. Naturally, the urgent task was the implementation of catalytic asymmetric Michael reaction using substrate **68**.

One of the possibilities to perform the reaction stereoselectively is the asymmetric catalytic protonation of the intermediate carbanion. Only a few examples are described in the literature with asymmetric catalytic formation of the C–H bond in the Michael reaction without the step of enantioselective formation of the C–C bond.

In this section, reactions exactly of this type are described [65, 88]. The 1,4-addition reaction of diethyl malonate to substrate **68** in PTC promoted by chiral chelating catalysts was selected as a model system (see Scheme 8.33).

As already noted, without the catalyst in the presence of a base the coupling reaction of the malonic ester to substrate **68** proceeds quite fast in a quantitative chemical yield. Derivatives of chiral aminobinaphthols and diols were used as PTC catalysts at 10 mol% concentration (see Figures 8.16 and 8.17).

As distinct from the previous Michael reaction with substrate **65a**, in this case asymmetric induction catalyzed by both sodium and potassium salts of (*R*)-NOBIN **34a** was less than 12%. Similar situation was observed with the use of derivatives of (*R*)-*iso*-NOBIN. Chiral quaternary ammonium salt based on cinchonidine **83** (see Figure 8.16) also proved to be ineffective in this reaction.



Scheme 8.33

At the same time, the reaction conducted in methylene chloride in the presence of 20 mol% of *t*-BuOK promoted by 10 mol% of chiral diol TADDOL **33a** (see Figure 8.16) was complete at room temperature in 4 min in high chemical yield and 36% ee of the final product.

The stereoselectivity of this reaction substantially depends on the type of the base used, its amount, and nature of the solvent. The results are shown in Table 8.14. The maximum value of asymmetric induction in methylene chloride was achieved for potassium cation and equaled to 36% (see Table 8.14, No. 5).

Sodium and lithium salts of TADDOL turned out ineffective catalysts of Michael reaction (see Table 8.14, No. 1–4). From the asymmetric induction

Table 8.14 Results of 1,4-addition reaction of substrate **68** to the $\text{CH}_2(\text{CO}_2\text{Et})_2$ promoted by (*R,R*)-TADDOL **33a** in the presence of a base.^{a),b)}

No.	Solvent	Base (0.2 equiv.)	<i>T</i> (°C)	Time (min)	Yield 80c (%) ^{c)}	ee (<i>S</i>)- 81c (%) ^{d)}
1	CH_2Cl_2	NaH	20	4	79	12
2	CH_2Cl_2	NaH	40	4	88	15
3	CH_2Cl_2	NaH	–20	5	35	12
4	CH_2Cl_2	<i>t</i> -BuLi	20	4	82	9
5	CH_2Cl_2	<i>t</i> -BuOK	20	4	82	36
6	Hexane	<i>t</i> -BuOK	20	30	8	0
7	Toluene	NaH	20	30	30	21
9	Toluene	<i>t</i> -BuOK	20	5	15	54
10	Toluene	KOH	20	5	17	54
11	Toluene	NaOH	20	5	20	29

a) Substrate concentration 0.115 M; 10 mol% **33a**.

b) Used 4 equiv. of $\text{CH}_2(\text{CO}_2\text{Et})_2$.

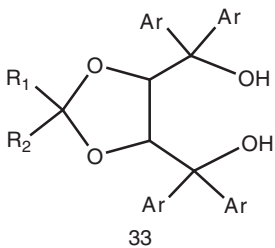
c) Yield determined by weight of **81c**.

d) Determined by chiral GLC analysis.

viewpoint, the optimal solvent is toluene, wherein the reaction catalyzed by potassium salt of TADDOL proceeds with 54% enantioselectivity (Table 8.14, No. 9, 10). In hexane, the reaction proceeds giving a racemic mixture (Table 8.14, No. 6).

The dependence of stereoselectivity of 1,4-addition reaction of substrate **68** to the malonic ester on the structure of a catalyst was investigated under optimum conditions. A great variety of TADDOL derivatives were used as catalysts (see Table 8.15).

Table 8.15 The addition reaction of substrate^{a)} **68** to CH₂(COOEt)₂ in toluene, catalyzed by derivatives of TADDOL **33a–s** in the presence of 2 equiv. of *t*-BuOK.

No.			R ₁	R ₂	Ar	Yield 80c (%) ^{b)}	ee (S)-81c (%) ^{c)}
1	A		Me	Me	Ph	18	54
2	B		Me	Me	Ph	28	19
3	C		Me	Me	Ph	25	13
4	D		Me	Me	Ph	25	19
5	E		Me	Me	Ph	30	25
6	F		Me	Me	Ph	26	18
7	G		Me	Me	Ph	31	22
8	h [*] OEt ₂		Me	Me	Ph	11	15
9	i [*] MeOH		Me	Me	Naphthyl-1	30	75
10	J		Me	Me	Naphthyl-2	32	35
11	K		Ph	Ph	Ph	30	44
12	L		Ph	H	Ph	34	34
13	M		<i>p</i> -BrPh	H	Ph	28	18
14	N		<i>p</i> -BrPh	H	Ph	28	9
15	O		<i>p</i> -BrPh	H	Ph	16	18
16	P		Naphthyl-1	H	Ph	31	30
17	Q		<i>t</i> Bu	H	Ph	33	37
18	R		<i>t</i> Bu	H	Naphthyl-1	30	56–62
19	S		–(CH ₂) ₅ –	H	Ph	30	50
20	T		–(CH ₂) ₅ –	H	Naphthyl-1	29	62
21 ^{d)}	U		Me	Me	Ar	90	0
22 ^{e)}	V		Me	Me	C ₆ F ₅	54	(R)-41

a) Reaction conditions: solvent-toluene, substrate **68** concentration 0.115 M, ratio of CH₂(COOEt)₂/**68** = 4/1, **33**/**68** = 1/10, *t*-BuOK/**33** = 2/1, RT, time 15 min, under Ar.

b) Yield was determined after separation from unreacted starting complex **68**.

c) Determined by enantiomeric GLC analysis.

d) Reaction was performed at 70 °C for 4 min.

e) Reaction was conducted at 70 °C for 15 min in the ratio of CH₂(COOEt)₂/**68**/**33**/*t*BuOK = 4/1/0.05/1.2.

Substitution of hydroxy groups in a molecule of TADDOL **33a** with chlorine atom, SH-, NHCOCF_3 -, or NH-group leads to a significant reduction in the stereodifferentiating ability of TADDOL (see Table 8.15, No. 1–6, 8). When a dual structure of TADDOL **33g**, obtained from the dibromo-*m*-xylene, was used as a catalyst for the addition reaction of **68** to malonate, the stereoselectivity of the reaction was 22% (see Table 8.15, No. 7). It should be noted that even under the catalysis by TADDOL derivative **33f** in which both hydroxy groups are replaced by chlorine atoms, some asymmetric induction is still observed (see Table 8.15, No. 6).

Structure of a protective group of TADDOL also influences the degree of asymmetric induction. Thus, catalysts **33k**, **33l**, **33q**, and **33s** provide average values of enantioselectivity within the range of 34–50% (see Table 8.15, No. 11, 12, 17, 18). Use of TADDOL derivatives as catalysts, in which the protective group contains a bromosubstituted aryl moiety (**33m**, **33n**, **33o**), leads to a greater reduction in enantioselectivity of the reaction (see Table 8.15, No. 13–15).

Studying the dependence of reaction stereoselectivity on the nature of aromatic moiety of the catalyst, a sharp difference in the values of enantiomeric purity of the resulting amino acid was observed. So, TADDOL, phenyl groups of which are substituted with naphthyl moiety (**33j**), connected via position 2, is a pretty moderate catalyst for the Michael reaction, providing the maximum value of only 35% ee (see Table 8.15, No. 10).

Compound **33i**, naphthyl moiety of which is attached via position 1, is an excellent catalyst for Michael reaction and provides 75% of the enantiomeric purity of the final product (see Table 8.15, No. 9). The reason for this difference in ee in transition from β -naphthyl TADDOL to TADDOL with phenyl groups and further to the α -naphthyl TADDOL can be due to a large spatial load at the proton of OH group, which can play a specific role in stereocontrol in proton transfer during the protonation process. When (*R,R*)-TADDOL derivatives are used in this reaction similar to the Michael reaction catalyzed by (*R*)-derivatives of NOBIN, described in the previous section, the amino acid of (*S*)-configuration is formed.

At the same time, complete fluorination of aromatic rings of TADDOL **33v** reverses the stereochemical direction of the reaction affording an amino acid of (*R*)-configuration induced by (*R*)-catalyst (see Table 8.15, No. 22). Furthermore, fluorinated TADDOL, unlike other catalysts, requires greater amount of the base, which appears to be related to the possible substitution of the fluorine atoms in the reaction by *t*-butanol molecule. In the catalysis of Michael reaction with CF_3 -substituted TADDOL **33u**, the reaction rate increases dramatically as compared with the rest of the catalysts but the product is obtained as a racemate (see Table 8.15, No. 21).

After screening the whole series of catalysts to determine the optimal structure for the implementation of highly stereoselective Michael reaction, a derivative of TADDOL with α -naphthyl moieties **33i** was revealed, OH groups of which were not substituted (see Table 8.15 No. 9). For this reason, the reaction conditions were further optimized specifically for this catalyst. The results are shown in Table 8.16.

Table 8.16 Reaction of substrate^{a)} **68** with CH₂(COOEt)₂ catalyzed by (*R,R*)-**33i** in toluene.^{a)}

No.	33i (equiv.)	Base (equiv.)	<i>T</i> (°C)	Time (min)	Yield 80c (%) ^{b)}	ee 81c (%)
1	0.1	NaOH (0.2)	20	15	31	32
2	0.1	KOH (0.2)	20	15	31	67
3	0.1	<i>t</i> -BuOK (0.2)	20	15	30	75
4	0.1	<i>t</i> -BuOK(0.1)	20	15	18	65
5	0.4	<i>t</i> -BuOK (0.8)	20	15	44	55
6	0.05	<i>t</i> -BuOK (0.1)	70	4	80	80
7	0.05	50% RbOH (0.1)	70	4	76	52
8	0.05	CsOH·H ₂ O (0.1)	70	4	70	77
9	0.05	<i>t</i> -BuOK (0.1)	70	20	91	55
10	0.05	<i>t</i> -BuOK(0.1)	20	360	48	76

a) Reaction conditions: Substrate **68** concentration is 0.115 M, the ratio of CH₂(COOEt)₂/**68** = 4/1, under Ar.

b) Yield determined after the removal of unreacted complex **68**.

The enantioselectivity and the chemical yield of the reaction depend essentially on the nature and amount of the base used. With increasing amounts of base, chemical reaction yield increases and at the same time stereoselectivity decreases (see Table 8.16, No. 3–5). The best result in terms of stereoselectivity was obtained using 0.2 equiv. of base relative to the catalyst (see Table 8.16, No. 3).

In addition, the stereoselectivity of the reaction increases with increasing the cation size. The lower stereoselectivity of the CsOH·H₂O and 50% aqueous RbOH compared with potassium *tert*-butoxide is possibly associated with the availability of water, which, similar to the catalyst, may participate in the protonation of the intermediate carbanion (see Table 8.16, No. 1–3, 6–8). The optimal ratio of *substrate 68*/catalyst **33i**/base for the best results at room temperature is 1/0.1/0.2.

Despite high value of ee in these conditions (see Table 8.16, No.3), the reaction yield is quite low, and at room temperature it is only 30% in 15 min. To increase the chemical yield, the reaction was carried out at higher temperatures.

Search for suitable temperature and reaction conditions revealed the most optimal parameters for the addition reaction of substrate **68** to malonic ester. Catalysis with 5 mol% dipotassium salt **33i** at 70 °C provides a product in a quantitative yield and 80% ee in 4 min (see Table 8.16, No. 6).

The enantiomeric purity of the final amino acid reaches 90% after a single crystallization at the production step of obtaining the complex (before decomposition).

Catalyst **33i** and optimized conditions were used for the implementation of the Michael reaction with other nucleophiles. The results are presented in Table 8.17.

Acetoacetic ether enters into this reaction forming a product with 30% ee (see Table 8.17, No. 4). Acetyl acetone in these reaction conditions does not react with complex **68**, which is possibly due to the formation of an inactive chelate between nucleophile and base cation (Table 8.17, No. 5). The reaction with thiophenol flows

Table 8.17 The results of substrate **68** attachment to various nucleophiles in toluene at 70 °C, promoted by (R)-**33i**.^{a)}

No.	NuH	80	<i>t</i> -BuOK (equiv.)	Time (min)	Yield 80 (%) ^{b)}	ee 81 (%)
1		c	0.1	4	80	(<i>S</i>)- 80 ^{c)} (90%) ^{d)}
2		k	0.1	4	65	(<i>S</i>)- 70 ^{e)} (70%) ^{d)}
3		l	0.1	4	56 ^{b)}	(<i>S</i>)- 64 ^{e)} (80%) ^{d)}
4		m	0.1	7	75	(<i>S</i>)- 30 ^{e)}
5		n	0.1	60	—	—
6		a	0.1	4	64	0

a) Reaction conditions: toluene, concentration of **68** – 0.115 M, ratio **68**/NuH/**33i**/*t*-BuOK = 1/4/0.05/0.1, 70 °C, Ar.

b) Yield was determined after separation from unreacted starting complex **68**.

c) Determined by chiral GLC.

d) ee value after crystallization of complex **80**.

e) ee value determined by optical rotation.

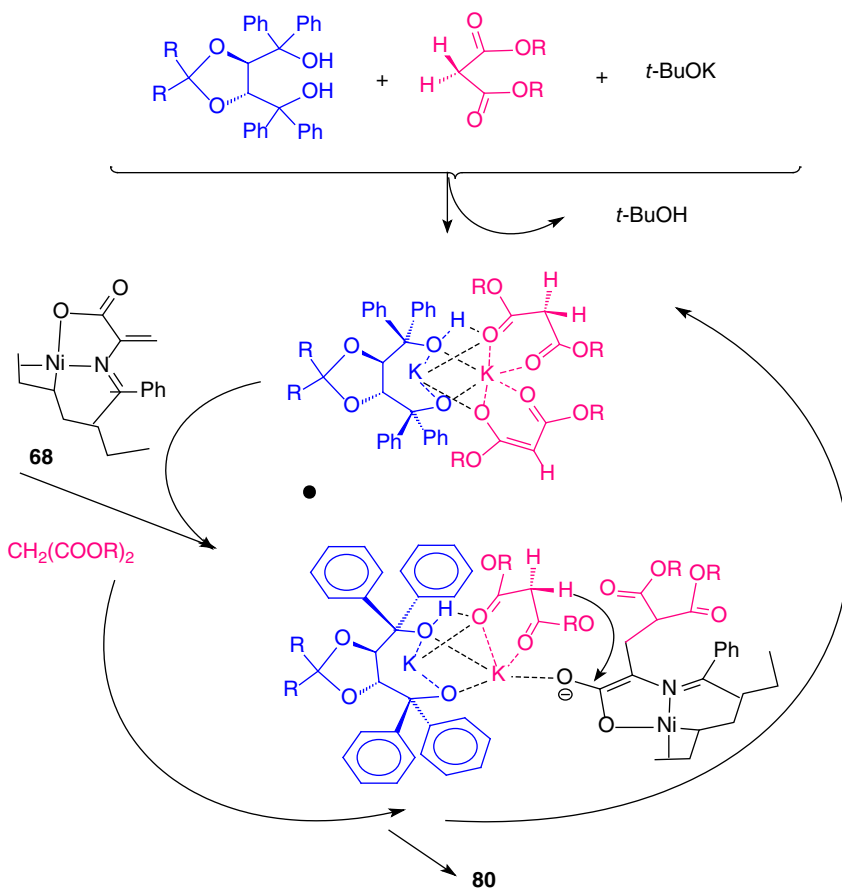
with high chemical yield but without asymmetric induction (see Table 8.17, No. 6). The malonic ester derivatives in respect of both stereoselectivity and yield proved to be the most active nucleophiles (see Table 8.17, No. 1–3).

Since enantioselectivity in the reaction is determined by protonation of intermediate α -carbanion, it follows from the observed results that the true active fraction providing the proton is not the TADDOL, but the nucleophile. If the protonating agent had been the TADDOL, then the stereochemical results would have not been so much dependent on the nature of the nucleophile used. Besides this, the pK_a values of TADDOL in DMSO are supposed to be 28–30, whereas substrate **80** as well as other complexes of similar structure has pK_a values in the range of 17–19 [80].

From this, it is unlikely that TADDOL is a source of proton. Furthermore, compound **33f**, in which hydroxyl groups are substituted by chlorine atoms, also catalyzes a reaction with some asymmetric induction. On the other hand, the malonic ester has a close to complex **80** pK_a value (16.3) and hence it is able to

chelate alkali metal ions, and the presence of enantioselectivity dependence on the size of the cation emphasizes the importance of chelation for the stereoselectivity of the reaction.

The hypothetical mechanism of 1,4-addition reaction of malonic ester to complex **68**, promoted by dipotassium salt of TADDOL, possibly involves the formation of a mixed chelate between TADDOL and malonic ester, providing proton for the intermediate carbanion **80** (see Scheme 8.34).



Scheme 8.34

The function of the TADDOL probably lies in increasing the acidity of the malonic ester by the formation of hydrogen bonds via the hydroxyl groups, thus providing chiral surroundings for detecting prochiral sides of carbanion **80** in proton transfer. Thus, a possibility for the synthesis of optically active derivatives of glutamic acids by catalytic enantioselective protonation in the reaction of Michael addition of nucleophiles to new dehydroalanine substrate promoted

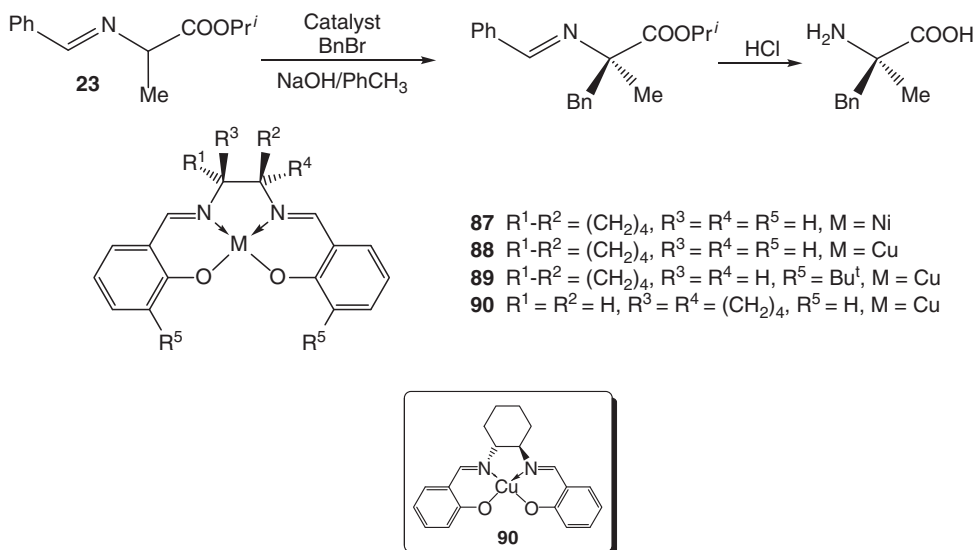
by chelating chiral diol was demonstrated. In addition, this reaction provides a unique example of an effective high asymmetric induction.

8.2

Salen Complexes as Chiral Catalysts for PTC Alkylation

In the field of asymmetric PTC of particular note is the research of Belokon's group wherein transition metal complexes were used as phase-transfer catalysts for the first time [89, 90].

It was shown that Ni^{II} salen complexes, and in particular, those of Cu^{II} , could function as phase-transfer carriers in the reaction of the asymmetric interphase alkylation. As a model reaction, alkylation of substrate **23** by benzyl bromide (substrate concentration – 0.2–0.3 M), in toluene using solid base (NaOH) and 1–10 mol% catalyst was selected (see Scheme 8.35).

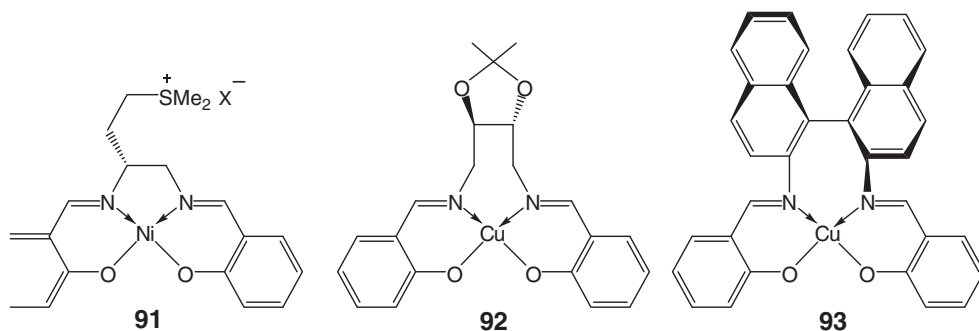


Scheme 8.35

The alkylation results presented in Table 8.18 show that Cu^{II} ion complexes **88** and **90** are highly efficient catalysts for the asymmetric phase-transfer alkylation. A similar Ni^{II} ion complex **87** also leads the alkylation process, but the enantioselectivity and the chemical yield of the process are much lower than in the copper ion complex catalysis. Cu^{II} ion complex **89** also shows low stereoselectivity, wherein the reaction proceeds almost with complete conversion of the initial substrate.

Table 8.18 Enantioselectivity in the alkylation reactions of **23** with benzyl bromide, catalyzed by salen complexes.

No.	Catalyst	Mole (%)	Base (equiv.)	Conversion (%)	ee (%)
1	89	10	NaOH, 1.2	34	30 (<i>R</i>)
2	90	10	NaH, 1.2	82	89 (<i>R</i>)
3	91	10	NaOH, 1.2	97	6 (<i>R</i>)
4	92	1	NaOH, 3.0	71	92 (<i>S</i>)
5	92	2	NaOH, 3.5	91	88 (<i>S</i>)

**Figure 8.23** The structures of modified salen-type catalysts.

Interestingly, the use of Ni^{II} complex **91** (see Figure 8.23) containing a sulfonium group in the side chain of a ligand leads to the formation of the racemic product (50% conversion).

In the course of work, the catalysts were synthesized on the basis of (*S,S*)-1,3-oxa-2,2-dimethyl-4,5-di(aminomethyl)cyclopentane **92** and (*R*)-2,2'-diamino-1,1'-binaphthyl **93**. However, asymmetric induction in the reaction, catalyzed by these complexes, did not exceed 8%.

Thus, from a number of salen complexes used, the Cu^{II} complex with (*R,R*)-[*N,N'*-bis(2'-hydroxybenzylidene)]-1,2-diaminocyclohexane **90** stands out for its ability to efficiently catalyze the asymmetric interphase alkylation.

For an effective asymmetric synthesis, salen complex **90** was used as a chiral catalyst and a series of substituted (*S*)- and (*R*)- α -amino acids were synthesized by C-alkylation of substrate **23** with alkyl halides (ee >80–90%).

It should be emphasized once again that a prerequisite for highly stereoselective asymmetric synthesis under phase-transfer catalysis with onium catalysts is the formation of tight ion pairs where besides electrostatic forces of attraction there are hydrophobic interactions. The method of using salen complexes fundamentally differs from the other methods of asymmetric phase-transfer alkylation by the fact that between the particles in the ion pair along with the above-mentioned interactions additional coordination interactions can occur. This property enables

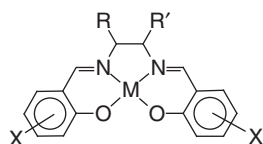
to clearly define the ion pair preferably in one of the possible conformations, thus ensuring high stereoselectivity of the process. In this regard, a detailed study of these catalytic systems was conducted and the factors that influence the effectiveness of PTC alkylation were determined and the mechanism of their action investigated [91].

8.2.1

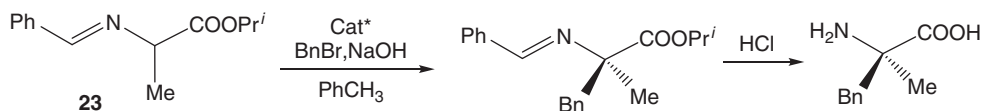
Structural Features of Salen Complexes

It seems logical to begin the study of asymmetric alkylation reaction catalyzed by salen complexes, with a systematic study of the influence of changes in the structure of the catalyst on the stereoselectivity of the reaction catalyzed by it. Considering the structure of the salen complexes, we can assume three approaches to change their structure:

- use of different metals;
- use of various substituted salicylic aldehydes;
- use of different chiral diamines.



To conduct research, alkylation reaction of Schiff base of benzaldehyde and isopropyl of racemic alanine **23** by benzyl bromide was chosen as a model [91] (see Scheme 8.36). Alkylation proceeded under interphase conditions, as solid NaOH was used as a base insoluble in toluene, where the reaction was carried out. The reaction proceeds only in the presence of all components: base, catalyst, alkylating agent, and substrate. In the absence of at least one of components, the reaction does not proceed.



Scheme 8.36

Initially, in an interphase, alkylation reaction of **23** Cu^{II} complex based on salen ligand synthesized from (*R,R*)-cyclohexanediamine and salicylaldehyde was used. Based on the high efficiency of this complex just the structure of its salen ligand was used for the synthesis of several transition metal complexes (see Figure 8.24).

The complexes were synthesized by standard methods [33] as described for complex Cu^{II} (**90**). In some experiments, catalysts were prepared *in situ*, wherein

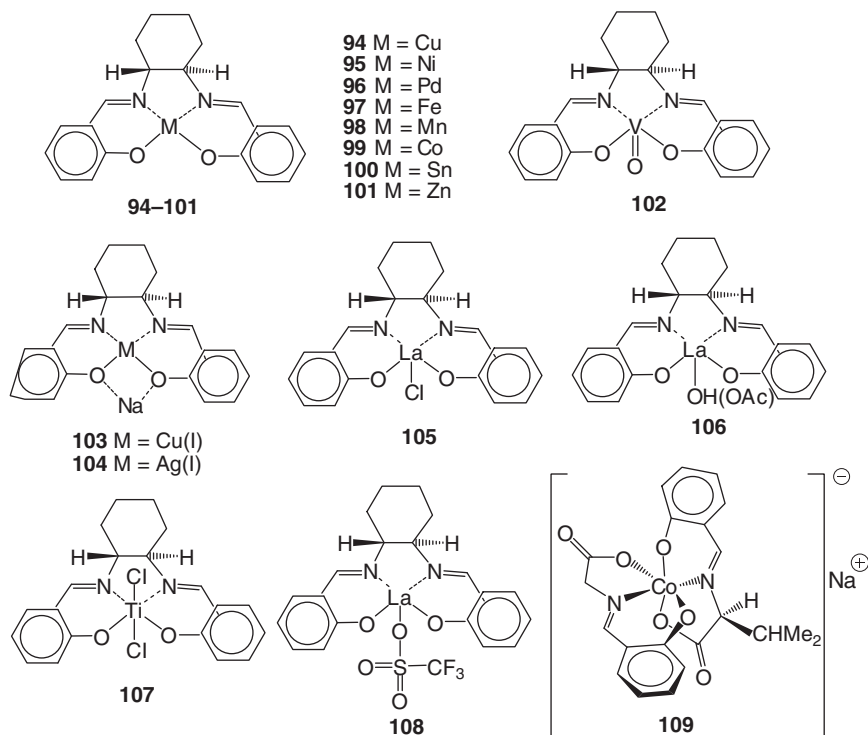


Figure 8.24 The structure of metal salen complexes and Δ -[N-salicylidene-glycinate-N-salicylidene-(S)-valinate]Co^{III}.

the preliminary experiments (on the example of Cu^{II} complexes) established that the chemical yield and the magnitude of the asymmetric induction in these cases were in good agreement with the results obtained using pure individual catalysts.

Various metal complexes with identical ligand environment were investigated [91, 92]. Complexes having different apical coordination ability were compared: for example, in the case of square-planar complexes of Cu^{II} apical coordination was typical, whereas Pd^{II} complexes did not have any, and Ni^{II} complexes occupied an intermediate position in this series. However, as it turned out, the maximum stereoselectivity value was observed in catalysis by copper complex [92].

Among the synthesized complexes were also charged complexes of Co^{III}, Sc^{III}, La^{III}, and Ag^I. These complexes catalyze the alkylation (see Table 8.19, No. 11–14), but racemic product is formed at that.

Based on the obtained data, it could be assumed that the coordinate-labile and coordinate-unsaturated complexes should have stereodifferentiating ability. To test this assumption, inert coordination-saturated charged complex Δ -[N-salicylidene-glycinate-N-salicylidene-(S)-valinate] Co^{III} of sodium (**109**) (see Figure 8.25) was specially synthesized and alkylation was carried out catalyzed by this complex. As expected, the result proved to be a racemic product in 8%

Table 8.19 The effectiveness of catalysts based on various metal ions.^{a)}

No.	M	Yield (%)	ee (%) ^{b)}
1	Cu ^{II} (or Na ⁺ /Cu ^I) ^{c)}	>95	90
2	Ni ^{II}	36	31
3	Zn ^{II}	62	20
4	Pd ^{II}	50	5
5	Sn ^{II}	35	6 ^{d)}
6	Fe ^{II}	38	17
7	Co ^{II}	84	80
8	Mn ^{II}	28	3
9	Cl ₂ Ti ^{IV}	0	—
10	O = V ^{IV}	60	31
11	Co ^{III}	41	0
12	Sc ^{III}	50	11
13	ClLa ^{III}	>95	0
14	Na ⁺ /Ag ^I	>95	0

a) Reaction conditions: 1 equiv. of Schiff base **23**, 1.2 equiv. of BnBr, 0.05 equiv. of catalyst, 2.5 equiv. of NaOH; 5 mol% catalyst.

b) Determined by chiral GLC.

c) During alkylation, very quickly (about 20 min) the catalyst is oxidized to form a Cu^{II} complex, as evidenced by the appearance of characteristic color.

d) (*S*)- α -Methyl phenylalanine was obtained as a result of the reaction catalyzed by Sn^{II} complex based on (*R,R*)-diaminocyclohexane.

chemical yield. A similar result was also obtained for chiral salen complex of Co^{III} (see Table 8.19, No. 11).

When using the uncharged complexes of Pd^{II} or Sn^{II}, which are incapable of any further coordination, the chemical yield and ee of the product were very low (Table 8.19, No. 4 and 5, respectively). At the same time, the Ni^{II} and vanadium complexes show almost similar results, although somewhat lower than their isostructural complexes of Cu^{II}. Complexes with significant Lewis acidity are ineffective in this reaction; for example, Ti^{IV} complex (see Table 8.19, No. 9).

Based on the data presented in Table 8.19, no generalization can be made; however, it is clear that Cu^{II} complexes providing high chemical yield and high asymmetric induction notably differ from a number of other catalysts. This is probably due to the structure of the outer electron shell of the metal (3d⁹), whereby, for Cu^{II} complexes the formation of pyramidal structure complexes (square pyramid) with the remote apical ligand is typical. This ligand being in an apical position is sufficiently labile and can be easily replaced.

In this case, the competitive coordination of the apical position in the complex can be done by substrate. Perhaps this provides high efficiency of stereoselective catalysis of alkylation.

Results of XRD of Cu^{II} [93] and Ni^{II} [94] complexes of Schiff bases of (*R,R*)-diaminocyclohexane and salicylaldehyde (bond lengths M–O and angles of

Complex of Cu(II)	Complex of Ni(II)
Cu-O(1) 1.92Å	Ni-O(1) 1.85Å
Cu-O(2) 1.88Å	Ni-O(2) 1.75Å
Cu-N(1) 1.96Å	Ni-N(1) 1.84Å
Cu-N(2) 1.95Å	Ni-N(2) 1.76Å
O(1)-O(2) 2.66Å	O(1)-O(2) 2.57Å
N(1)-N(2) 2.61Å	N(1)-N(2) 2.63Å
N(1)-O(1) 2.61Å	N(1)-O(1) 2.51Å
N(1)-Cu-N(2) 84°	N(1)-Ni-N(2) 94°
N(1)-Cu-O(2) 89°	O(1)-Ni-O(2) 91°
O-Cu-N 93°	O-Ni-N 88°

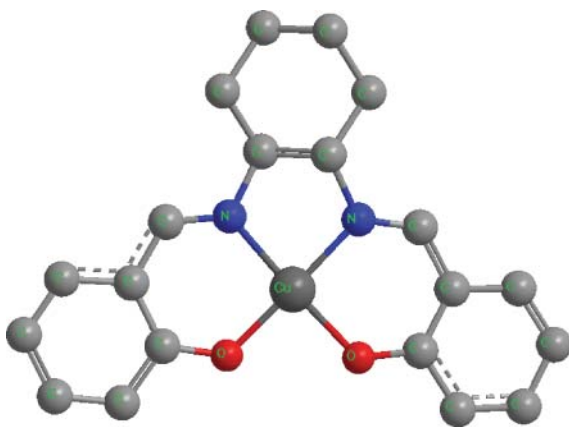


Figure 8.25 The molecular structure of Cu^{II} complex of Schiff base of salicylaldehyde and (*R,R*)-diaminocyclohexane (two different projections).

O–M–O, N–M–N, and O–M–N), as well as molecular structure of complex Cu^{II} are listed here. According to these data, Cu^{II} forms a complex of planar structure with weak pyramidal distortion (see Figure 8.25) and Ni^{II} forms a planar complex with weak tetrahedral distortion.

In this case, the possibility of the apical coordination and positional relationship of the oxygen atoms of salicylic phenolic moiety, apparently, are the key factors determining the catalytic activity and stereodifferentiating ability of catalysts.

8.2.1.1 The Influence of the Structure of Salen Ligand

To establish other factors affecting the amount of asymmetric induction in inter-phase alkylation catalyzed by the chiral salen complexes, salen-type complexes of various structures were synthesized. Thus, we studied the influence of steric and electronic effects when different substituents were introduced into the molecule of salicylaldehyde; we also synthesized salen complexes based on various diamines

and used them in the interphase asymmetric alkylation reaction of substrate. Each case will be considered individually.

Complexes Based on Various Salicylaldehydes

To study the relationship between the structure of a chiral ligand and stereodifferentiating ability of the catalyst, ligands were synthesized on its basis using various functionally substituted salicylaldehydes. Thus Cu^{II} , Ni^{II} , and Pd^{II} complexes based on (*R,R*)-cyclohexanediamine were used [91, 95, 96].

It could be assumed that complexes containing functional groups such as hydroxy, methoxy, and nitro will more effectively chelate sodium cation (counterion of substrate's carbanion chelates sodium cation), thereby increasing the stereocontrol of alkylation process.

For this purpose, salen complexes on the basis of (*R,R*)-diaminocyclohexane and 3-substituted salicylaldehydes were synthesized. However, the use of 3-hydroxysalicylaldehyde in complexes **110**–**112** (see Figure 8.26) in alkylation reaction of substrate **23** resulted in the formation of racemic products (see Table 8.20, No. 1–3) and drop in catalyst efficiencies (yields of two products are 2.20% and 43%, respectively).

Apparently, due to the presence of two hydroxyl substituents, that are located close to phenolic oxygen atoms of the salicyl moiety, more efficient chelation of the ion of the alkali metal is observed (possibly even the formation of sodium phenolate), preventing the formation of catalytically active polar structure of catalyst ((+)-NLE, see Figure 8.21). Stereodifferentiating ability of the catalyst is also reduced by the introduction of a methoxy group in *ortho*-position relative to salicylaldehyde's phenolic oxygen atom (catalysts **116**–**118**, see Table 8.20, No. 7–9, respectively). Use of a catalyst based on 3-nitrosalicylaldehyde **127** (see Table 8.20, No. 18) similarly affects the results of the reaction.

Meanwhile, complexes containing a hydroxyl substituent in the *meta*-position of the salicyl fragment (catalysts **113**–**115**) in alkylation reaction of **23** exhibit average catalytic activity – 63%, 65%, and 55%, respectively (see Table 8.20, No. 4–6), but just as with complexes **107**–**109**, a racemic product is formed. With the introduction of methoxy groups in *meta*- or *para*-position in relation to phenolic oxygen of salicylaldehyde, stereoselectivity of the catalysis by such complexes is changed insignificantly (catalysts **119**–**121** and **123**–**125**, respectively).

Catalysts on the basis of (*R,R*)-diaminocyclohexane and 5-nitro- or 5-sulfonium derivatives of salicylaldehyde (**128** and **129**, respectively) in the alkylation reaction of **23** exhibit average catalytic activity and lead to the formation of racemic product (see Table 8.20, No. 19–21).

It is important to note that the solubility of salen complexes in toluene is low, and to increase the solubility complexes containing benzyloxy group and *tert*-butyl substituents in salicylaldehyde fragment have been specially synthesized. Use of complexes **122** and **123**, containing fragments of 4-benzyloxysalicylaldehyde, allows to effectively carry out the process of alkylation (yield >80%), but the enantioselectivities of this process are 27% and 14%, respectively (see Table 8.20, No. 13 and 14).

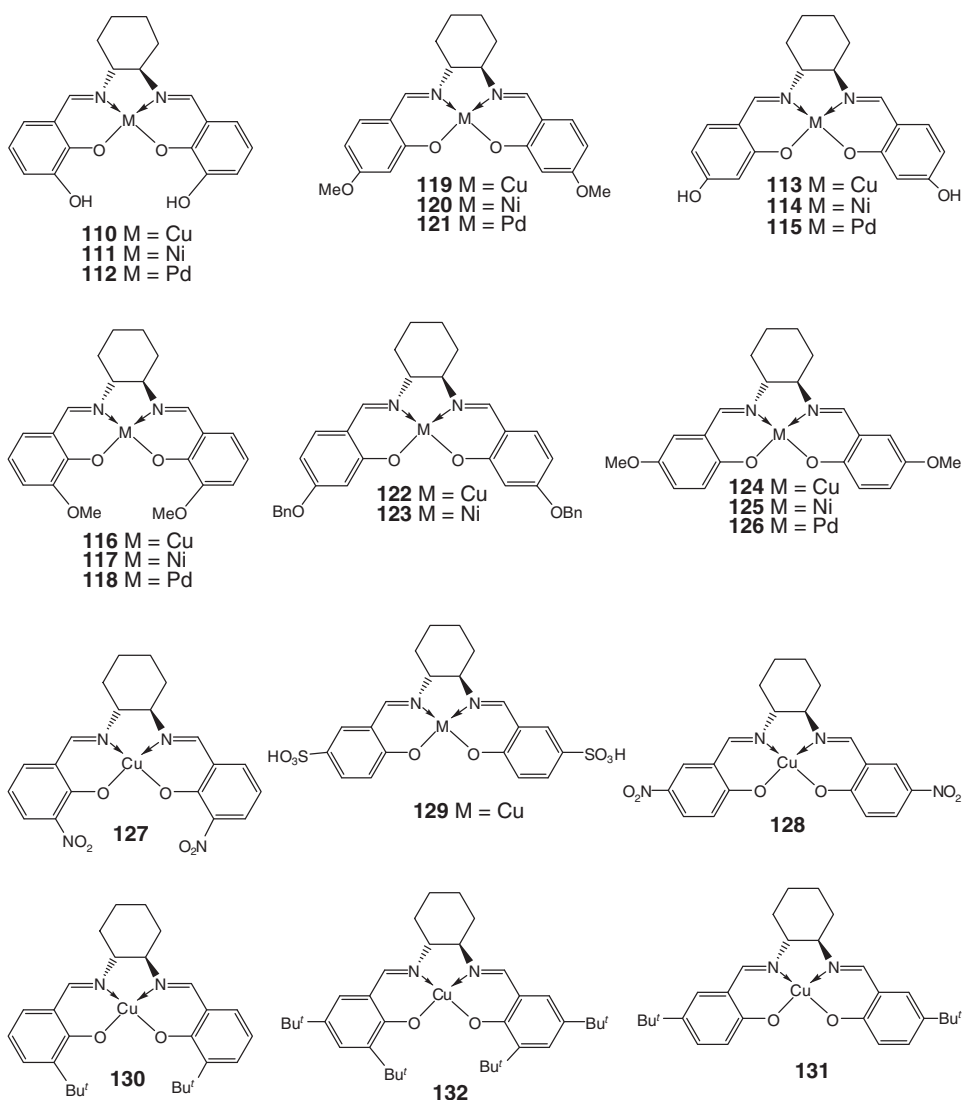


Figure 8.26 Catalysts based on substituted salicylaldehydes.

Table 8.20 Alkylation of $\text{PhCH}=\text{N-CHMeCOOPr}^{\text{I}}$ (**23**) with benzylbromide.^{a)}

No	Catalyst	Yield (%)	ee (%)
1	110	20	0
2	111	2	0
3	112	43	0
4	113	63	0
5	114	65	0
6	115	55	0
7	116	15	9 (<i>R</i>)
8	117	74	0
9	118	57	28 (<i>R</i>)
10	119	48	70 (<i>R</i>)
11	120	67	58 (<i>R</i>)
12	121	60	22 (<i>R</i>)
13	122	>85	27 (<i>R</i>)
14	123	85	14 (<i>R</i>)
15	124	51	64 (<i>R</i>)
16	125	84	25 (<i>R</i>)
17	126	88	5 (<i>R</i>)
18	127	62	6 (<i>R</i>)
19	128	78	7 (<i>S</i>)
20	129	70	0
21	130	>95	6
22	131	85	65 (<i>R</i>)
23	132	>95	0

a) Reaction conditions: 1 equiv. **23**, 0.05 equiv. catalyst, 1.2 equiv. BnBr, 2.5 equiv. NaOH, in toluene under argon, room temperature, reaction time 24 h.

It is known that in other areas of asymmetric catalysis with the introduction of alkyl substituents to the fragment of salicylaldehyde catalyst of the salen type an increase in stereoselectivity of catalysis is observed. Based on this, Cu^{II} complexes on the basis of various substituted *tert*-butylsalicylaldehydes were synthesized. It turned out that in this case the enantioselectivity of the reaction decreases (Table 8.20, No. 22).

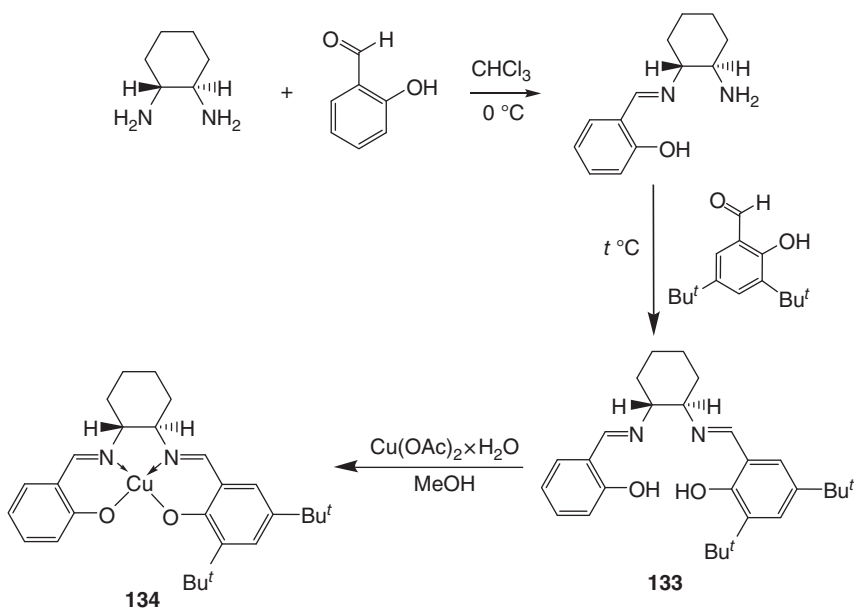
Introduction of a *tert*-butyl substituent in position 5 of salicylaldehyde (**131**) affords the product in 85% yield and 65% optical purity. At the same time, use of Cu^{II} complex based on cyclohexanediamine and 3,5-di-*tert*-butylsalicylaldehyde (**132**) increases the reaction rate, increases the chemical yield of the product, and sharply decreases stereoselectivity, resulting in a racemic product (see Table 8.20, No. 24). It should be noted that the solubility of the complexes based on *tert*-butylsalicylaldehydes is much higher than of those based on unsubstituted salicylaldehyde. This probably explains the increase in the reaction rate and, accordingly, high chemical yields of alkylated products.

Based on these results it can be concluded that the introduction of substituents into the aromatic ring of salicylaldehyde lowers the stereodifferentiating ability of catalysts; moreover, the closer the substituent is to the phenolic oxygen atom of salicyl moiety, the stronger its chelating ability, the lower is stereodifferentiating capacity and efficiency of the catalyst. At the same time, increased solubility of catalysts in toluene increases the efficiency of catalysts, suppressing their stereodifferentiating ability.

Salen Complexes of Asymmetric Structure

As can be seen from the above-mentioned data, the introduction of substituents into the salicyl aldehyde fragment of salen complexes adversely affects the stereodifferentiating abilities of the catalysts; however, their effectiveness in some cases increases significantly. Complexes of symmetrical structure with substituents in both salicylic fragments of salen ligand were used. This raised a question regarding the impact of introducing substituents into only one of the aromatic rings of the salen ligand on efficiency of the catalyst.

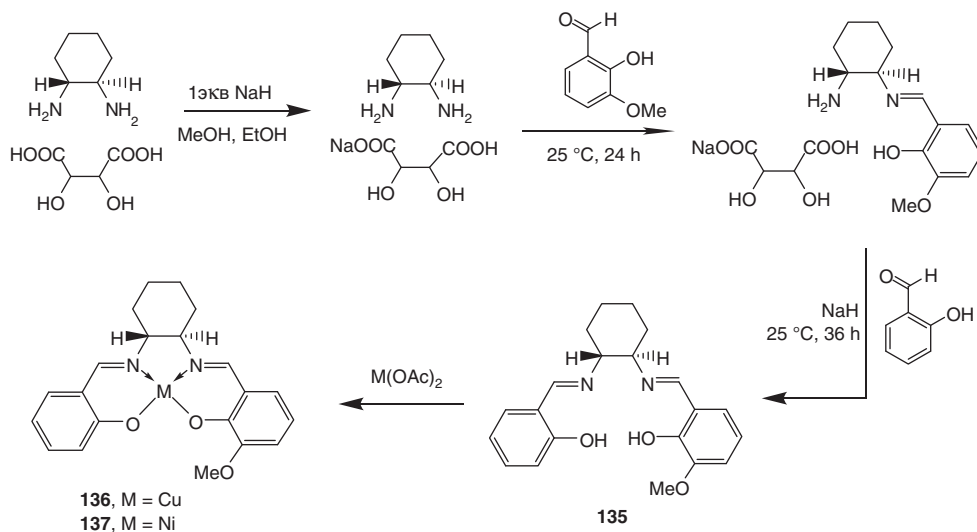
In order to combine the advantages of complexes **90** and **132**, specifically high stereodifferentiating capacity of **90** and high activity of **132**, salen ligand containing unsubstituted salicyl aldehyde and 3,5-di-*tert*-butylsalicyl aldehyde moieties (**133**) was synthesized based on the previously described methods [97, 98] (see Scheme 8.37). Synthesized on its basis Cu^{II} complex **134** was used in the alkylation reaction of Schiff base **23** with 85% enantioselectivity and 81% yield. Thus, catalyst



Scheme 8.37

of asymmetric structure **134** catalyzes the reaction of asymmetric phase-transfer alkylation of **23** almost as efficiently as symmetric complex **90**.

To investigate the influence of electronic effects of substituents in the complexes with asymmetric ligands, asymmetric salen ligands containing methoxysalicyl aldehyde fragment were synthesized (**135**). Syntheses of these ligands were carried out by a slightly modified procedure using 3-methoxy- or 4-methoxysalicyl aldehydes (see Scheme 8.38). Complexes of Cu^{II} and Ni^{II} were synthesized on the basis of these ligands [91, 96].



Scheme 8.38

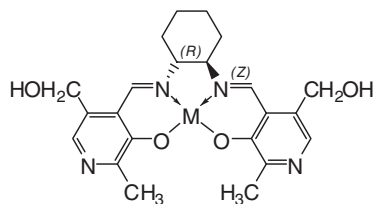
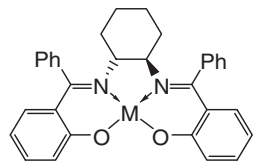
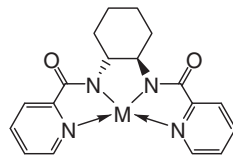
Complexes of Cu^{II} and Ni^{II} based on asymmetric ligand containing 3-methoxysalicyl aldehyde fragment catalyze alkylation process of **23** ineffectively with the formation of a racemic product. At the same time, Cu^{II} and Ni^{II} complexes containing 4-methoxysalicyl aldehyde fragment catalyze the interphase alkylation reaction asymmetrically with ee of 66% and 30%, respectively. Chemical yields of isolated amino acids were 62% and 70%, respectively.

Along with the various derivatives of salicyl aldehyde used in the synthesis of complexes other aldehydes, ketones, and carboxylic acids were also used. Thus, the use of pyridoxal in complexes Cu^{II} **136** and Ni^{II} **137** resulted in a dramatic decrease in both stereodifferentiating properties of catalysts and their effectiveness (see Table 8.21).

A similar result is observed during catalysis with complexes based on pyridine-2-aldehyde (absence of phenolic oxygens and charge on the metal ion).

Complexes of Cu^{II} **138** and Ni^{II} **139** synthesized on the basis of 2-hydroxybenzophenone effectively catalyze the interphase alkylation, but the enantioselectivity of the process is very low (see Table 8.21).

Table 8.21 Enantioselectivity in alkylation reactions of substrate **23** with benzylbromide catalyzed by salen-like complexes.^{a)}

Catalyst		Yield (%)	ee (%)
	136 (M = Cu)	43	6
	137 (M = Ni)	44	3
	138 (M = Cu)	82	2
	139 (M = Ni)	68	4
	140 (M = Cu)	30	0
	141 (M = Ni)	70	5

a) Reaction conditions: 1 equiv. of the substrate **23**, 1.2 equiv. BnBr, 0.05 equiv. catalyst, 2.5 equiv. of NaOH, toluene, room temperature, under argon atmosphere.

Transition to amide ligands through complexes based on pyridine-2-carboxylic acid was implemented. In these complexes, there are no phenolic oxygens, and coordination with the metal occurs with the involvement of the nitrogen atoms of pyridine. However, use of this type of complexes proved to be ineffective. Thus, reaction catalyzed by Cu^{II} amide complex **140** is not stereoselective (ee 0%), with a conversion of only 30%; catalysis with amide complex Ni^{II} **141** affords the reaction product with 5% ee and 70% yield (see Table 8.21).

Thus, the results indicate that for effective interphase asymmetric alkylation catalysis the presence of phenolic oxygen atoms in catalyst molecule is required, the introduction of any substituents or change in salicylic fragment of salen ligands leads to decreased stereodifferentiating ability of catalysts. Typically, this refers to Cu^{II} complexes. In this case, the following pattern is observed: the closer the substituents are to the phenolic oxygen atoms of salicylic fragment of the catalyst, more strongly drops the asymmetric induction in the reaction catalyzed by it. The efficiency of catalysis is also reduced. The only exception is Cu^{II} complex **132**, which catalyzes the model alkylation reaction of **23** fast and with full conversion.

It should be noted that among Ni^{II} complexes relatively high stereodifferentiating ability in model alkylation reaction of substrate **23** exhibits Ni^{II} complex based on diaminocyclohexane and 4-methoxysalicyl aldehyde (**119**, 58% ee), and among Pd^{II} complexes – the complex comprising 3-methoxysalicyl aldehyde (**117**, 28% ee).

8.2.1.2 Chiral Diamine-Based Complexes

In the previous chapter, it was shown that introduction of substituents into salicyl aldehyde fragment of the salen complexes reduced the stereoselectivity of catalysis in phase-transfer alkylation of Schiff base **23**. As noted earlier, studies of the relationship of the catalyst structure and its stereodifferentiating ability can be also carried out by changing the chiral salen ligand moiety.

The task was to investigate the influence of structure rigidity and steric loading of the chiral fragment of the catalyst on its stereodifferentiating ability [91, 99]. A number of catalysts based on various chiral diamines were synthesized, and the resulting complexes were tested in a model alkylation reaction of substrate **23** by benzyl bromide. The results of these experiments are summarized in Table 8.22.

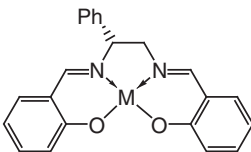
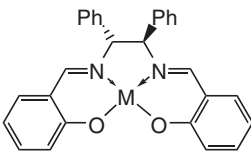
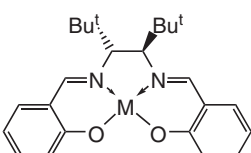
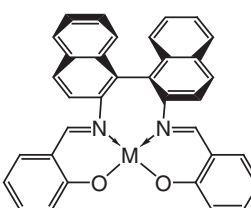
Complexes **142** and **143** on the basis of (*R*)-phenylethylenediamine were also synthesized. It turned out that these complexes catalyzed the reaction with low stereoselectivity (14% and 2%, respectively) and provided low yields of the resulting product (53% and 25%, respectively; Table 8.22, No. 1, 2). Complex of Schiff base of (*R,R*)-diphenylethylenediamine and salicyl aldehyde **144** catalyzed the same interphase alkylation reaction more stereoselectively (58% ee, 90% yield; Table 8.22, No. 3). The isostructural complex **145** carries out the process less efficiently (36% ee, 50% yield; Table 8.22, No. 4).

Use of the (*R,R*)-(1,2-di-*tert*-butyl)ethylenediamine as a chiral component of salen complexes strongly suppresses not only the stereodifferentiating abilities of the catalysts, but drastically reduces the efficiency of the catalyst (see Table 8.22, No. 5, 6). Complex **146**, though not stereoselectively, but nevertheless carries out the alkylation process, but complex **147** does not at all catalyze this reaction. In these complexes, there is an effective bilateral shielding of the central metal ion of the catalyst, which leads to loss of catalytic activity of the catalyst.

The (*R*)-2,2'-diamino-1,1'-binaphthyl, which has an axial chirality, was also used as a diamine for the synthesis of the salen ligand. Cupric complex on its basis (**148**) in the presence of NaOH as a base catalyzes investigated reaction effectively with 90% conversion, but the enantioselectivity of the process is very low (8% ee) (see Table 8.22, No. 7). When KOH or LiOH are used as a base the reaction does not occur, and after 30 h the conversion does not exceed 3%.

The data indicate that with increasing volume of the groups introduced to the chiral diamine moiety the effective shielding of the central metal ion in the catalyst occurs, which reduces its catalytic activity. The optimal structure for interphase alkylation catalysis has the complex on the basis of a six-membered 1,2-diaminocyclohexane. The enantioselectivity of the reaction product, not exceeding 30% when using a five-membered cyclic diamine in the bivalent cupric complex supports the above-mentioned statement.

Table 8.22 The enantioselectivity of the alkylation reaction of substrate **23** with benzyl bromide in the presence of various chiral diamine-based catalysts.^{a)}

Catalyst		No.	Yield (%)	ee (%)
	142 (M = Cu)	1	53	14
	143 (M = Ni)	2	25	2
	144 (M = Cu)	3	90	58
	145 (M = Ni)	4	50	36
	146 (M = Cu)	5	26	0
	147 (M = Ni)	6	0	0
	148 (M = Cu)	7	90 (3 ^b)	8 (- ^b)

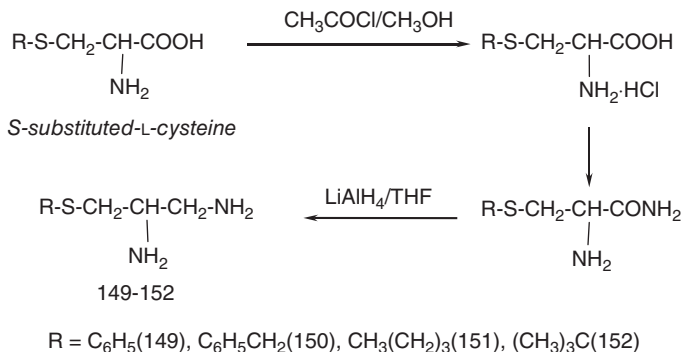
a) Reaction conditions: 1 equiv. of substrate **23**, 1.2 equiv. of BnBr, 0.05 equiv. of the catalyst, 2.5 equiv. of NaOH in CH₃C₆H₅ at room temperature under argon, 24 h.

b) KOH was used as a base.

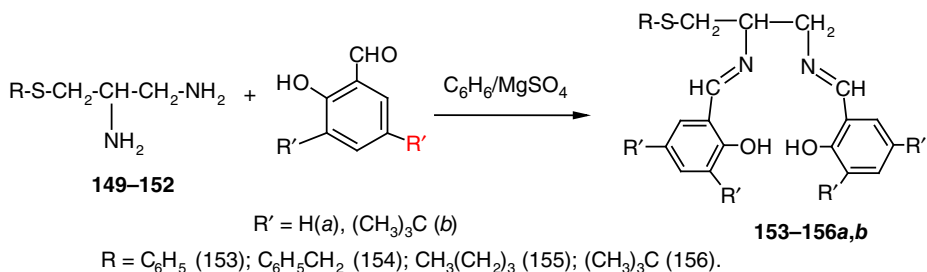
Salen Complexes Based on Chiral Diamines Containing SR-Groups

In order to reveal the effect of active electron-donating groups of the chiral diamine moiety on stereodifferentiating ability of salen complex-catalysts, chiral diamine ligands containing *S*-substituted groups (phenyl, benzyl, *n*-butyl, and *t*-butyl) in the side radical of the diamine moiety were synthesized (see Scheme 8.39) [100, 101]. As precursors for preparing such ligands optically active nonprotein analogs of L-cysteine were used: *S*-phenyl-L-cysteine, *S*-benzyl-L-cysteine, *S*-*n*-butyl-L-cysteine, and *S*-*t*-butyl-L-cysteine.

The interaction of synthesized chiral diamines **149–152** with salicyl aldehyde or its 3,5-di-*t*-butyl derivative gave bis-salicylidene Schiff bases **153–156** (see Scheme 8.40).



Scheme 8.39



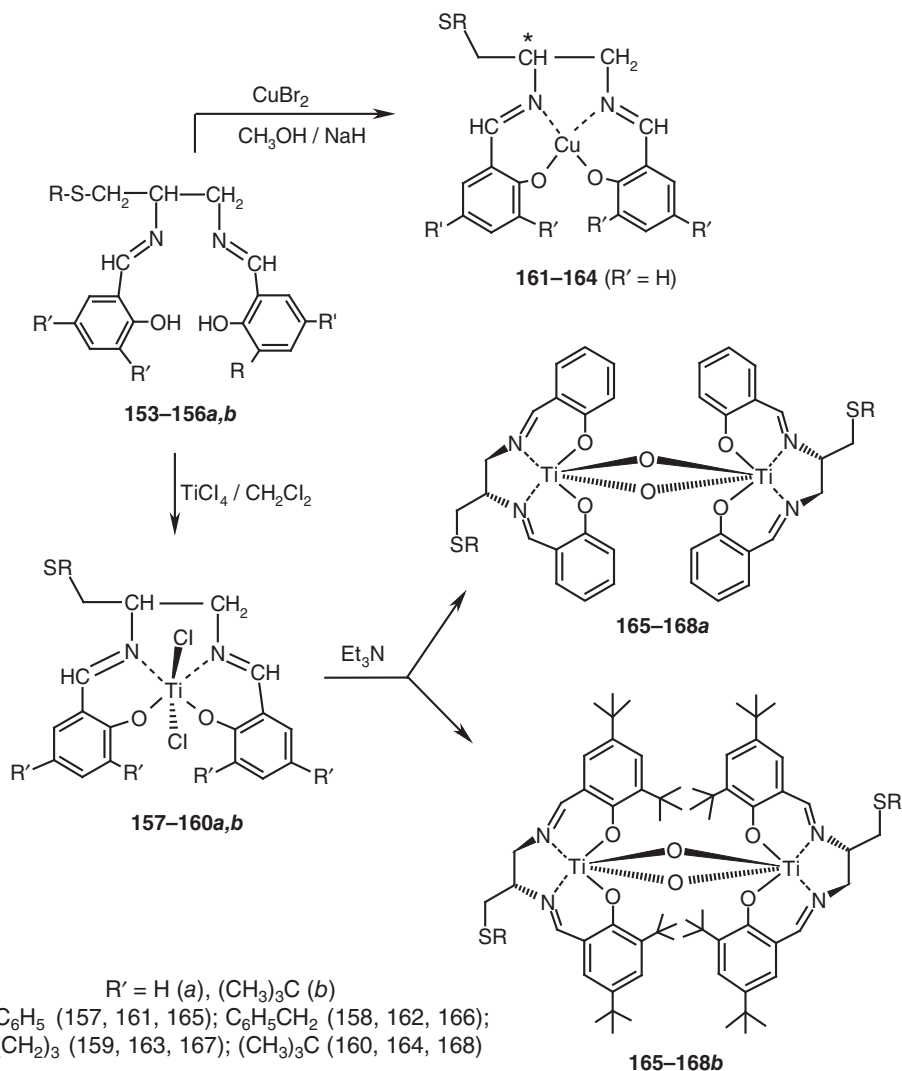
Scheme 8.40

The resulting bis-salicylidene ligands **153–156a,b** react readily with Cu^{II} and Ti^{IV} ions with the formation of corresponding salen complexes. Moreover, as a result of the complexation reaction with Ti^{IV} ion dichloro monosalene complexes of C_1 symmetry are formed (**157–160a,b**), which are dimerized in the presence of triethylamine to form dimeric complexes of C_2 symmetry (**165–168a,b**) (see Scheme 8.41).

IR spectroscopy revealed that the complex-catalysts in solution also retain their binuclear dimeric structure (see Figure 8.27). This is evidenced by the presence of enhanced absorption at 700 cm^{-1} characteristic of the Ti-O-Ti bond.

Molecular weights and their CD spectra (circular dichroism) determined by ultracentrifugation method also confirm the binuclear structure of these complexes.

Synthesized copper salen complexes **161–164** were investigated in asymmetric C-alkylation reactions of benzylidene derivative of alanine isopropyl ester and salen complexes of Ti^{IV} ion **165–168a,b** – in reactions of trimethylsilylcyanation of aldehydes leading to the formation of important intermediate adducts for the synthesis of optically active amino alcohols and amino acids.



Scheme 8.41

Salen Catalysts 165–168 in Reactions of Trimethylsilylcyanation of Aldehydes

Salen dimer complexes of Ti^{IV} ion **165–168a,b** without isolation from the reaction medium were investigated in reactions of trimethylsilylcyanation of benzaldehyde as chiral catalysts (see Scheme 8.42) [101].

The enantiomeric purity of the trimethylsilyl derivative **169** separated from the reaction mixture chromatographically was determined by chiral GLC analysis. The results are shown in Table 8.23.

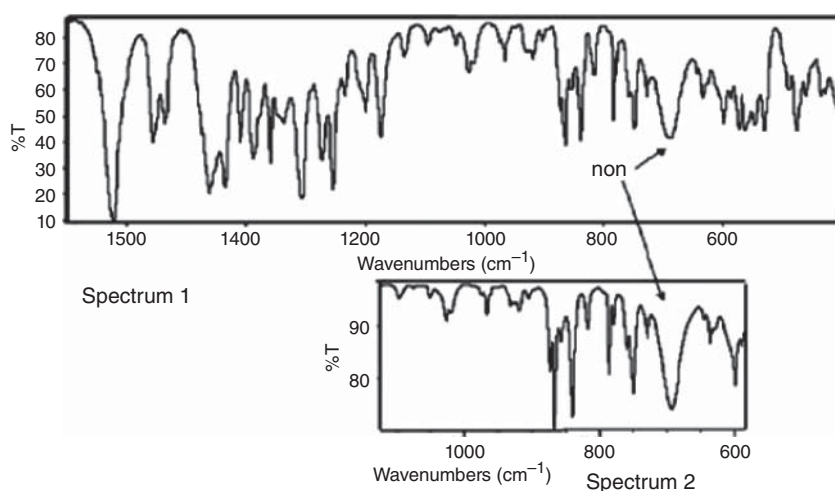
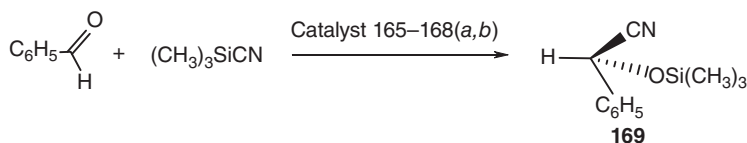


Figure 8.27 IR spectra of **165b** complex in a crystalline state (spectrum 1) and in solution (spectrum 2).



Scheme 8.42

Table 8.23 The results of trimethylsilylcyanation of benzaldehyde.

No. ^{a)}	Complex catalyst	<i>T</i> (°C)	Time (h)	Yield (%)	ee (%) ^{b)}
1	165b	25	1	78	57.4
2	165b	2	12	74	64.8
3	166b	25	12	76	0
4	166b	2	24	71	0
5	167b	25	12	80	0
6	167b	2	24	75	0
7	168b	25	12	68	0
8	168b	2	24	72	0
9 ^{c)}	165b	−78	24	0	0
10	165a	25	24	74	15.6
11	166a	25	24	73	7.4
12	167a	25	24	65	5.8
13	168a	25	24	69	4.2

a) In all experiments, a ratio of substrate/catalyst is 100/1.

b) The enantiomeric purity and (*S*)-absolute configuration of final products were determined by chiral GLC analysis.

c) At −78 °C the complex-catalyst precipitates and is not involved in catalysis.

An increase in stereoselectivity of the reaction during trimethylsilylcyanation of benzaldehydes at -78°C could be expected, as it was noted previously in the case of similarly structured complex-catalysts on cyclohexyldiamine basis [102]. However, the only catalytically active **165b** complex precipitates due to a sharp decrease in solubility at -78°C and is not involved in the process of trimethylsilylcyanation of the aldehyde. Comparison of catalytic activities in the series of **165–168** complexes shows that the introduction of *t*-butyl substituents in positions 3 and 5 of the salicyl aldehyde fragment enhances enantioselectivity of the trimethylsilylcyanation reaction (from 15% to 64%).

As can be seen from Table 8.23, complexes **166–168a** and **166–168b**, containing *S*-benzyl, *S*-*n*-butyl, and *S*-*t*-butyl substituents in the side chain radical, actually do not show catalytic activity in reactions of benzaldehyde trimethylsilylcyanation. Presumably, this is due to the presence of active sulfur atom in a side radical of the diamine moiety of these complexes capable of further coordination with Ti^{IV} ion.

According to the developed version [102], the reactions of aldehydes trimethylsilylcyanation, catalyzed by dimeric salen complexes of Ti^{IV} ion of C_2 symmetry, proceed directly on the coordination plane of the central metal ions. The ions of Ti^{IV} are further coordinated with the individual substrates (trimethylsilyl cyanide and benzaldehyde), and their interaction takes place on the coordination plane of the metal.

It can be believed that the inactivity of Ti^{IV} complexes with *S*-benzyl, *S*-butyl, and *S*-*t*-butyl substituents in the side radical of the diamine ligand moiety (**166–168a,b**) is due to the presence of active sulfur atoms within their structure, which can additionally be coordinated with the metal ions and inhibit the reaction of trimethylsilylcyanation of aldehydes.

Theoretically, this kind of inhibition can be excluded in the case of catalysis by the complex containing *S*-phenyl group in the side radical of the diamine moiety (**165a,b**) due to the delocalization of the electron pair of the sulfur atom caused by conjugation with the benzyl ring. Consequently, in dimer salen complex of Ti^{IV} ion containing *S*-phenyl group in the side radical of the ethylenediamine moiety, additional orbitals of two Ti^{IV} ions are free and can be coordinated with molecules of substrates to conduct the catalytic act.

Figure 8.28 presents hypothetical models of the reaction mechanisms of trimethylsilylcyanation of benzaldehyde with participation of **165** and **166–168** complex-catalysts.

In active dimeric complex **165a,b**, the free coordinate orbitals of two Ti^{IV} ions are occupied by the CN^- ion and benzaldehyde, and the trimethylsilylcyanation reaction of benzaldehyde occurs on the coordination plane of the metal ion. In this reaction, stereoselectivity of the trimethylsilylcyanation is provided by *t*-butyl substituents of salicyl aldehyde moieties of complex-catalysts, which produce a specific chiral environment around the interacting groups and promote the asymmetric formation of (*S*)-enantiomers of the reaction products.

Thus, the binuclear Ti^{IV} ion complex of C_2 symmetry on the basis of bis-salicylidene of Schiff base of 3,5-di-*t*-butylsalicyl aldehyde and chiral diamine,

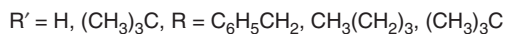
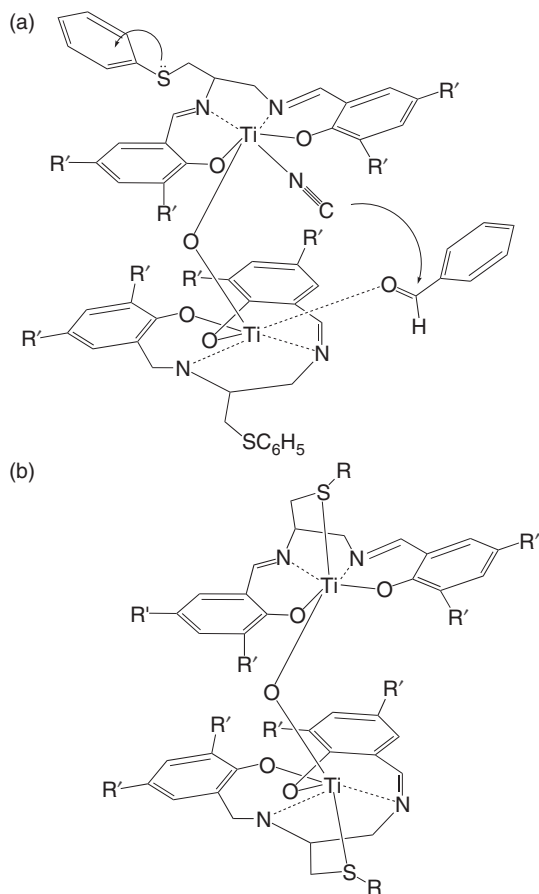
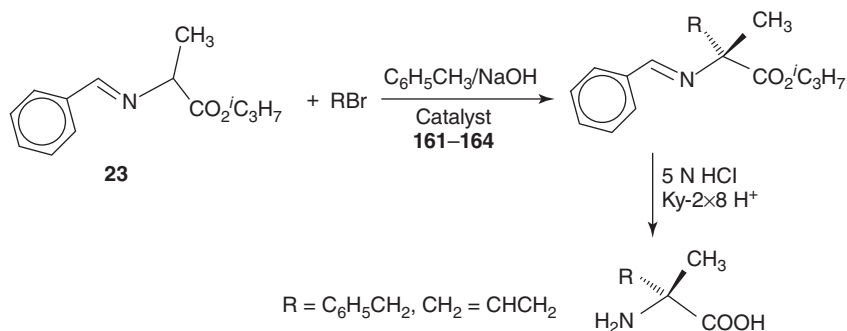


Figure 8.28 Hypothetic models of reaction mechanisms of trimethylsilylcyanation of benzaldehyde. (a) An effective asymmetric catalysis involving complex **165** and (b) inefficient asymmetric catalysis in the presence of complexes **166–168**.

obtained from the nonprotein amino acid *S*-phenylcystein is an effective chiral catalyst in trimethylsilylcyanation reactions of aldehydes and after improvement it can be recommended for use in producing optically active β -aminoalcohols.

Salen Catalysts **161–164** in Asymmetric C-Alkylation Reactions of Amino Acids

Synthesized salen complexes **161–164** containing S atom in the side radical of ethylene-diamine moiety were investigated as chiral catalysts in asymmetric synthesis reactions of α -amino acids. C-alkylation of Schiff base of alanine isopropyl ester and benzaldehyde (**23**) with alkyl halides (C₆H₅CH₂Br, CH₂=CH-CH₂Br) (see Scheme 8.43) was selected as a model reaction of amino acid synthesis [103].



Scheme 8.43

The alkylation reaction was conducted under PTC in the presence of solid NaOH in toluene. After acid decomposition of a mixture of C-alkylation products (without crystallization), the target α -substituted α -amino acids were isolated from hydrolysates by ion-exchange methods.

The absolute configuration and the enantiomeric purity of amino acids (α -methylphenyl-alanine and α -allylalanine) obtained as a result of C-alkylation were determined by chiral GLC analysis and polarimetric measurements (after crystallization of isolated samples). Analytical data indicate that the obtained amino acids have (*R*)-absolute configuration. Optical purity values of the synthesized (*R*)- α -amino acids are shown in Table 8.24.

The dependence of the catalytic activity of complexes on the molar ratio of catalyst/substrate and the dependence of the enantiomeric purity of the reaction products on the enantiomeric purity of the catalyst were investigated [90].

Table 8.24 Results of C-alkylation of Schiff base of isopropyl ether of alanine with benzaldehyde.^{a)}

No.	Chiral catalyst	Alkylating agent	<i>(R)</i> - α -Substituted- α -amino acid	
			Chemical yield (%)	ee (%) ^{b)}
1	161	$\text{C}_6\text{H}_5\text{CH}_2\text{Br}$	78	64
2	161	$\text{CH}_2=\text{CH}-\text{CH}_2\text{Br}$	81	68
3	162	$\text{C}_6\text{H}_5\text{CH}_2\text{Br}$	74	82
4	162	$\text{CH}_2=\text{CH}-\text{CH}_2\text{Br}$	77	73
5	163	$\text{C}_6\text{H}_5\text{CH}_2\text{Br}$	83	76
6	163	$\text{CH}_2=\text{CH}-\text{CH}_2\text{Br}$	81	75
7	164	$\text{C}_6\text{H}_5\text{CH}_2\text{Br}$	76	82
8	164	$\text{CH}_2=\text{CH}-\text{CH}_2\text{Br}$	79	84

a) The reaction conditions – 1 equiv. Schiff base of isopropyl ether of alanine and benzaldehyde, 1.5 equiv. $\text{C}_6\text{H}_5\text{CH}_2\text{Br}$ (or $\text{CH}_2=\text{CH}-\text{CH}_2\text{Br}$), 5 mol% catalyst, 2.2 equiv. NaOH.

b) Enantiomeric purity (ee) was determined by chiral GLC analysis.

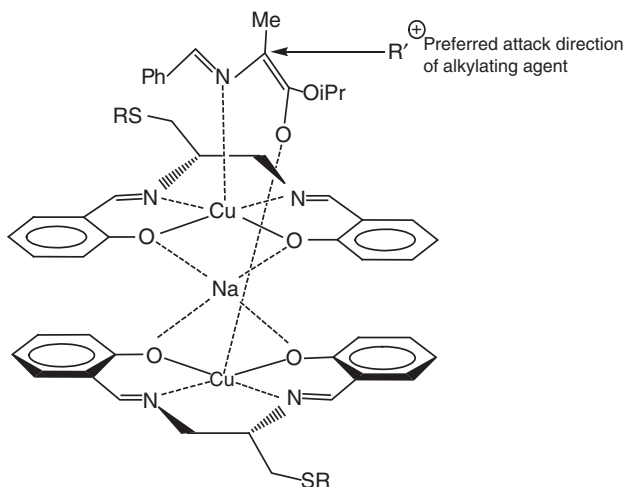


Figure 8.29 Hypothetic model of the transition state of interphase alkylation reaction of the Schiff base of alanine isopropyl ester. The arrow shows the preferable direction of the attack of the alkylating agent.

From the results of other studies, it follows that at stereo differentiating stage of alkylation at least two molecules of the catalyst are involved, and the alkylation process proceeds via the intermediate formation of homochiral ion pair (see Figure 8.29).

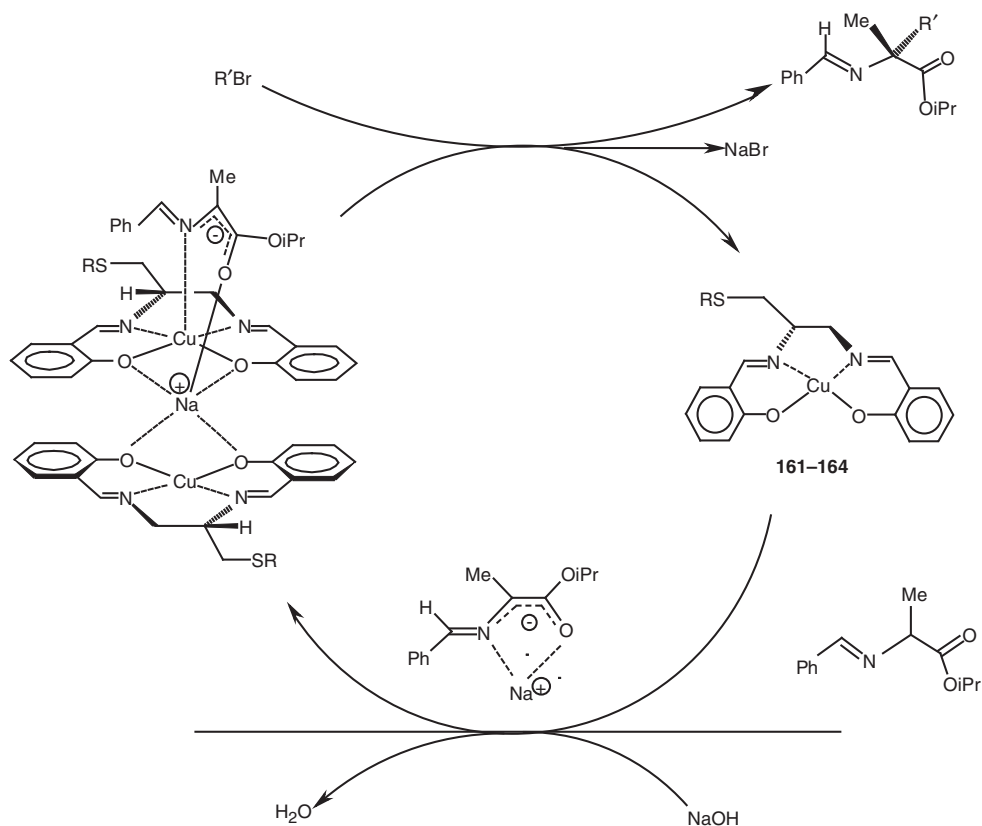
Apparently, in the transition state the molecules of a chiral catalyst solvate Na^+ ion on the phase boundary (on the surface of solid NaOH) of counterion of carbanion, formed from Schiff base of benzaldehyde and alanine isopropyl ester. Consequently, the ion pair acquires sufficient lipophilicity to pass into the solution where it is involved in C-alkylation reaction.

Such processes were also observed in alkylation reactions of Schiff bases of amino acids by alkylhalides when salen metal complexes based on chiral cyclohexyldiamine were used as catalysts.

Based on these data, the following possible mechanism of interphase alkylation of alanine Schiff base might be suggested (see Scheme 8.44).

Initially, on the phase boundary under the influence of a solid base, a substrate carbanion is formed, which is then solvated with two molecules of Cu^{II} complex and in this form passes into the organic solvent. As with the catalysis by quaternary ammonium salts, in this case transport of the substrate carbanion into the solution is also carried out by ion pair formation with the catalyst.

In case of using metal complexes in alkylation transition state besides weak hydrophobic interactions (as it is observed in the case of catalysis by quaternary ammonium salts), strong coordination interactions are additionally formed, due to which metal complexes are readily solvated with the carbanion of the substrate and fast transfer it to an organic solvent. Simultaneously, a part of Cu^{II} complex moiety binds with an alkyl halide to form the specific “metal complex alkylating



Scheme 8.44

agents.” The reaction of chelated carbanion alkylation by “metal complex alkylating agent” in the organic phase proceeds with high stereoselectivity as two chiral molecules interact with each other. The reaction provides an alkylation product and the initial complex-catalyst, which participates in the catalysis of alkylation of next molecules of substrate is released.

Studies show zero stereoselectivity in C-alkylation reactions of Schiff base **23** catalyzed by Cu^{II} salen complexes on the basis of 3,5-di-*t*-butylsalicyl aldehyde. Presumably, this is due to steric hindrances of additional coordination of the alkylating agent with a substrate on a coordination plane of two molecules of the chiral complex-catalyst connected via an ion pair with the Na^+ .

It should be noted that this mechanism does not take into account all the features of the studied reaction. In particular, the role of oxygen is neglected, though in its absence the reaction does not proceed. The mechanism of direct alkylation is also unclear.

However, based on the analysis of all the data available, it can be summarized that as in the case of catalysis by quaternary ammonium salts, the mechanism of

interphase C-alkylation reaction of Schiff bases of amino acids catalyzed by salen complexes of transition metal ions includes three major steps: (i) formation of the carbanion, (ii) transfer of the carbanion into the solution and (iii) the alkylation process itself.

As a result of research related to the study of the relationship of the structure of the catalyst and its catalytic and stereodifferentiating abilities in the reaction of asymmetric alkylation of substrate **23** under PTC, it was found that for the effective catalysis of asymmetric interphase alkylation the presence of phenolic oxygen atoms in the catalyst molecule was required. In addition, the introduction of substituents into the aromatic nucleus of salicyl aldehyde leads to a decrease in stereodifferentiating ability of the catalysts, moreover, the closer the substituent is located to the phenolic oxygen atom of the salicylic fragment and the stronger its chelating ability, the lower is the stereodifferentiating ability and efficiency of the catalyst. Along with this, increase of complex solubility in toluene enhances efficiency of the catalysts, simultaneously inhibiting their stereodifferentiating ability. Increase in the volume of groups introduced into a fragment of chiral diamine leads to an effective shielding of the central metal ion in the catalyst, thereby reducing its catalytic activity. The nature of the central metal ion in the catalyst structure plays a key role at that.

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9

Stoichiometric Asymmetric Synthesis of α -Amino Acids

The asymmetric synthesis of chiral molecules is considered stoichiometric when a chiral inductor involved in the conversion of a substrate is in stoichiometric amounts. Stoichiometric asymmetric synthesis is considered effective if the chiral inductor is regenerated after the synthesis with full retention of original optical activity, allowing it to be reused in the asymmetric synthesis reactions.

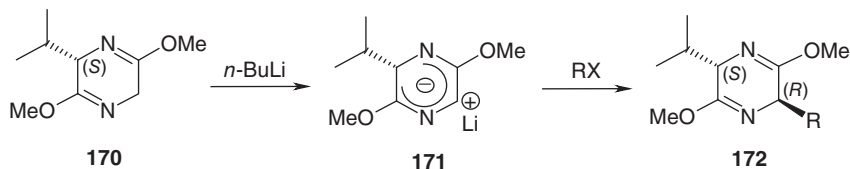
The diastereoselective stoichiometric asymmetric synthesis is the most common, as the initial chiral inductor contains a chiral center, and the reaction results in diastereomers differing by physical properties. Asymmetric synthesis can be controlled by both thermodynamic and kinetic factors.

In the field of diastereoselective synthesis of amino acids, the methods proposed by Evans [1], Seebach [2], Schöllkopf [3], Oppolzer [4], and Belokon [5, 6] were given the greatest recognition.

One of the universal methods of the eighties of the last century was for the synthesis of amino acids using bis-lactim esters **170** derived from valine and glycine esters suggested by Schöllkopf [7] (see Scheme 9.1). Alkylation of lithium salt **171** provides predominantly *trans*-disubstituted derivative **172**, and usage of (*S*)-valine leads to amino acid of (*R*)-configuration.

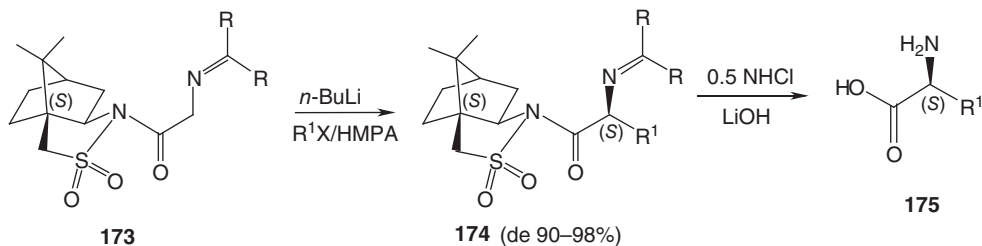
In addition to alkylation, bis-lactim esters were also involved in other reactions. Thus, in the presence of $\text{CuBr} \times \text{Me}_2\text{S}$ complex, lithium salt **171** reacts with α,β -unsaturated carbonyl compounds, and, after transmetallation by $\text{ClTi}(\text{NEt}_2)_3$, is involved in aldol reactions [8, 9]. To improve stereoselectivity of reactions, additives of Cu^{I} and Ti^{IV} complexes are used. In some cases, these reactions allow obtaining amino acids which are impossible to get using alkylation reactions, particularly in the case of passive or inaccessible alkylating agents. Despite the fact that Schöllkopf's method allows obtaining various polyfunctional amino acids with high enantioselectivity, the chemical yields of products are generally low (19–42%); moreover, the conditions for isolation of the amino acid and separation of the starting chiral inductor for each substrate are selected separately [10].

Another approach to the synthesis of α -amino acids using camphorsultam as chiral auxiliary for diastereoselective alkylation of glycine imines **173** ($\text{R} = \text{SMe}$) was implemented by Oppolzer. By deprotonation of **173** followed by alkylation with alkyl iodides or bromides in the presence of hexamethylphosphoramide



Scheme 9.1

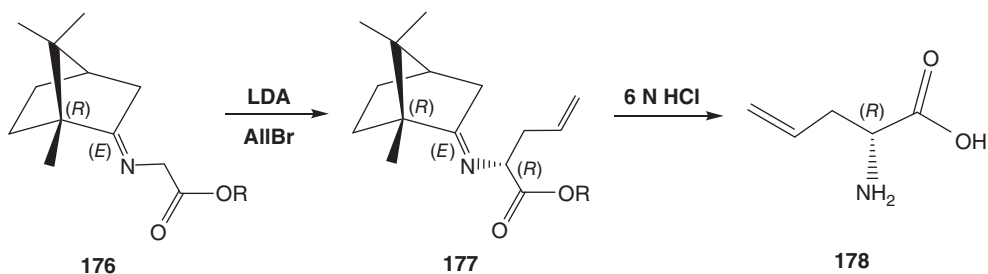
(HMPA), **174** was synthesized with high diastereoselectivity and chemical yields [11, 12] (see Scheme 9.2). Purification of the isolated diastereomer **174** and its subsequent hydrolysis afforded amino acid **175**.



Scheme 9.2

This method, in a modified version, was successfully used by other research groups, also with high diastereoselectivity (de >90%) [13].

Efficient substrates for the asymmetric synthesis of amino acids are Schiff bases derived from glycine ester and chiral ketones. These include glycine imines based on (1*R*,4*R*)-camphor **176** [14, 15] (see Scheme 9.3). By alkylation of these imines using lithium diisopropylamide (LDA) as a base followed by hydrolysis of alkylation products, **177** (*R*)-amino acids [14, 15] are obtained; with that, a significant impact on the stereoselectivity of the alkylation process has the starting synthon in the form of an ester.



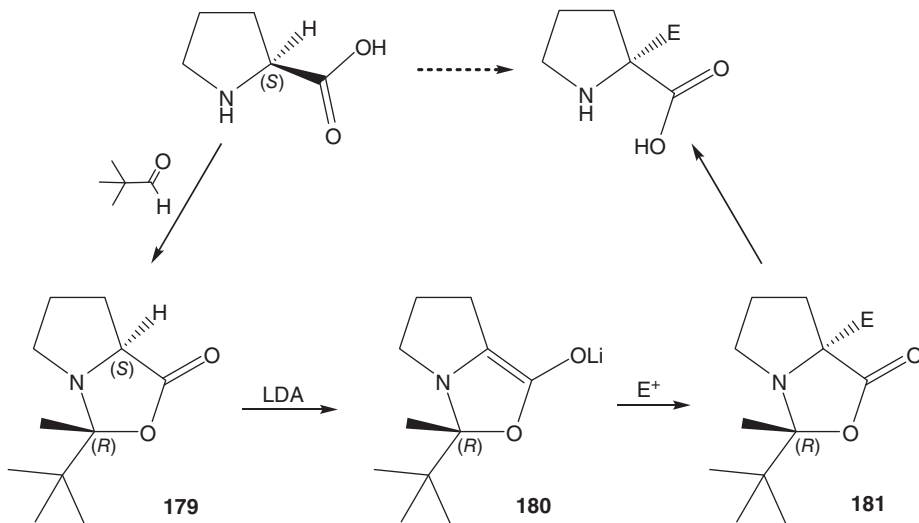
Scheme 9.3

Among the used esters were the *tert*-butyl, *cyclo*-hexyl, as well as chiral esters of (+) and (–)-menthol; with that, the maximum asymmetric induction of product

178 was achieved using (+)-menthyl ester (85% ee), and in the case of (–)-menthyl ester the ee of the product did not exceed 3%.

Chiral derivatives **176** were also used in the reactions of 1,4-Michael addition [16].

The original method of “self-reproducing chirality” was proposed by Seebach [17], which is based on the alkylation of chiral cyclic carbanion obtained by the action of lithium bases (LDA, BuLi) on the interim aminoacetal synthesized by condensation of optically pure amino acids with pivaloyl aldehyde (see Scheme 9.4).

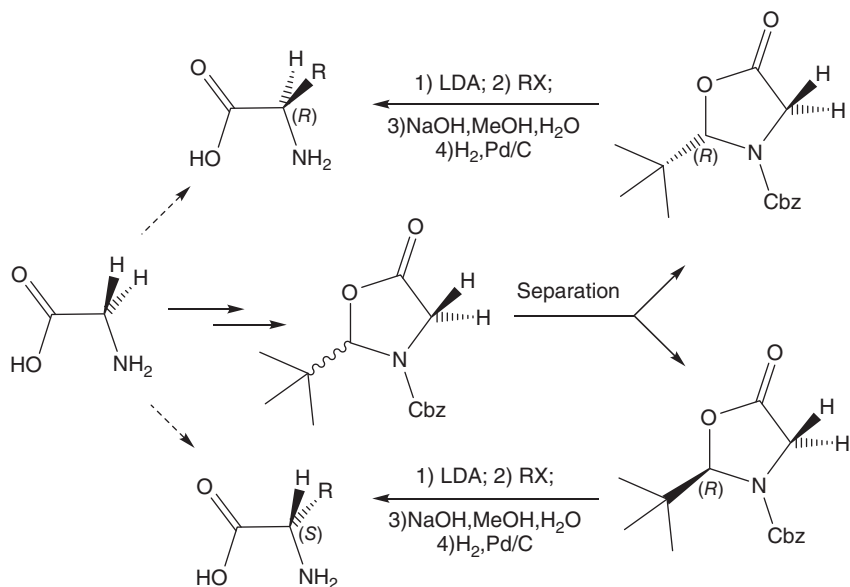


Scheme 9.4

During formation of cyclic compound **179**, the chiral center at the carbon atom of the amino acid induces selective formation of a new asymmetric center, thereby forming a single diastereomer. Under the action of a base, chiral enolate **180** is formed from **179** due to detachment of α -proton, and the initial asymmetric center of amino acid disappears. The electrophile then selectively attacks from the *re*-side of the chiral enolate, and a new substituent at the carbon atom of the amino acid fragment always enters into *trans*-position with respect to the *tert*-butyl group of **181**. Enantiomeric purity of the amino acids obtained by this method is 90–98% [18].

The reaction of glycine with the pivaloyl aldehyde leads to formation of enantiomers, rather than diastereomers. The enantiomers can be separated by crystallization with a mandelic acid [19] or by chromatography on a chiral phase [20] (see Scheme 9.5).

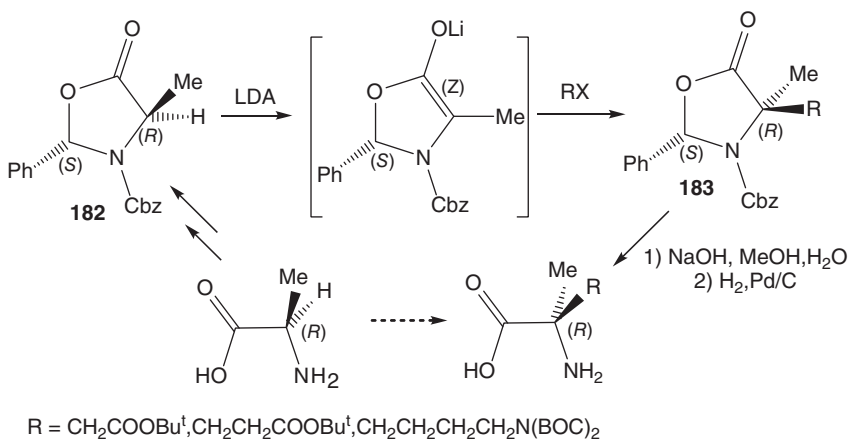
Alkylation reaction is carried out as described in the case of proline synthon. The attack of the electrophile also selectively comes from the *re*-side of the chiral enolate and the substituent enters into *trans*-position relative to the *tert*-butyl



Scheme 9.5

group. Enantiomeric purity of amino acids obtained by this method exceeds 95% [21–25].

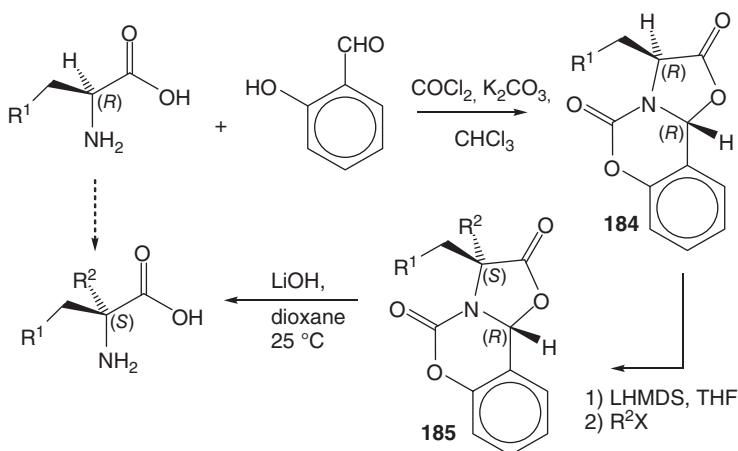
The principle of “self-reproducing chirality” has been successfully used by other authors [26–28]. In Altmann’s work [26], by interaction of (*R*)-alanine with benzaldehyde the Schiff base is obtained, which is then cyclized with benzylchloroformate into (2*S*,4*R*)-2-phenyl-4-methyl-oxazolidinone **182** in the form of a single diastereomer (see Scheme 9.6).



Scheme 9.6

By alkylation of **182** with various alkyl halides products of *trans*-configuration, **183** were obtained; these were then subjected to alkaline hydrolysis (hydrolysis, followed by removal of protecting groups by hydrogenation), resulting in isolation of α -methyl- α -amino acids of (*R*)-configuration. This approach was successfully used in the synthesis of α -methyltryptophane and its derivatives by Zhang and Finn [29].

The method of “self-reproducing chirality” has been modified [27]. Condensation of (*S*)-alanine, (*S*)-phenylalanine or (*S*)-leucine with salicyl aldehyde and phosgene resulted in tricyclic analogs of oxazolidinone **184** in 45–50% yields (see Scheme 9.7).



Scheme 9.7

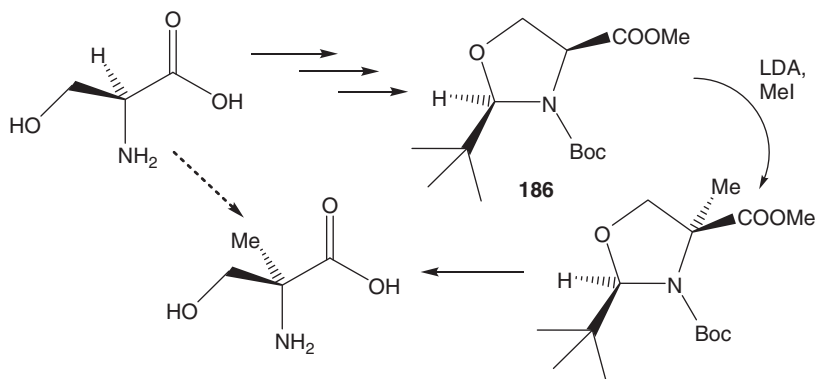
The asymmetric center of α -amino acid induces stereoselective formation of a new chiral center at C10; with that, **184** is formed with de >99%. Alkylation of the lithium enolate, derived from **184** under the action of LHMDS, proceeds predominantly with retention of configuration (product **185**), indicating that the electrophile attacks from the side opposite to the hydrogen of aminoacetal group. The results are shown in Table 9.1.

After hydrolysis of the alkylated oxazolidinone **185**, α -alkyl- α -amino acids were isolated with 60–100% enantiomeric purity.

Table 9.1 Chemical yield and de of product **185**, obtained by alkylation of **184**.

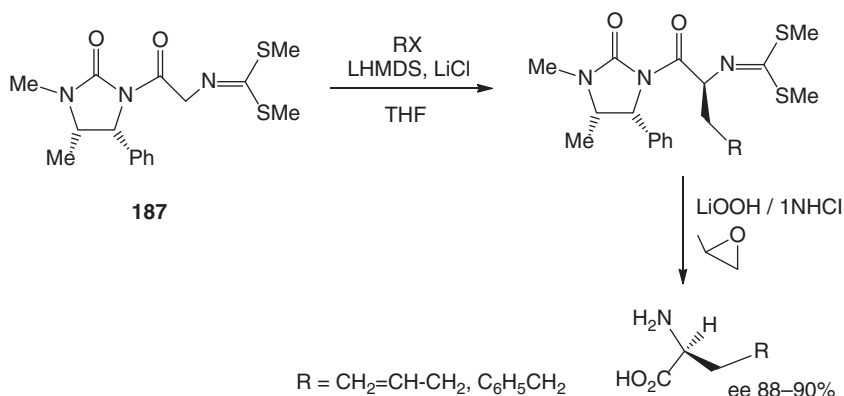
R	Ph	Ph	Ph	<i>i</i> -Pr	<i>i</i> -Pr	H
R'X	$\text{CH}_2=\text{CH}-\text{CH}_2\text{Br}$	EtI	MeI	$\text{CH}_2=\text{CH}-\text{CH}_2\text{Br}$	MeI	$\text{CH}_2=\text{CH}-\text{CH}_2\text{Br}$
de 185 (%)	97	97	89	97	84	92
Yield (%)	94	74	66	81	82	74

The method of “self-regenerating chirality” was developed more than 20 years ago, but it turned out successful to the extent that it is actively used to this day. One of the most recent papers [30] of this series relates to obtaining of α -methylserine from serine by alkylation of methyl ester of N-BOC-2-*tert*-butyl-oxazolidinone-4-carboxylate **186** with methyl iodide (see Scheme 9.8).



Scheme 9.8

Najera and coworkers proposed the use of (4*R*,5*S*)-1,5-dimethyl-4-phenyl-imidazolidin-2-one as a chiral inducer for diastereoselective alkylation of the corresponding imines of glycine [31]. For example, its N-protected glycinate **187** interacts with activated alkyl halides in THF in the presence of lithium hexamethyldisilazide (LHMDS) as a base (see Scheme 9.9).



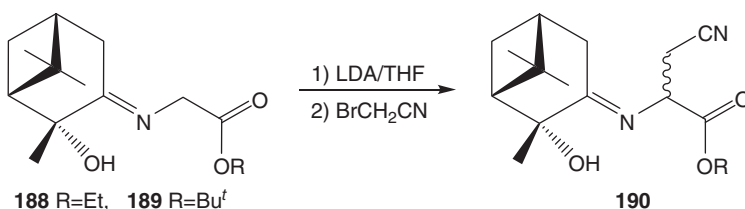
Scheme 9.9

Michael addition reactions proceed under the same conditions [32]. It was found that to achieve high (up to 98% de) diastereoselectivity in the case of using compound **187**, it is necessary to add >1 equiv. of LiCl.

Hydrolysis of the alkylated derivatives by aqueous peroxide or lithium hydroxide with addition of H_2O_2 allows isolating the appropriate (*S*)- α -amino acid with 94% ee and regenerating the original chiral derivative in 73–83% yield.

However, this technique is inapplicable for the synthesis of quaternary α -amino acids; attempts to alkylate alanine templates of this type have proved unsuccessful.

Another direction of synthesis of chiral compounds is the use of the Schiff base of glycine ester with 2-hydroxypinan-3-one **188** [33]. Alkylation of this substrate with bromoacetonitrile leads to imine **190** as a mixture of diastereomers in a ratio of 60/40 that are separated by chromatography (see Scheme 9.10).



Scheme 9.10

After hydrolysis of ketamine bond with 10% HCl, hydrogenation of the nitrile group ($\text{PtO}_2/\text{EtOH}/\text{HCl}$), and additional hydrolysis of the ester group (6N HCl), both enantiomers of diaminobutyric acid were isolated.

Panini and coworkers suggested synthesis of lipophilic nonprotein amino acids from substrate **189** [34]. Alkylation by dodecyl-, tetradecyl-, and hexadecyliodides of the carbanion, derived from **189** under the action of LDA in THF at -78°C , leads to products with 95–96% de.

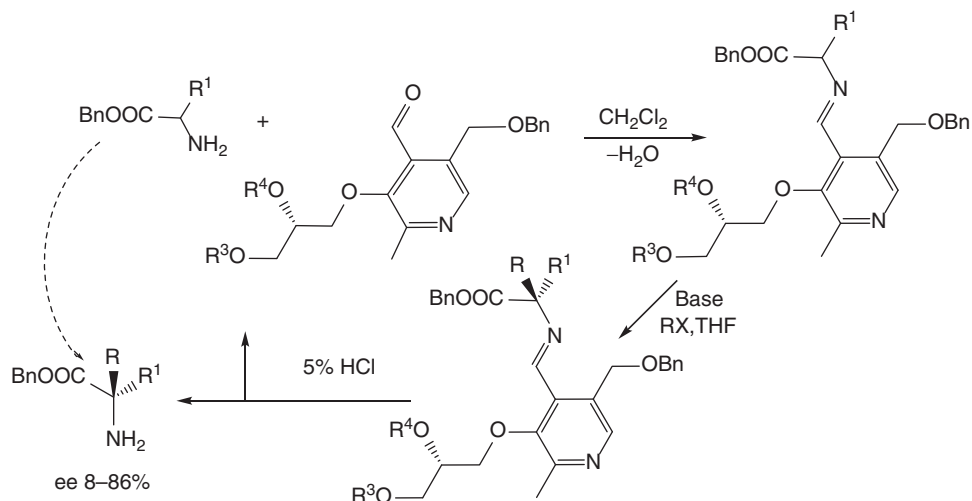
Imanishi and coworkers proposed a method for the synthesis of esters of α,α -dialkylamino acids by the stereoselective alkylation of aldimines derived from α -amino acid esters and chiral derivatives of pyridoxal (see Scheme 9.11) [35].

It is shown that the structure of the chiral side chain of the pyridoxal fragment and the nature of the metal ion of the base used to play an important role in achieving high stereoselectivity. Convenient substituents are the 2-naphthylmethyl and methyl groups (R^3 and R^4 , respectively) in the presence of sodium ions, wherein the ee of the alkylation product is 86%.

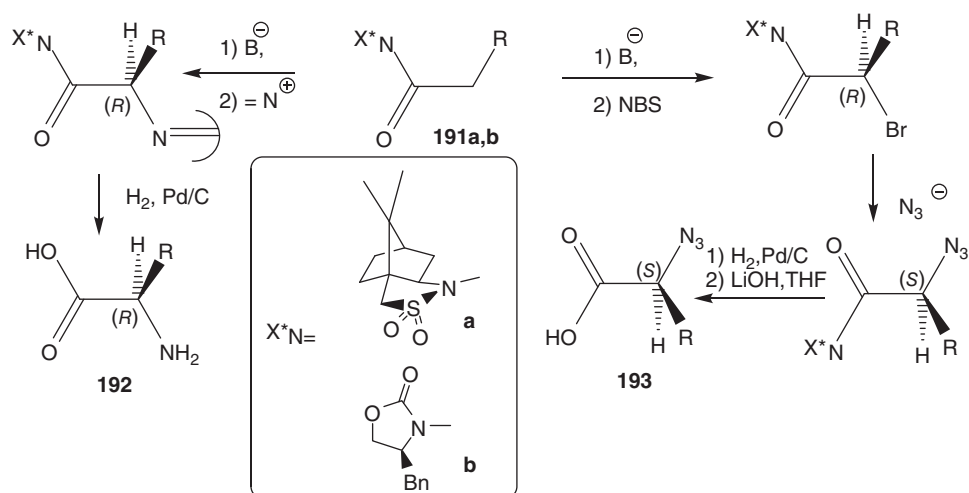
Apart from alkylation of fragments of the simplest amino acids, the asymmetric synthesis of α -amino acids via formation of C–N bond is also possible in the corresponding chiral precursors, for example, by amination of chiral imides of carboxylic acids **191**¹⁾ (see Scheme 9.12).

Direct amination of the N-acylsultam **191a** [36] or N-acyloxazolidinone **191b** [37–39] using various reagents (di-*tert*-butylazodicarboxylate, 2,4,6-trisopropylbenzylsulfonyl azide, 1-chloro-1-nitrosocyclohexane), leads to the

1) The method was proposed by Oppolzer, who also developed a method for the synthesis of amino acids by alkylation of chiral glycine synthon based on camphorsultam, discussed earlier (Scheme 9.2) [11, 12].



Scheme 9.11

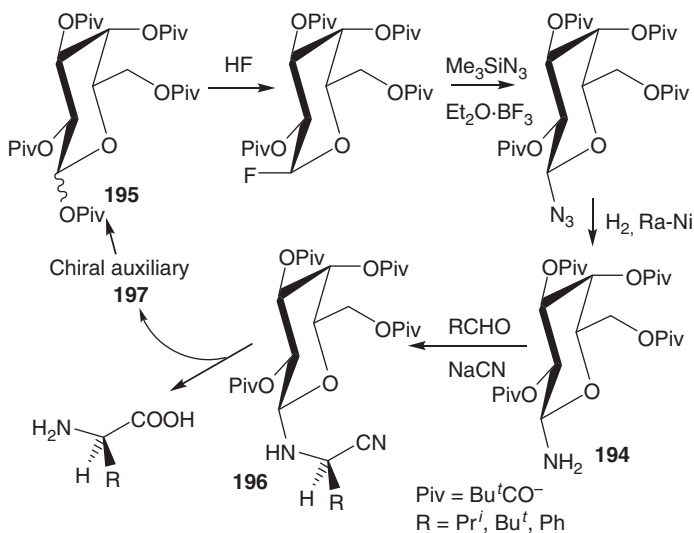


Scheme 9.12

formation of α -amino acids **192** of (*R*)-configuration. The optical purity of amino acids **192** derived from **191a** exceeds 99%. When using **191b**, the enantiomeric purity of (*R*)- α -amino acid depends on the R radical of **191** (ee is 82% for the $\text{R} = \text{Ph}$, 95% for the $\text{R} = \text{Me}$, Bn, Pr^i , and >98% for $\text{R} = \text{Bu}^t$).

During generation of the C–N bond by the consecutive electrophilic bromination of **191** with *N*-bromosuccinimide followed by subsequent $\text{S}_{\text{N}}2$ substitution of bromine by the azido group, α -amino acid **193** of (*S*)-configuration (90–99% ee) was obtained (see Scheme 9.12).

In Kunz's work [40, 41] as a chiral reagent was used, enantiomerically pure 3,4,6-tetra-*O*-pivaloyl-(*R*)-galactosylamine **194** was produced by three-stage synthesis from penta-*O*-pivaloyl galactopyranose **195** (see Scheme 9.13).



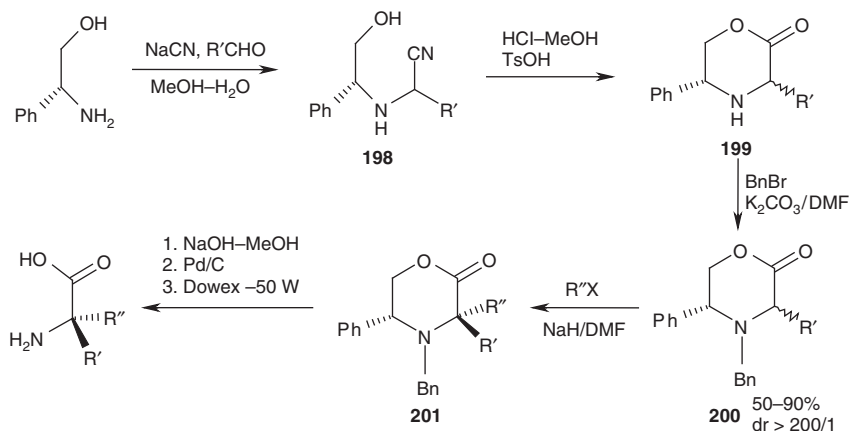
Scheme 9.13

Stereoselective Strecker reaction of compound **194** with aldehyde and NaCN in the mixture of PrⁱOH/AcOH 25:1 (see Scheme 9.13) leads to the formation of *N*-galactosyl- α -aminonitrile **196** in quantitative yield (reaction time 2–4 weeks). Diastereoselectivity of the reaction is 3/1–7/1, depending on the used aldehyde. After hydrolysis of **196**, α -amino acid of (*R*)-configuration and galactose derivative **197**, which can be reused for preparation of chiral reagent **194**, were isolated.

From the examples of asymmetric synthesis of α -amino acids it is evident that, in most cases, as the key stage of the process appears, the enantioselective reaction of chiral nucleophile-carbanion is obtained under the action of the base from the chiral CH-acid with electrophilic reagents.

It is known that α,α -disubstituted α -amino acids in peptides enhance their resistance to chemical and enzymatic degradation [42, 43].

Methods for the asymmetric synthesis of α,α -disubstituted α -amino acids based on electrophilic α -alkylation of amino acid enolates are well known. Thus, Ma and Ding showed that oxazinones **199**, obtained from Strecker's reaction products **198**, could be used as substrates for the diastereoselective alkylation to α,α -disubstituted α -amino acids (see Scheme 9.14) [44]. Alkylation of benzyl-protected oxazinone **200** by various electrophiles resulted in bis-alkylated products **201** in a diastereomeric ratio of >200:1, wherein electrophiles took the *cis*-position relative to the auxiliary phenyl group. Aldehydes were also investigated in the reaction with **200**. It turned out that in this case, mixtures

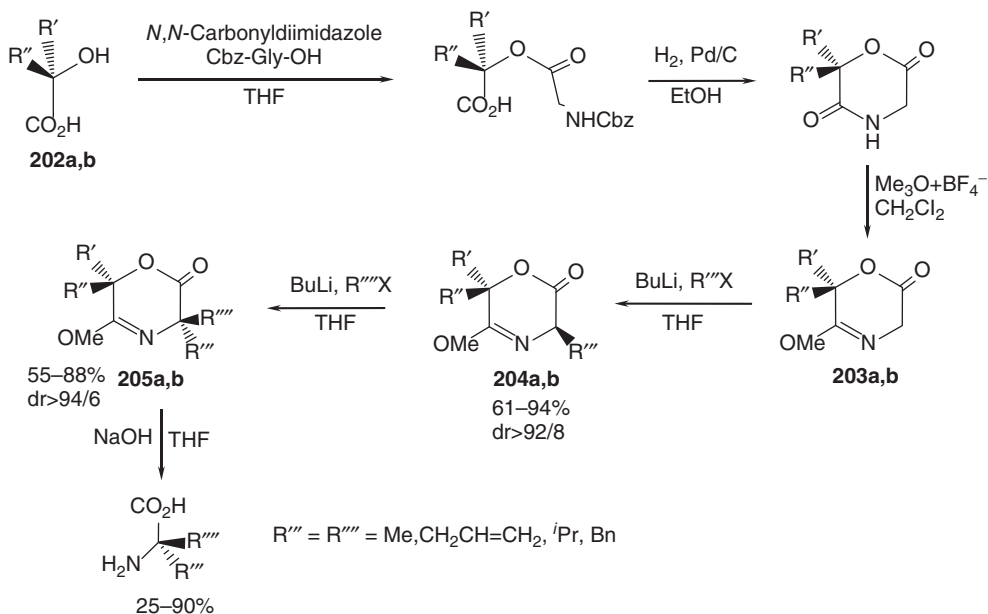


Scheme 9.14

of two diastereomers with the opposite configuration at the secondary carbonyl center in a ratio of 9 : 1 were formed.

Wanner *et al.* [45] used two related auxiliary reagents **202a** and **202b** in the synthesis of derivatives of Schiff bases of glycine and oxazolines **203a** and **203b** that were obtained from an auxiliary reagent in four steps (see Scheme 9.15).

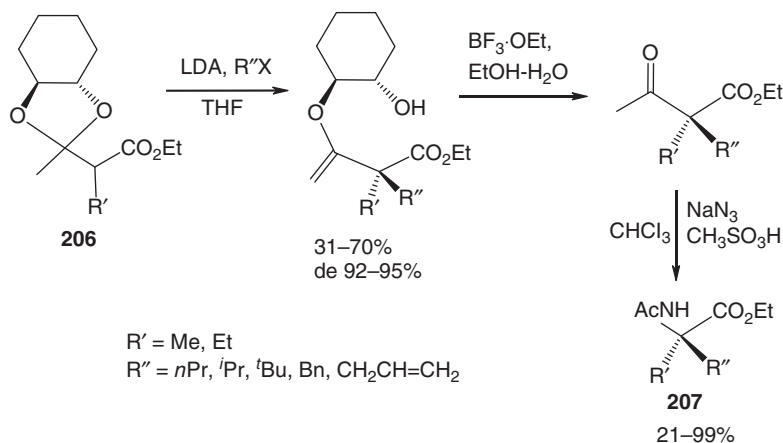
Deprotonation followed by treatment with alkyl halides and led to the monoalkylated product **204** with high diastereoselectivity. The electrophile was



Scheme 9.15

introduced into *trans*-position of enolate with respect to the *tert*-butyl group (in the case of **203b**). Bisalkylated products **205a,b** were synthesized similarly from monoalkylated oxazinones **204a,b**. The product **205** was then subjected to alkaline hydrolysis, leading to the formation of α,α -disubstituted α -amino acid. The authors also carried out cyclopropanation reaction of enolate **203a** with an enantiomerically pure epichlorohydrin.

Tanaka's group synthesized α,α -disubstituted β -keto esters by diastereoselective alkylation of acetal **206** (see Scheme 9.16) [46]. While an attempt to produce α,α -disubstituted α -amino acids in acceptable yields by the initially envisaged Beckmann rearrangement failed, the stereospecific Schmidt rearrangement led to *N*-acylated amino esters **207** in excellent yields.



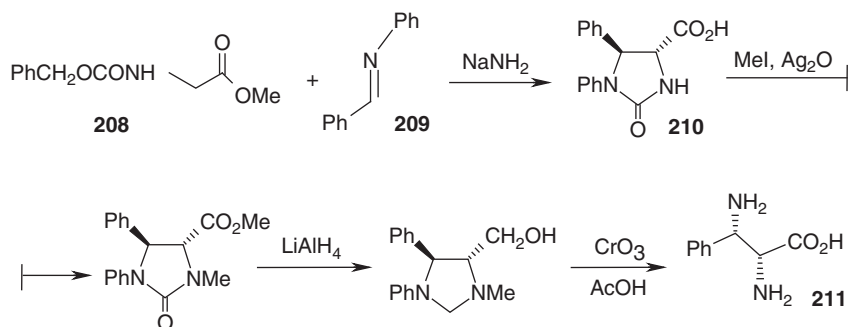
Scheme 9.16

In the review article, Cativiela and Diaz-de-Villigas have demonstrated progress in the development of new methods and surveyed the existing methods for the synthesis of α,α -dialkyl-amino acids [47].

The existing methodologies of diastereoselective alkylation of enolates, self-reproducibility of stereocenters, and alkylation of chiral substrates were widely and effectively used in the synthesis of α,α -dialkylamino acids with different side radicals. The article describes in detail the methods for the synthesis of amino acids by self-reproducibility of stereocenters through oxazolidinones [2, 48, 49], imidazolidinones [50–52], tetrahydropyrimidinones [53, 54], oxazolidines [55, 56], and oxazolines [57, 58]; methods for the diastereoselective alkylation of enolates of acyclic [59–62] and cyclic [63–67] chiral amino acids; attachment techniques of nucleophiles to imines [68–70], sulfimines [71, 72], oxime esters [73], and nitrones [74]; and methods for the enantioselective synthesis of amino acids by alkylation in PTC [75, 76] conditions, electrophilic amination [77], and so on.

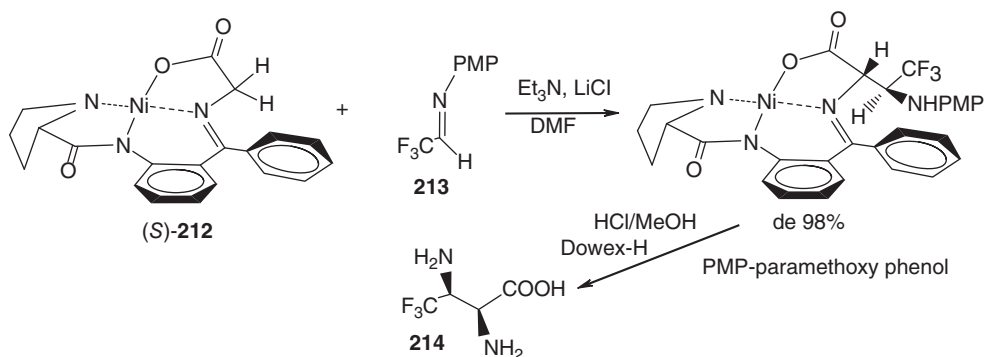
Many important peptide antibiotics contain fragments of optically active α,β -diamino acids, in particular, napsamycins [78], mureidomycins [79], laven-damycins [80], glutamycins [81], bleomycin A₂ [82], peplamycin [83], viomycin [84], capreomycin [85], tuberactinomycin [86], and so on. Therefore, development of methods for the stereoselective synthesis of optically active α,β -diamino acids is in the focus of synthetic chemists.

The method for the stereoselective synthesis of $(\pm)$ -2-oxo-1,5-diphenyl-4-carboxylic acid (**210**) by reacting *N*-Cbz-glycinate **208** with imine **209**, which is further subjected to reduction and transformed to $(\pm)$ -2,3-diamino-3-phenyl-propionic acid (**211**), was described (see Scheme 9.17) [87].



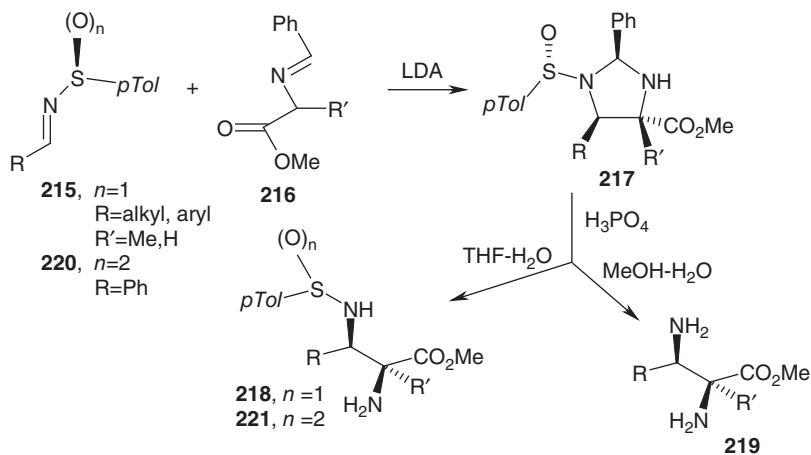
Scheme 9.17

The asymmetric version of this synthesis using chiral glycinate was developed by Soloshonok [88]. The reaction of enantiomerically pure Ni^{II} complex of α -iminoglycine **212** with trifluoromethyl imine **213** proceeds with high diastereoselectivity, resulting in *syn*-3-trifluoromethyl-2,3-diamino acid **214** with 98% de (see Scheme 9.18).



Scheme 9.18

Enantiomerically pure esters of *syn*-*N*-sulfinyl- α,β -diamino acids **218** or free esters of α,β -diamino acids **219** were obtained from enantiopure 2-carbomethoxy-*N*-sulfinyl imidazolidines **217**, which in turn were obtained with high selectivity by reacting α -iminoethers **216** with sulfinylimine **215** (see Scheme 9.19) [89]. Sulfinylimine **215** simultaneously participates in the reaction as a chiral inductor. Interestingly, in the case of using the achiral *N*-sulfonylimine **220** ($R = \text{Ph}$) and α -iminoglycinate **216** ($R' = \text{H}$), the racemic *N*-sulfonyl- α,β -diamino esters **221** were formed with low diastereoselectivity.



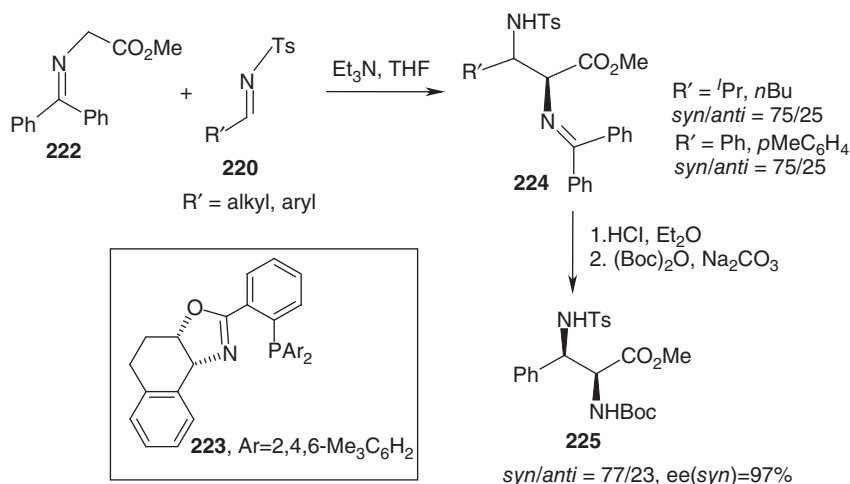
Scheme 9.19

The method for the asymmetric synthesis of α,β -diamino acids from Lewis acid-stabilized chiral enolate of iminoglycinate, which is obtained from **222** and triethylamine in the presence of 10% CuClO_4 and 10% chiral oxazoline **223**, was also described. This enolate is reacted with *N*-sulfonyl imine group **220**, forming as major products *syn*- α,β -diamino ethers **224** in good enantiomeric yields (88–97%).

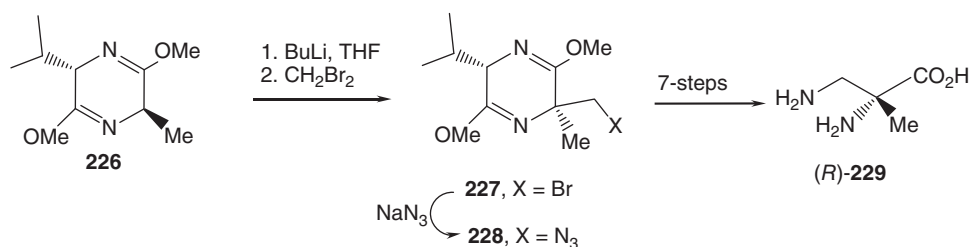
Interestingly, the aliphatic nature of *N*-sulfonyl imines **220** is very important to ensure good *syn/anti* diastereoselectivity (95/5) (see Scheme 9.20).

Acid hydrolysis of benzhydryl group and introduction of the *tert*-butoxycarbonyl group ultimately led to the formation of esters of *N*-protected α,β -diamino acids **225** [90]. Reactions of glycinate and related compounds with electrophiles other than imines were also used to construct carbon–carbon bond of α,β -diamino acids and their derivatives.

In 1991, Mittendorf's group [91] reported enantioselective synthesis of α,β -diamino acid **229** by diastereoselective alkylation of bislactim ether **226** using dibromomethane followed by nucleophilic substitution of bromine in bromomethyl bislactim ether **227** with sodium azide. After reducing the resulting azide **228**, a six-step cycle of transformations leads to enantiomerically pure α -methyl- α,β -diamino acid **229** in hydrochloride form (see Scheme 9.21).



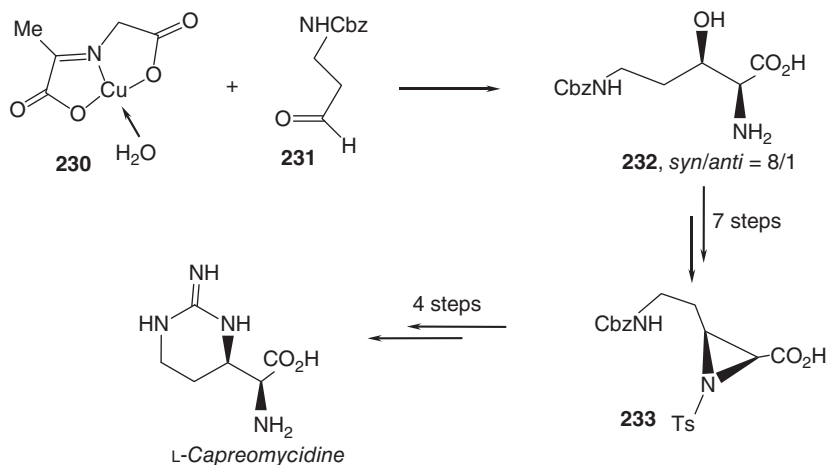
Scheme 9.20



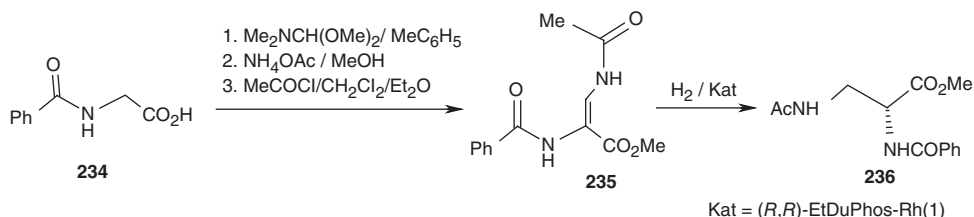
Scheme 9.21

In the synthesis of α,α -disubstituted α,β -diamino acids as fragments of cyclic amidine containing peptidomimetics, other electrophiles were also used, for example, *N*-bromomethyl phthalimide. The synthesis of L-capreomycin was performed by carbon–carbon bond construction. In this procedure, the main synthetic intermediate product was a derivative of β -hydroxy-L-ornithine **332**, which was readily obtained by condensing copper (II) complex of *N*-pyruvylidenglycinate **230** with electrophilic β -(benzyloxycarbonylamino)propion aldehyde **231** as a mixture of *syn/anti* isomers in a ratio of 8/1. After separation, the *syn* (threo) isomer was acylated and cleaved by acylase. Finally β -hydroxy-L-ornithine was transformed to L-capriomicidine by sequential synthesis, comprising the formation of an intermediate, and then cleavage of the *cis*-aziridine ring to **233** (see Scheme 9.22) [92].

Amide acetals also turned out to be useful electrophiles in the synthesis of α,β -diamino acids similar to the synthesis of piperidine and pyrrolidine diamino acids, the streptolitin analogs. Furthermore, using this method, it became possible to carry out highly enantioselective synthesis of derivatives of α,β -diaminopropionic acid **236** (see Scheme 9.23) [93].



Scheme 9.22

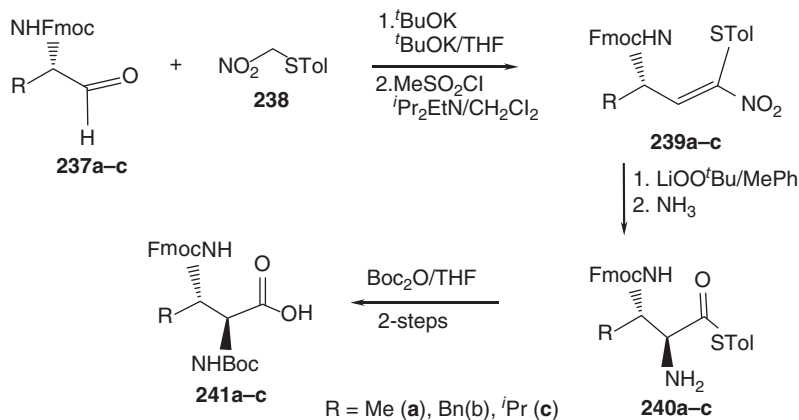


Scheme 9.23

As can be seen from Scheme 9.23, the condensation of hippuric acid **234** with dimethylacetal of dimethylformamide followed by treatment with NH_4OAc in MeOH, and acylation of the resulting enamide leads to ester of α,β -dehydro- α,β -diamino acid **235**. A key step for the enantioselective synthesis of **236** is the asymmetric hydrogenation of **235** using complex $(R,R)\text{-EtDuPhos-Rh(I)}$, leading to the ester of α,β -diamino acid in a yield of 99% and 99% ee.

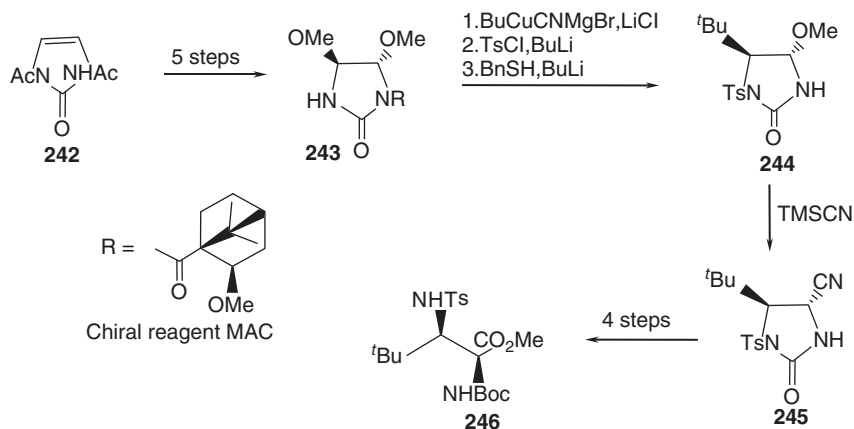
Construction of the carbon–carbon bond in synthesis of α,β -diamino acids is also possible by introducing a nucleophilic synthetic equivalent into a molecule. Nitro compounds were used as nucleophiles. Thus, Jackson's group developed a new method to obtain enantiopure *anti*- α,β -diamino acids by gradual condensation of (*p*-tolylthio)nitromethane **238** with α -amino aldehydes **237a–c**. The nitroalkenes **239a–c** formed were subjected to nucleophilic epoxidation with lithium *tert*-butyl hydroperoxide and diastereoselective epoxide cleavage using NH_3 , leading to α,β -diamino thioesters **240a–c** that, in two stages, were further transformed to protected *anti*- α,β -diamino acids **241a–c** (see Scheme 9.24) [94].

The synthesis of ester of *syn*- α,β -diamino acid **246** by consecutive addition of cyanocuprate and cyanide to dimethoxyimidazolidinone was recently reported. Enantiomerically pure key intermediate dimethoxy imidazolidinone



Scheme 9.24

243, obtained from **242** in five steps, was involved in the reaction of nucleophilic addition with *iso*-butylcyanocuprate (see Scheme 9.25) [95].



Scheme 9.25

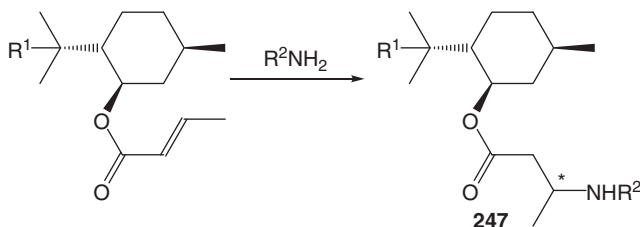
Further introduction of the tosyl group and removal of the chiral auxiliary reagent MAC provided *N*-tosylmethoxy imidazolidinone **244**, which then reacted with TMSCN in the presence of Lewis acid to give **245**. As a result of the four-step process consisting of acid hydrolysis of the nitrile group and cleavage of the imidazolidinone, enantiomerically pure ester of *syn*- α,β -diamino acid **246** was obtained in good yield.

More details about the synthesis and biological properties of α,β -diamino acids are reported in a review article by Viso *et al.* [96].

Optically active β -amino acids in a series of biologically active chiral molecules are of certain interest. Currently, there are many books [97], a number of reviews

[98, 99] and articles [100] relating to the stereoselective synthesis of optically active β -amino acids, so this monograph will cover only the most general aspects.

One of the common methods of stoichiometric asymmetric synthesis of β -amino acids is the addition of amines to acrylic-type chiral systems. The most typical example to consider is the research [101] on stereoselective addition reactions of primary amines to chiral esters of crotonic acid, as shown in Scheme 9.26. It was found that in the case of 1-menthylcrotonate ($R^1 = H$), the asymmetric induction did not exceed 25%.

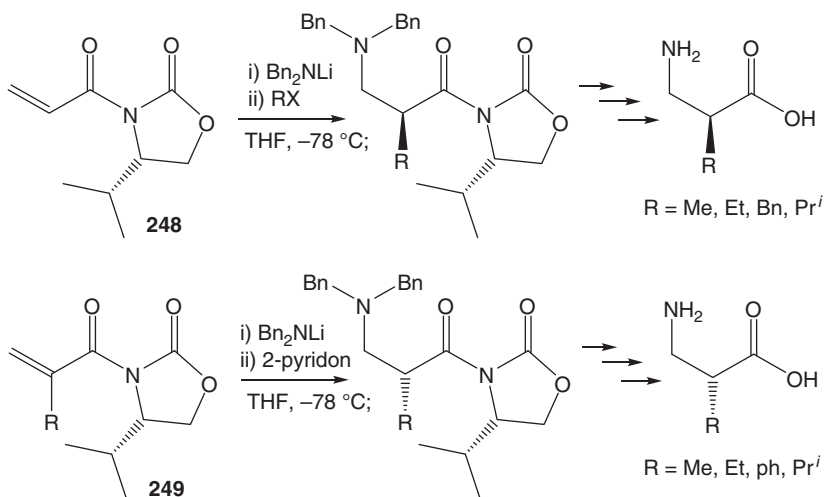


Scheme 9.26

In the transition to 8-phenylmenthol ($R^1 = Ph$) and its *para*-substituted derivatives, the diastereomeric purity of product **247** reaches 60–99%, depending on the volume of substituent R^1 in the menthol fragment.

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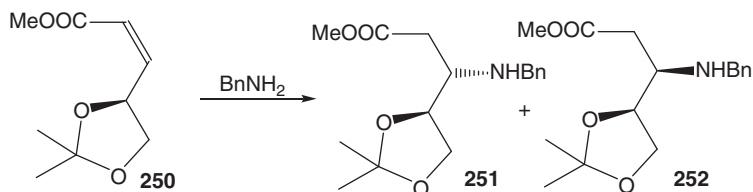
The use of similar acrylic systems **248** and **249** (but with a chiral inducer of different structure) was recently proposed by Davies [102] (see Scheme 9.27).



Scheme 9.27

Attachment of lithium dibenzylamide followed by asymmetric protonation of the resulting anion by 2-pyridone or by alkylation with alkyl halides allows obtaining a set of different enantiomers of α -alkyl- β -dibenzylamino-propionic acid in enantiomerically pure form with high diastereoselectivity (96–97% de).

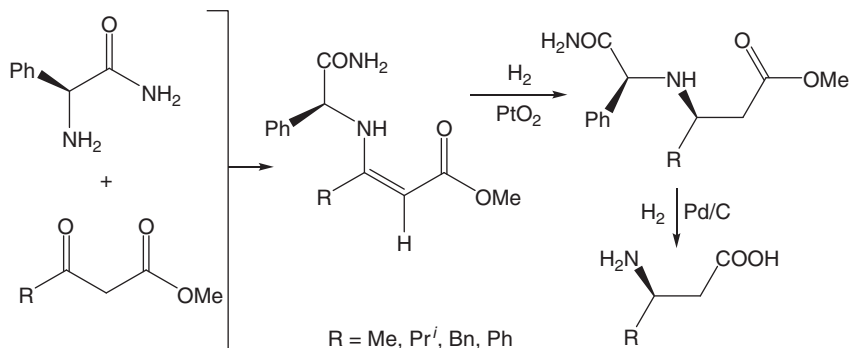
Stereoselectivity of addition can also be provided by the chiral moiety with activated C=C bond. Attachment of achiral amines to chiral α,β -unsaturated system **250** (see Scheme 9.28) also leads to the formation of optically active β -amino acid derivatives [103].



Scheme 9.28

By reaction of **250** with benzylamine proceeding at -50°C within 50 h, (3*R*)-benzylamino ester **252** was obtained in 85% yield. It is shown that the stereoselectivity of the reaction depends on the temperature. Thus, at -20°C , a mixture of **251** and **252** is formed in a ratio of 1/15, and at 0°C – in a ratio of 1/4.

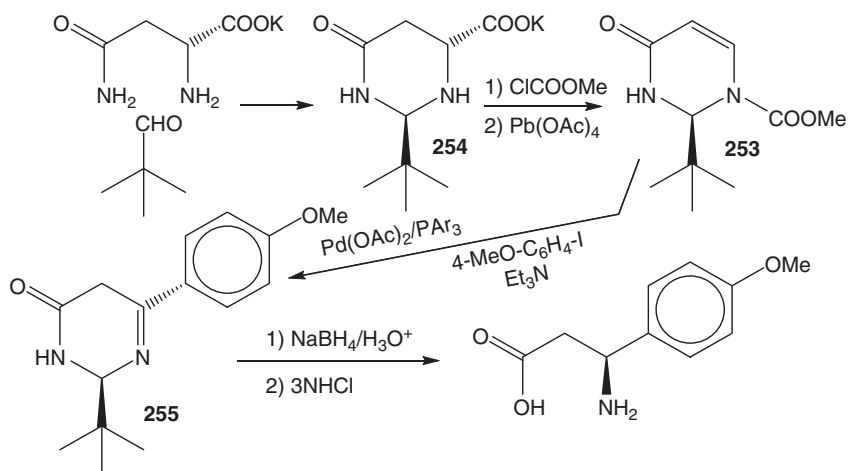
A group of researchers from Merck Company [104], which includes Grabowski who has spearheaded the industrial use of asymmetric phase-transfer catalysis, carried out attachment of chiral amines to the prochiral system followed by reduction of chiral enamines (see Scheme 9.29). As a chiral amine, a low-cost and accessible amide of (*S*)-phenylglycine was used.



Scheme 9.29

Diastereoselective reduction of enamines proceeds in quantitative yield and with 90–99% ee of the products. The next step – removal of the protecting group – also flows smoothly enough in yields exceeding 85%.

A method for the synthesis of optically pure β -aryl- β -amino acids by conjugate addition of aryl halides to the chiral enamine type system was developed by Konopelski and coworkers [105]. Heterocyclic chiral dihydropyrimidinone **253** was synthesized by the principle of “self-reproducing chirality” on the basis of (*S*)-asparagine (see Scheme 9.30). By reaction of potassium salt of (*S*)-asparagine with pivaloyl aldehyde— substituted pyrimidinone, **254** containing two asymmetric carbon atoms was obtained. One of them belonged to the original asparagine; the second was formed by condensation with pivaloyl aldehyde. This compound was subjected to oxidative decarboxylation under the action of $\text{Pb}(\text{OAc})_4$ to form **253**. This eliminated the chirality of the starting amino acid fragment, but the secondary asymmetric center formed by pivaloyl aldehyde was retained (enantiomeric purity of **253** was 98%).



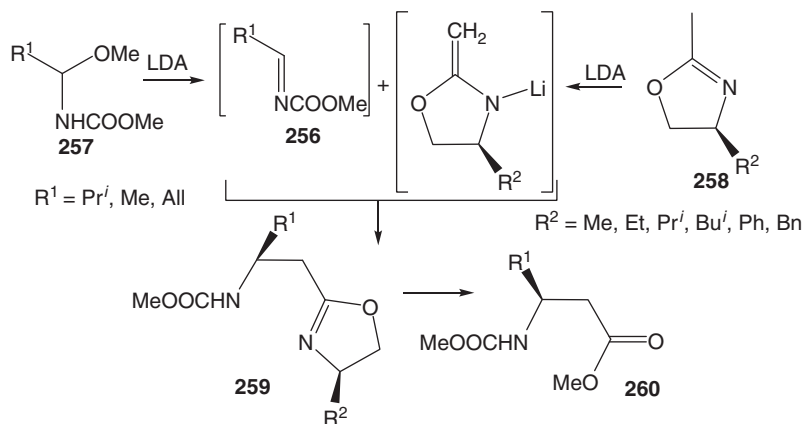
Scheme 9.30

Along with the methods based on the conjugate addition to α,β -unsaturated systems, addition of carbanions to the imine $\text{C}=\text{N}$ bond is widely used in stereoselective synthesis of β -amino acids.

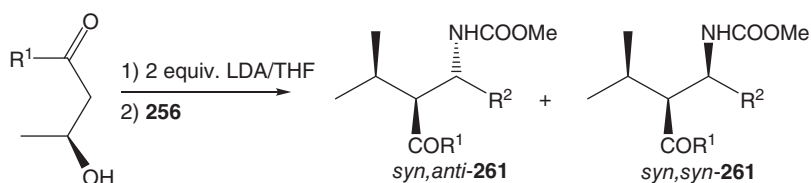
Interaction of *N*-methoxycarbonyl imine **256**, obtained *in situ* from α -methoxycarbamate **257**, with a carbanion in its turn obtained from chiral reagent **258**, proceeds enantioselectively [106] to produce an excess of one of the enantiomers – a derivative of α -unsubstituted β -amino acid **259** (see Scheme 9.31).

The enantiomeric purity of **259** depends significantly on the R^2 radical in the chiral oxazoline; and when $\text{R}^2 = \text{Pr}^i$ (oxazoline **258** obtained from (*S*)-valinol), has the highest ee value (72–90%). Hydrolysis of **259** leads to target β -amino acid **260**.

Similarly, *N*-methoxycarbonyl imine **256** was used in enantioselective synthesis of β' -hydroxy- β -amino acids [107]. Interaction of **256** with dilithium enolate ester of (*R*)-hydroxybutanoic acid leads to the formation of a mixture (*syn,anti*)- and (*syn, syn*)-**261**. Moreover, the (*syn, anti*)-isomer is formed in excess (see Scheme 9.32).



Scheme 9.31



Scheme 9.32

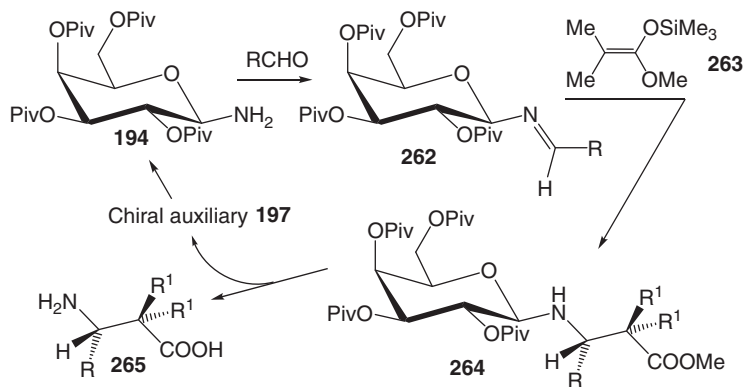
The ratio of (*syn,anti*)/(*syn,syn*) diastereomers increases in transition from methyl and/or *iso*-propyl ester of hydroxybutanoic acid (ratio about 2/1) to more bulkier *t*-butyl ether (8/1).

In some cases, the opposite approach was used [108]: chiral imine **262**, prepared from 3,4,6-tetra-*O*-pivaloyl- β -(*R*)-galactosylamine **194**,²⁾ is reacted in Mannich reaction with an acetal of silyl ketene **263**. As a result of the reaction, an ester of *N*-galactosyl- β -amino acid **264** is formed with high enantiomeric purity (>90%) (see Scheme 9.33).

After hydrolysis of **264** (HCl in MeOH), enantiomerically pure α,α -dialkyl- β -amino acid **265** is obtained and initial chiral auxiliary **197** is recovered in a yield >90% (see Scheme 9.33).

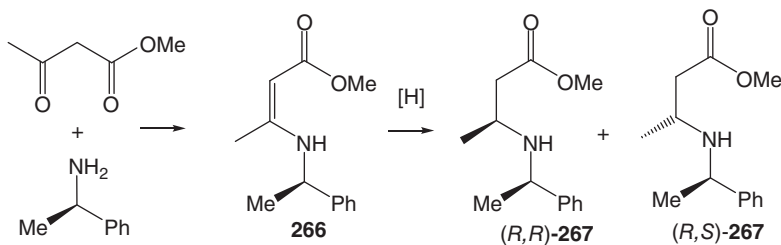
The method for the asymmetric synthesis of β -amino acids by reduction of enamines derived from esters of β -oxocarboxylic acid by reaction with a chiral amine was also described [109, 110]. Condensation of methyl ester of 3-oxobutanoic acid with (*R*)-phenylethylamine resulted in enamine **266**; and, by reduction of **266**, a mixture of diastereomers **267** was formed, which was separated as follows: phenethyl group was removed by hydrogenation affording

2) The same authors used **194** also in the stereoselective Strecker reaction [40, 41] (see Scheme 9.13).



Scheme 9.33

3-aminobutanoic acid of (*S*)-configuration from (*R,S*)-**267**, and 3-aminobutanoic acid of (*R*)-configuration from (*R,R*)-**267** [109] (see Scheme 9.34).



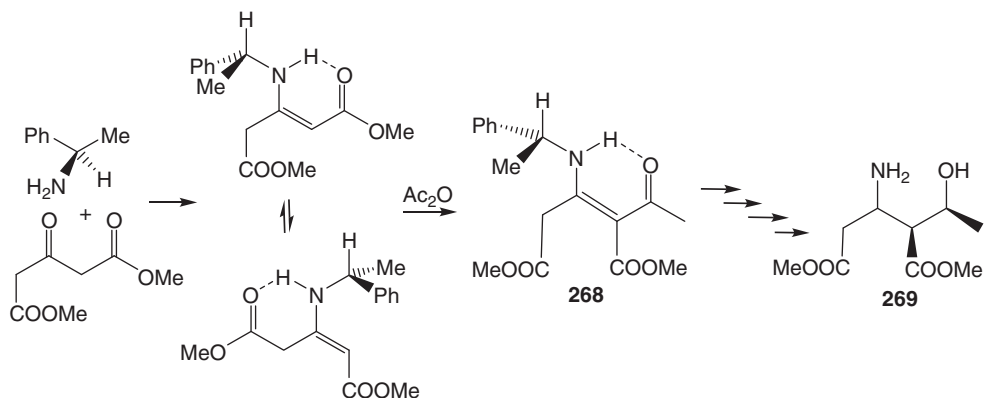
Scheme 9.34

In Melillo's work [110], by condensation of dimethyl acetonedicarboxylate with (*R*)-phenylethylamine, a mixture of enamines was obtained, which was then subjected to acylation leading to enamine ketone **268** in a yield >95% (see Scheme 9.35).

To reduce **268**, two methods were used: catalytic hydrogenation over Pt/C in a mixture of H₃PO₄ and AcOH and reduction using catecholborane at -78 °C. In both cases, only one diastereomer of β -amino acid **269** was obtained with enantiomeric purity >96%. Thus, despite the multistep process, this method enables obtaining multifunctional β -amino acids in optically pure form.

The literature describes examples [111–113] of stereoselective alkylation of chiral cyclic (**270** [111] and **271** [112]) and acyclic (**272** [113]) enolates of β -amino acids in α -position, as shown in Figure 9.1.

Authors [113] showed that the alkylation of dilithium enolate of methyl or ethyl ester of *N*-acyl derivative of (*R*)- β -aminobutyric acid resulted in a product of



Scheme 9.35

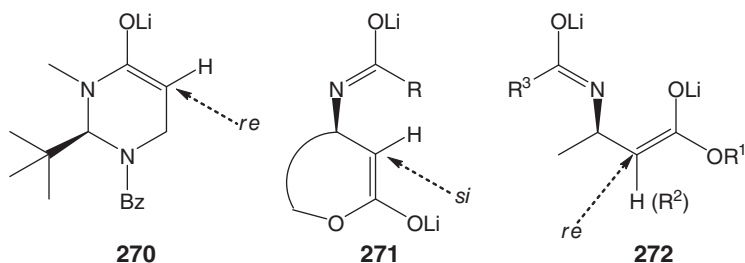
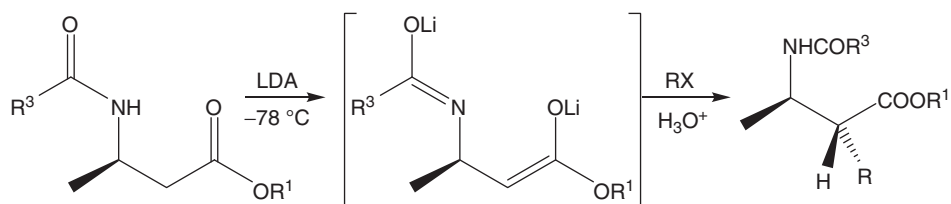


Figure 9.1 Enolates used for the stereoselective alkylation.

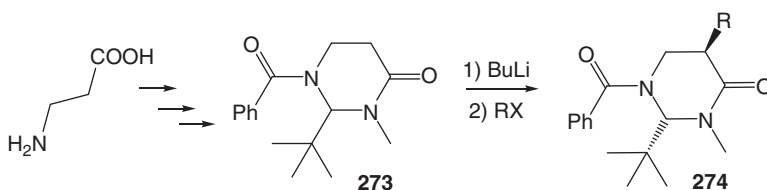
erythro configuration (see Scheme 9.36) with de 67–99%, which indicated the attack of the electrophile in *trans*-position relative to the methyl group at the asymmetric β -carbon atom of β -aminobutyric acid.



Scheme 9.36

The method for obtaining analogs of β -amino acids based on achiral amino acid – β -alanine was also proposed [111]. In three steps, β -Ala is converted to

tetrahydropyrimidinone **273**, alkylation of which using BuLi as a base affords predominantly *trans*-addition product **274** (de >96%) (see Scheme 9.37).



Scheme 9.37

Hydrolysis of **274** in 6 N HCl leads to α -alkyl- β -amino acids in 62–69% chemical yields. The authors point out that the use of enantiomerically pure tetrahydropyrimidinone **273** opens up the possibility for preparation of enantiomerically pure α -alkyl- β -amino acids.

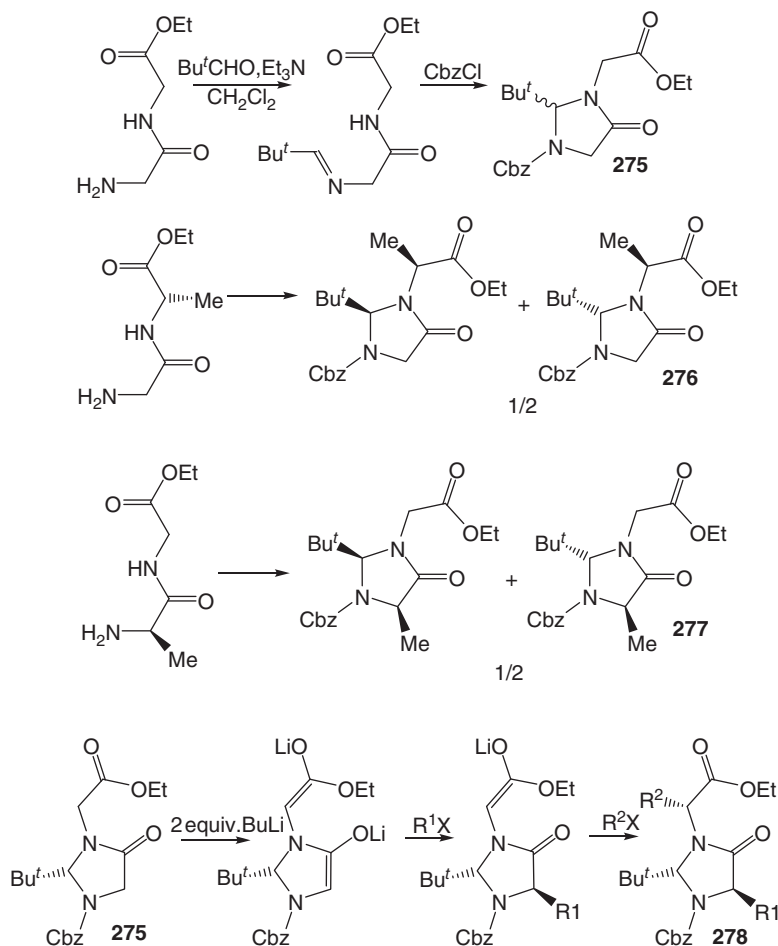
Today, one of the important tasks of modern pharmaceutical chemistry is the preparation of optically active small peptides containing fragments of nonprotein amino acids.

Classical chemical peptide synthesis allows obtaining both fragments of natural proteins and peptides containing nonprotein amino acids. However, when producing peptides containing α -dialkylsubstituted amino acids, traditional methods of synthesis do not always lead to positive results [114].

Therefore, it is an urgent task to develop methods for the asymmetric introduction of alkyl groups into already existing dipeptide. From the literature it is known that for this purpose several approaches, used in the asymmetric synthesis of α -amino acids, can be used [115–120]. Particularly, esters of dipeptides (glycylglycine, alanyl-glycine, glycyl-alanine) were condensed with pivaloyl aldehyde, forming the corresponding diastereomeric imidazolinones (see Scheme 9.38) [115, 116].

The diastereomers were separated and, using bases (LDA, LHMDs), imidazolinones **275**–**277** were converted to dilithium enolates; their reactions with alkyl halides proceeded diastereoselectively, providing dialkylated product **278**. Unfortunately, this method has several drawbacks that do not allow its use for preparative purposes. Thus, in the case of Gly-Gly racemic product **275** is obtained, and with the use of dipeptides Gly-(*S*)-Ala and (*S*)-Ala-Gly imidazolinones **276** and **277** are formed in low chemical yields (38% and 45%, respectively) and with low diastereoselectivity (diastereomers ratio of no more than 2/1).

The method of bis-lactim ethers developed by Schollkopf for the synthesis of optically pure α -amino acids was also used in asymmetric synthesis of dipeptides with both N- and C-terminal nonprotein amino acid [117]. A nonprotein amino acid, which is a part of the dipeptide, is synthesized on the basis of the bis-lactim

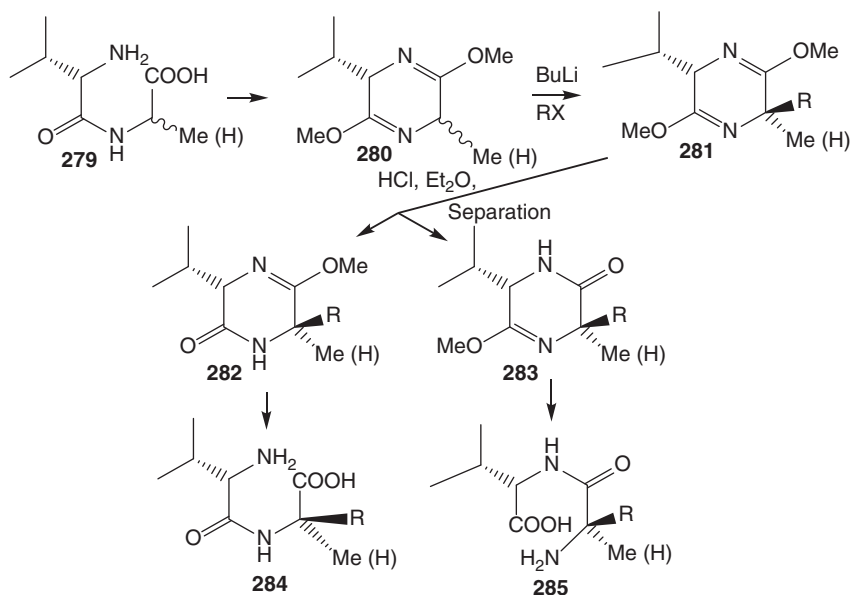


Scheme 9.38

ether **280**, prepared from dipeptide **279** ((*S*)-Val-Gly, or (*S*)-Val-(*R,S*)-Ala) (see Scheme 9.39).

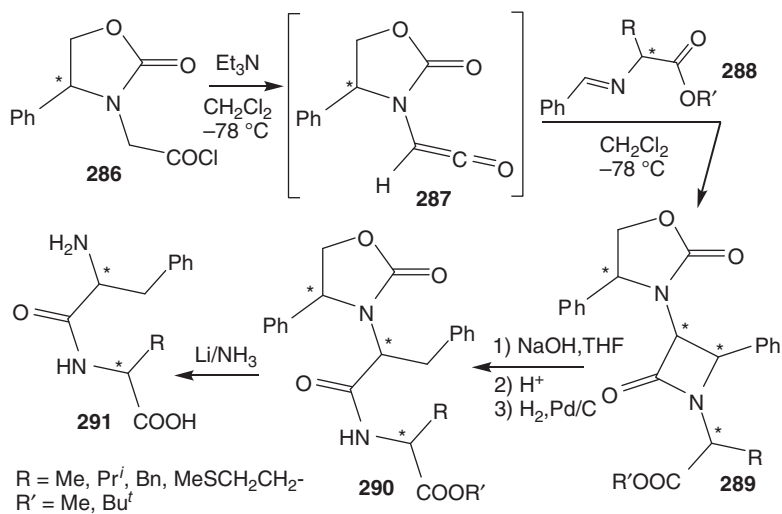
Alkylation of **280** under the influence of BuLi proceeds stereospecifically, resulting in *trans*-addition product **281** with respect to *iso*-propyl group at C-6 of bis-lactim ether (de 98%). Further treatment of **281** with hydrogen chloride leads to a mixture of monolactim esters **282** and **283** (ratio of **282**/**283** is from 23/1 to 8/1), which was separated by chromatography. Hydrolysis of **282** leads to the formation of **284**, whereas **283** leads to dipeptide **285**. Using the alkylation method of bis-lactim ethers, methyl esters of *N*-acetyl- and *N*-Boc-dipeptides Ac-(*S*)-Val-(*R*)- α -MePhe-OMe, Ac-(*S*)-Val-(*R*)-Iva-OMe, Ac-(*S*)-Val-(*R*)- α -MeNle-OMe, and Boc-(*S*)-Val-(*R*)- α -MePhe-OMe, (*R*)- α -MePro-(*S*)-Val-OEt were prepared.

For the asymmetric synthesis of dipeptides, the “ β -lactam synthon” method developed by Ojima and coworkers [118–120] was successfully used. Ketene **287**,



Scheme 9.39

prepared *in situ* from chiral 4-phenyl oxazolidinyl acetyl chloride **286** in reaction of [2+2] cycloaddition with chiral imine **288**, induces the formation of two asymmetric centers in β -lactam **289**. By using (*S*)-**286**, product **289** of (*3S,4R*)-configuration with $\text{de} > 99\%$ was prepared, and in the case of (*R*)-**286** – the one of (*3R,4S*)-configuration (see Scheme 9.40).



Scheme 9.40

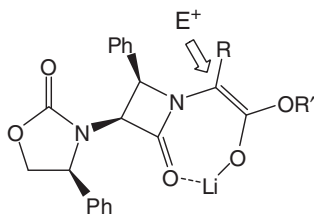
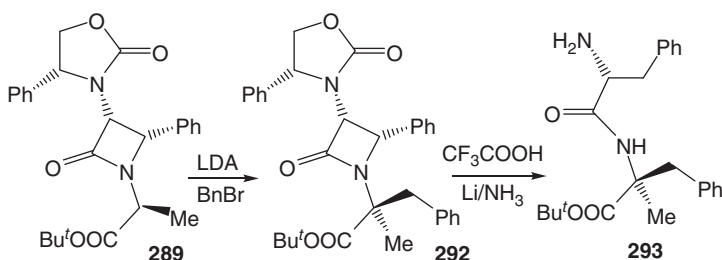


Figure 9.2 Electrophile attack on lithium enolate.

Catalytic hydrogenation (Pd/C in MeOH) of β -lactam **289** leads to the formation of N-substituted dipeptide **290**, the reduction of which under Li/NH₃/THF/Bu^tOH conditions resulted in chiral dipeptide **291** [118].

Reaction of lithium enolate prepared from chiral β -lactam ester **289** (wherein the 3-*N*-amino group is protected by the oxazolidinone structure) under the action of LDA (see Figure 9.2), with an electrophile proceeds with high stereoselectivity to give the product of *trans*-addition with respect to substituents at 3-C and 4-C in the β -lactam [119].

Thus, by alkylation of (3*R*,4*S*,1'*S*)-**289** with benzyl bromide after generation of the carbanion by LDA, **292** was obtained with de >99%, the reduction of which led to (*R*)-phenylalanyl-(*S*)- α -methylphenylalanine **293** (see Scheme 9.41).



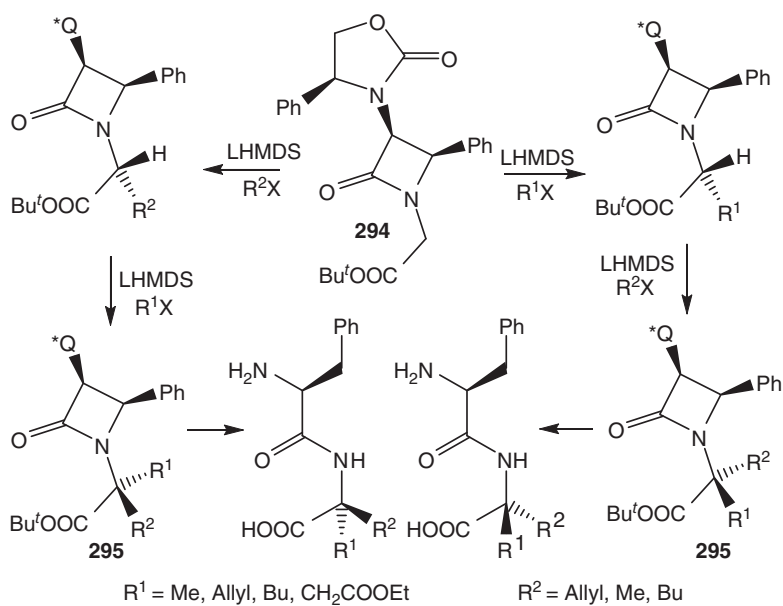
Scheme 9.41

Subsequent double alkylation of chiral β -lactamacetate **294** under the action of LHMDS afforded corresponding dialkylated β -lactam ester **295** with de >99% (chemical yield at each alkylation step was 70–90%); with that, the configuration of the resulting new chiral center can be changed depending on the order of addition of the alkyl halides ($R^1 = R^2$), as shown in Scheme 9.42 [120].

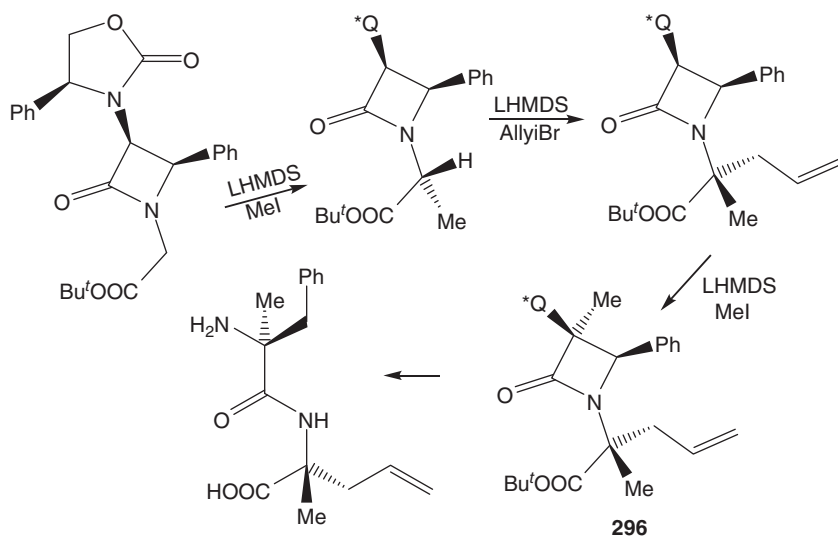
By alkylation of **294** sequentially with MeI, CH₂=CHCH₂Br and again with MeI, **296** was obtained, from which (*S*)- α -methylphenylalanyl-(*R*)- α -allylalanine was then separated (see Scheme 9.43).

Thus, the β -lactam method allows obtaining optically active dipeptides containing one or two nonprotein amino acids.

Typically, the deprotonation of the chiral substrates in these reactions proceeds in the presence of strong bases (BuLi, LDA, LHMDS, etc), in dry solvents under an inert atmosphere and at low temperatures, which is necessary for eliminating side reactions. It should be noted that in all these reactions the asymmetric guidance



Scheme 9.42



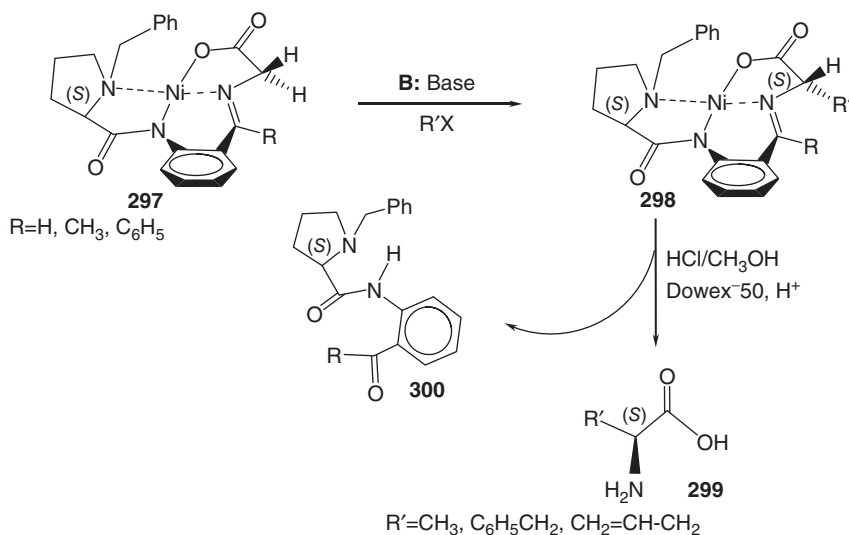
Scheme 9.43

is controlled by kinetic factors that allow achieving high enantiomeric yields of products synthesized in these reactions, but the methods themselves are not very convenient in terms of procedure and, what is more important, are difficult to be scaled up.

Thus, methods for the asymmetric synthesis of α - and β -amino acids and their derivatives discussed in this section allow obtaining amino acids of different structures, but in most cases they are not universal and are applicable to producing only a limited number of amino acids. As a general method, only some of the above-described methods can be considered; besides, all of them are based on the use of expensive chiral auxiliary reagents.

It is known that CH-acidity of amino acid moiety significantly increases when it is in coordination with a metal ion [121]. In such complexes, under the action of a base, there occurs formation of a carbanion center, which can react with an electrophile. It turns out that it is more convenient to use the chiral complexes, in which as a ligand can appear not a free α -amino acid but its Schiff base. In such complexes, with a greater mobility of the proton at α -carbon, the α -amino group is reliably protected, and a polydentate ligand forms a more rigid structure with greater enantioselective effect as compared to a free amino acid.

In this regard, the most original are works by Belokon and coworkers who used square-planar Ni^{II} ion complexes with Schiff base of glycine and chiral amide of (*S*)-proline **297** as anionic synthon of glycine [122–124] (see Scheme 9.44).



Scheme 9.44

This neutral complex is quite stable and has high CH-acidity of the amino acid moiety, readily soluble in organic solvents (CHCl_3 , CH_3COCH_3) and is practically insoluble in aqueous media, which facilitates its isolation from the reaction mixtures. The central metal ion in a complex is coordinated by ionized carboxyl and amide groups and nitrogen atoms of the pyrrolidone moiety and Schiff base.

The chelate rings are distorted and the phenyl group of *N*-benzylproline fragment shields the amino acid fragment from the *re* side of the Schiff base plane, thus providing high enantioselectivity in alkylation of amino acid fragments of these complexes.

By deprotonation of the glycine fragment and addition of electrophiles to the flat carbanion, different protein and nonprotein α -amino acid complexes of (*S*)-absolute configuration **298** were synthesized.

The stereoselectivity of electrophilic addition is controlled by thermodynamic factors; thermodynamically more stable (*S,S*)-diastereomers are obtained in excess, with high diastereomeric purity ($\sim 90\%$). The reason for less stability of (*S,R*)-diastereomers is the sterically nonbinding interaction between the phenyl group of *N*-benzylproline fragment and bulky side radical of the amino acid fragment in this diastereomer, which is absent in the (*S,S*)-diastereomer (see Figure 9.3).

After separation of the diastereomers and their acid hydrolysis, optically pure amino acids **299** are obtained with high enantiomeric purity ($ee > 98\%$) and the initial chiral auxiliary reagent **300** is regenerated with complete retention of the initial enantiomeric purity.

By this scheme, alkylation of the glycine moiety of complex **297** with various alkyl and aryl halides yielded different protein and nonprotein optically active (*S*)-amino acids, for example, alanine, phenylalanine, α -allylglycine, D-benzyltyrosine, and others.

This approach was used by Soloshonok and coworkers to produce various fluoro-substituted α -amino acids (2-fluoro-, 3-fluoro-, 4-fluoro-, 3-trifluoromethyl-, 2-tri-fluoromethyl-, 4-bromo-2-fluoro-, 6-chloro-2-fluoro-, 1,2,3,4,5-pentafluorophenylalanines) [125], and γ - ω -phosphono- α -amino acids (2-amino-3-phosphonopropionic, 2-amino-4-phosphonobutyric, and 2-amino-5-phosphonopentanoic acids) [126].

With the use of this anionic synthon of glycine, 1,4-Michael addition of α,β -unsaturated carbonyl compounds to a glycine fragment was performed and complexes with good stereocontrols in α,β - and sometimes γ -carbon atoms were

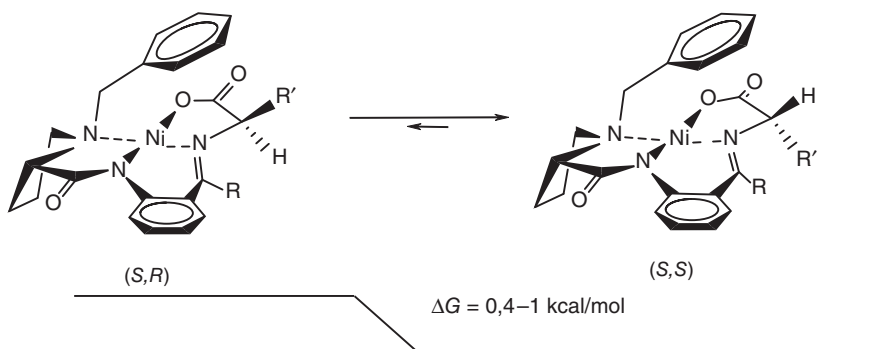


Figure 9.3 The thermodynamic equilibrium between the (*S,S*)- and (*S,R*)-diastereoisomers in the square-planar Ni^{II} ion complex.

formed. Thus, by addition of methylacrylate, acrylonitrile, methyl methacrylate, acrolein, and cinnamate, (*S*)- and (*R*)-2-amino-4-cyanobutyric acid, (*S*)-glutamic acid, (*2S,4R*)-, (*2S,4S*)- and (*2R,4S*)-4-methylglutaminic acid, (*2S,3S*)- and (*2S,3R*)-3-phenylglutaminic acid and others were obtained [127].

The synthesized glutamic acid derivatives were transformed to proline derivatives, for example, *cis/trans*-(*S*)-5-methylproline, *trans*-(*S*)-3-methylproline, *cis/trans*-(*S*)-4-methylproline, *trans*-(*S*)-3-phenylproline, and others [128].

Glycine complexes **297** as CH-acids were also used in the aldol condensation reactions, leading to β -hydroxy- α -amino acids. In this case, in the presence of a strong base, CH_3ONa (*R*)-absolute configuration of α -carbon atom is induced. The authors have shown that the cause of this abnormal phenomenon is the intramolecular rearrangement in the complex [129] associated with the ionization of β -hydroxyl group of the amino acid fragment, which displaces the carboxyl group from the main coordination sphere of metal. As a result of rearrangement in the newly formed complex, thermodynamically more stable proves to be the diastereomer with (*R*)-configuration of the amino acid moiety.

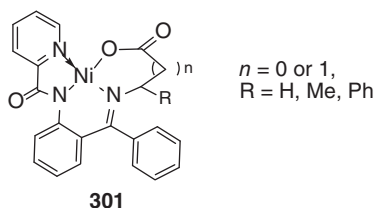
It should be noted that during the aldol condensation reaction in the presence of a weak base such as triethylamine, as expected, preferably β -hydroxy- α -amino acids with (*S*)-absolute configuration are formed. By this scheme, serine, threonine, β -hydroxyvaline, *threo*-(*o*-hydroxyphenyl)serine, *threo*-3,4-(methylenedioxy)- β -phenylserine of both (*S*)-, and (*R*)-absolute configurations were obtained.

Hong Liu and coworkers performed enantio- and diastereoselective Mannich reactions between a chiral Ni^{II} complex of glycine and α -aminosulfone with generation of the C–C bond with two chiral centers [130]. As a result, an effective method for the asymmetric synthesis of α,β -diamino acids has been developed.

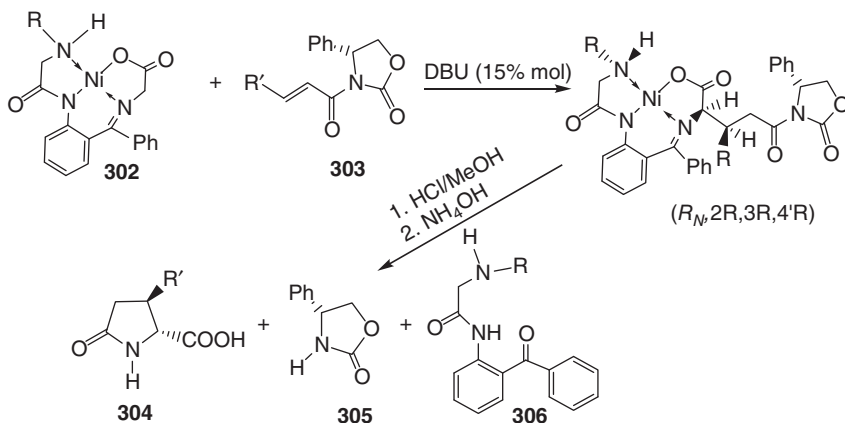
Correlation of *syn/anti* products exceeds 90/10, and ee of synthesized α,β -diamino acids lies in the range of 71–99%. The authors proposed an efficient method for the synthesis of N^β -Gbz-2,3-diamino-3-phenylpropyl acid with 99% ee.

The same authors used high CH-acidity of Ni^{II} glycine moiety of complex **297** and executed stereocontrolled synthesis of the optically active (*S*)- and (*R*)-2-amino-3,3-bis-(4-fluorophenyl) propionic acid [131]. The optical purity of the isolated amino acid was higher than 99%.

A simple preparative method for the synthesis of achiral Ni^{II} complexes of Schiff bases of β -amino acids with picolinic acid (**301**) was also developed, which is suggested for use in the synthesis of derivatives of β -amino acids [132].



Later, Soloshonok and Ellis synthesized a new generation of Ni^{II} complexes of glycine Schiff base with ligands **302**, containing a secondary amino group coordinatively bound to the metal ion of Ni^{II} (see Scheme 9.45).

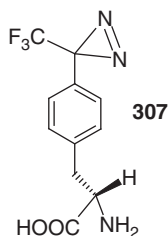


Scheme 9.45

The resulting complexes exhibit unusual chemoselectivity in reactions of alkylation by alkyl halides and Michael addition [133]. Depending on the reaction conditions, both C- and N-alkylation can occur. These complexes possess high nucleophilicity of the glycine moiety and provide high diastereoselectivity of the synthesis of β -substituted pyroglutamic acid derivatives (**304**) in reactions with chiral Michael acceptors (**303**).

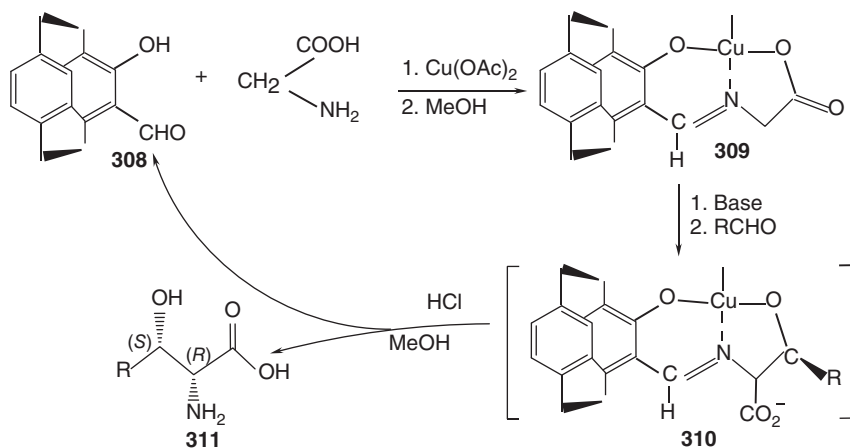
In this case, initial ligand **306** and chiral oxalidinone **305** are regenerated. Chemical yields of the obtained β -substituted pyroglutamic acid derivatives (**304**) are above 95%, de >98%.

Ni^{II} glycine complexes were also used for the synthesis of 4'-(1-azi-2,2,2-trifluoroethyl)-phenylalanine (**307**) and its *N*-Fmoc-derivative [134]. The resulting amino acid **307** and its *N*-Fmoc-protected analog possess high photosensitivity and therefore they are included in peptides having high biological and photoactivity.



In recent years, chiral derivatives of paracyclophanes have been successfully employed as chiral-inducing compounds in the asymmetric synthesis of

α -amino acids [135]. Optically active (*R*)- and (*S*)-4-formyl-5-hydroxy paracyclophanes **308** were obtained from their racemates via formation of Schiff bases with (*R*)- and (*S*)- α -phenylethylamine. They were used in the asymmetric synthesis of β -hydroxy- α -amino acids and α -methylphenylalanine. Scheme 9.46 illustrates the synthesis of β -hydroxy- α -amino acids using (*S*)-**308**. Michael condensation of aldehydes with complex (*S*)-**309** via intermediate carbanion **310** leads to the preferable formation of (*R*)-*threo*- β -hydroxy- α -amino acids (**311**) with diastereomeric purity of 94–98% depending on the reaction conditions. The use of (*R*)-**308** as a chiral-inducing agent enables formation of β -*threo*-hydroxy- α -amino acid of (*S*)-absolute configuration. It is shown that the stereoselectivity of aldol condensation is strongly dependent on the pH of the medium; thus, when conducting the reaction in the presence of Et_3N as a base, β -hydroxy-leucine is obtained as a racemic mixture.



Scheme 9.46

(*R*)-**308** and (*S*)-**308** were also used for the asymmetric synthesis of α -methyl-substituted amino acids from their esters. It is shown that if the initial cyclophane has (*R*)-configuration, the $\text{R}'\text{X}$ attack is preferable from the *si* side of the Schiff base plane with the formation of (*S*)-products; and with (*S*)-configuration of the initial cyclophane, the $\text{R}'\text{X}$ attack is preferable from the *re* side with the formation of (*R*)-products.

This approach can be used for the asymmetric synthesis of other α -alkyl-substituted α -amino acids.

Analysis of existing methods in stoichiometric asymmetric synthesis of amino acids has shown that among the known inducers, chiral carbonyl derivatives based on the natural amino acid (*S*)-proline – condensation products of *N*-benzyl-(*S*)-proline with 2-aminoacetophenone (BPA) and 2-aminobenzophenone (BPB) – are the most processable. These chiral auxiliary reagents readily form

square-planar complexes with transition metal ions (Ni^{II} , Cu^{II} , Co^{II} , etc) in the form of Schiff bases with amino acids.

The advantage of Ni^{II} complexes compared with other complexes is their diamagnetization, which allows using the ^1H NMR method to study their structures and reactivities. In addition, they are stereochemically inert and have high CH-acidity of the amino acid moiety, which allows easy conduction of C-alkylation of amino acids to form more complex protein and nonprotein (*S*)- α -amino acids. The presence of high enantioselective effects in these complexes enables asymmetric synthesis of (*S*)- α -amino acids with $ee \geq 90\%$, which allows, by a single recrystallization, obtaining enantiomerically pure products ($ee > 99\%$). Another advantage of these complexes is the regenerability of the initial chiral auxiliary reagents in quantitative chemical yield and complete retention of the original chirality (optical activity) after completion of the synthesis and isolation of the desired products. This allows multiple reuse of the chiral auxiliaries for the asymmetric synthesis reactions.

Ni^{II} complexes of Schiff bases of amino acids with chiral carbonyl derivatives of proline as starting synthons were used by us to develop methods for the asymmetric synthesis of (*S*)- and (*R*)- α -amino acids with various aliphatic, aromatic, and heterocyclic substituents in the side-chain radical.

Since the ultimate goal of the work is to develop a small-scale preparative production technology for optically active nonprotein α -amino acids, extensive studies aimed at modernization of the initial chiral auxiliaries and improvement of the technological parameters of their preparation have been carried out.

9.1

Synthesis of Chiral Auxiliary Reagents and Complexes Based on (*S*)- and (*R*)-Prolines

The efficiency of production of nonproteinogenic α -amino acids and optical purity of the synthesized samples depend primarily on the enantiomeric purity of the chiral auxiliary reagent. In the case of chiral carbonyl derivatives of the natural amino acid (*S*)-proline or its optical antipode, the stereodifferentiating ability of the auxiliary reagent mainly depends on the degree of optical purity of the proline moiety. Consequently, the development of efficient production technologies for enantiomerically pure (*S*)- and (*R*)-prolines is an important step in the production of optically active nonprotein (*S*)- and (*R*)- α -amino acids.

World production of (*S*)-proline is based on the microbiological synthesis using active producing strains. In this regard, as a basic technology for improvement the microbiological production of (*S*)-proline was selected, which, in particular, was successfully developed in the Scientific and Production Center "Armbiotechnology" (SPC "Armbiotechnology") of the National Academy of Sciences of the Republic of Armenia.

9.1.1

Effective Low-Waste Technology for Producing (S)-Proline

Currently, microbial production of (S)-proline has almost completely replaced the use of other known methods of production due to the presence of highly active producing strains of (S)-proline. Thus, in the SPC "Armibiotechnology," a highly active producing strain of (S)-proline was obtained, allowing to synthesize this amino acid in the fermentation solution in a concentration of 80–90 g l⁻¹ and concomitant amino acids (alanine, valine, glutamic acid, isoleucine, lysine) in the amount of no more than 15% of the total content of amino acids [136–139]. The most difficult step in ongoing technology for isolation of proline from fermentation solutions is to separate proline from accompanying amino acids due to the extreme proximity of the ionization constants of the functional groups of proline and related amino acids.

The problem of (S)-proline separation from other amino acids concerned researchers since the beginning of the twentieth century. Thus, in 1901, Fischer managed to isolate proline from casein hydrolysates by the method of its complexation with copper [140]. To isolate proline, other researchers used the relatively low solubility of proline picrate in alcohol compared to other picrates of amino acids [141, 142]. There are also methods for proline purification in the form of complexes with Reinecke's salt [143, 144], complexes of proline with trinitrobenzoic acid [145], with 2,4-dinitro-1-naphthol-7-sulfonic acid [146], hexachlorobicycloheptene dicarboxylic acid [147], and so on. Proline is isolated from gelatin hydrolysates in various ways, which are listed in the work of Gaweska [148]. Methods for obtaining (S)-proline from bioorganic solutions by forming water-insoluble complexes with chlorendic acid [149] and pentachlorophenone [150] were also investigated.

However, it should be noted that all these methods were not used in production because of low yields of proline, the use of expensive and scarce reagents, and low selectivity to the proline.

A new stage for qualitative separation of proline from other amino acids was the use of the structural difference of proline and other amino acids. On this basis, methods [139, 151–155] were developed to convert amino acids with primary amino groups to hydroxy acids by their deamination under the action of nitrous acid. Under the same conditions, proline, contained in solutions as imino acid, converts to a stable N-nitrozoproline, which easily undergoes acid hydrolysis to form a (S)-proline by refluxing in hydrochloric acid. This method provides complete purification of (S)-proline; however, it has several disadvantages: low yield of the target product (~45%), use of concentrated hydrochloric acid solutions, anti-corrosive hardware requirements, complete loss of valuable concomitant amino acids, formation of large amounts of carcinogenic nitroso gases which are not recycled and are released into the atmosphere, and so on.

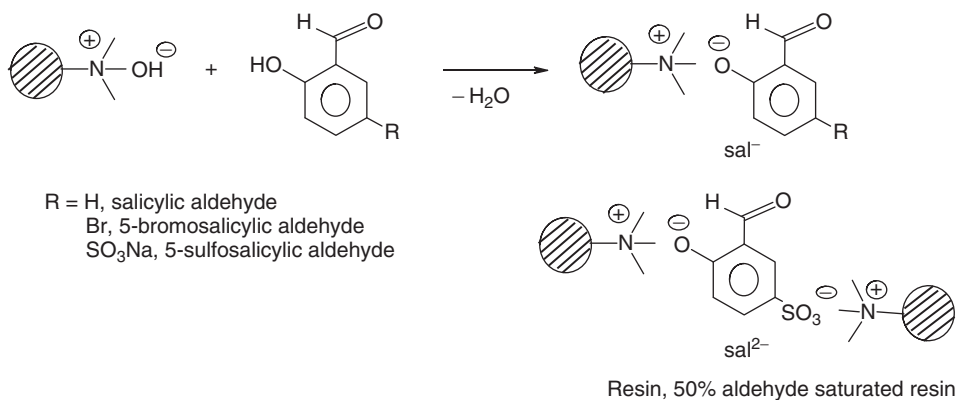
It is known that the primary amino acids can be covalently bound with carbonyl compounds to form Schiff bases, which in particular can be stabilized in a

solution by forming complexes with transition metal ions – Cu^{II} , Ni^{II} , Co^{III} , and so on [156–158].

Proline as imino acid is incapable of forming a stable Schiff base with aldehydes, and this property has been used to separate (*S*)-proline from related amino acids.

Technologically it is more acceptable to conduct coupling reactions of accompanying amino acids in dynamic conditions; therefore, the most important task is to produce effective carriers of reactive aldehyde molecules, that is, to choose the carrier (ion exchange resin) and counter ion (aldehyde) [159].

As suitable carriers of reactive molecules of aldehyde, anion exchange resins EDE-10p, AV-17, and Amberlite IRA-400, and as counter ions – salicylic acid, 5-bromosalicylic, and 5-sulfo-salicyl aldehydes – were tested. Transition of anion exchange resin to an aldehyde form is carried out by passing 8–10% aqueous-alcoholic solution of salicyl aldehyde or an aqueous solution of 5-bromosalicylic and 5-sulfosalicyl aldehydes through a column of resin in OH^- form in an upward direction at a rate of 0.4–0.6 volumes of solution per volume of resin per hour (see Scheme 9.47).

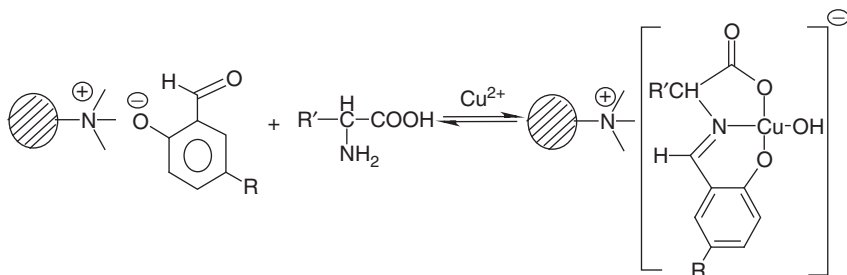


Scheme 9.47

Exchange capacity of the aldehyde resin (the amount of aldehyde on the surface of the resin) is determined on the basis of the amount of salicyl aldehyde in the solution before and after transmission.

Quantitative analysis of aldehydes is easily performed spectrophotometrically at 250 nm wavelength (molar extinction coefficient is $11\,900\text{ l mol}^{-1}\text{ cm}^{-1}$). In the case of 5-sulfosalicyl aldehyde, the aldehyde molecule is additionally rigidly bound to the resin matrix by a strongly acidic SO_3^- groups. Due to this, the exchange capacity of the aldehyde resin is reduced by half compared with salicyl aldehyde (resins for 50% saturated with aldehyde). As subsequent experiments demonstrated, sulfosalicyl aldehyde moiety in the experiment was hardly eluted from the surface of the resin, and such resins can be reused without additional regeneration.

In the initial stage, the possibility of binding of (*S*)-proline concomitant amino acids to the resin's aldehyde moiety in the form of copper complexes of Schiff bases [138] was investigated. For this purpose, a solution of amino acid mixture in the presence of an equimolar amount of CuSO_4 and $\text{Cu}(\text{CH}_3\text{COO})_2$ is passed through a column of anion exchange resin in the form of aldehyde. When the solution comes in contact with the resin, concomitant primary amino acids form copper complexes of Schiff bases with a fragment of ionized aldehyde of the resin and they are retained on the column (see Scheme 9.48).



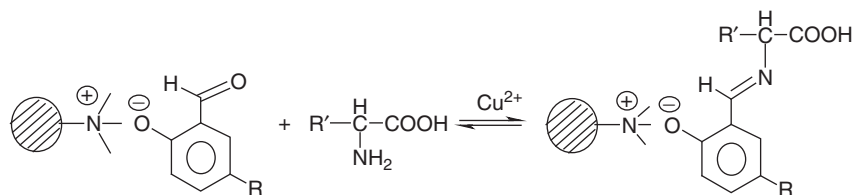
Scheme 9.48

The imino acid (*S*)-proline does not form a complex at that and exits the column. Experiments showed that when the total concentration of all amino acids in the solution was $40\text{--}80\text{ g l}^{-1}$ on condition that the content of (*S*)-proline was 85–90% of the total quantity of all amino acids, only 1.5–2 volumes of the solution could be passed through one volume of the resin to obtain pure (*S*)-proline. After separation of proline, to isolate concomitant to (*S*)-proline amino acids and regenerate resin, 8–10 volumes of (relative to the volume of resin) 4–8% aqueous-alcoholic solution of ammonia or 2 N HCl was passed through the column. Simultaneously, the copper complexes were decomposed directly on the resin surface and the mixture of concomitant amino acids was isolated.

However, during isolation of concomitant to (*S*)-proline amino acids, partial elution of aldehyde from resin's surface ($\sim 30\%$) is observed, which reduces the effective capacity of aldehyde resin. Partial elution of the aldehyde from the resin surface is also observed at the step of binding concomitant amino acids in the form of copper complexes because of the presence of SO_4^{2-} or CH_3COO^- anions in the solution (in the case of salicyl aldehyde, reduction in effective capacity of aldehyde-based resin is 30–50% and in the case of 5-sulphosalicyl aldehyde it is 5–10).

In order to eliminate the above-mentioned drawbacks and improve the process of proline separation from the mixture of amino acids, multiple studies were conducted, involving a transition from copper complexes of Schiff bases to free Schiff bases of concomitant to (*S*)-proline amino acids with salicyl aldehyde or its derivatives [138, 159–161]. For that reason, the same solution of amino acid mixture

without adding copper ion is passed through a column of anion exchange resin in the form of aldehyde. In this case, unlike the previous method, concomitant amino acids are retained on the resin in the form of stable free unstained Schiff bases with the aldehyde moiety of resin (see Scheme 9.49).



Scheme 9.49

Column elution curves for individual amino acids during separation of (*S*)-proline from the solution of amino acid mixture [(*S*)-proline – 55 g l^{-1} , (*S*)-valine – 5.1 g l^{-1} , (*R,S*)-alanine – 1.4 g l^{-1} , (*S*)-lysine – 0.9 g l^{-1} , (*S*)-isoleucine – 0.6 g l^{-1} , (*S*)-glutamic acid – 0.45 g l^{-1}] by this method using resin in a 5-sulphosalicyl aldehyde form (resin for ~50% saturated with aldehyde, sal^{2-}), obtained in the Abovyan biochemical pilot-plant, are shown in Figure 9.4.

After passing the amino acid solution through a column of resin in the form of an aldehyde and subsequent displacement of proline from intergranular space of resin with water, concomitant amino acids were eluted by using 3–4 volumes (relative to the volume of resin) of 4–6% aqueous ammonia solution. At that time, decomposition of Schiff bases occurs directly on the resin with liberation of concomitant primary amino acids.

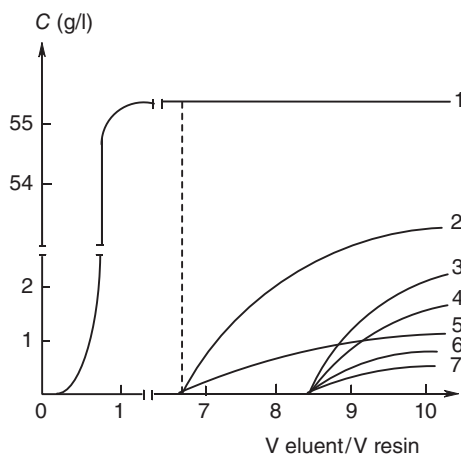


Figure 9.4 Release curves of individual amino acids from the column with resin AB-17 in 5-sulphosalicyl aldehyde form (resin for 50% saturated with aldehyde): 1 – (*S*)-Pro; 2 – (*S*)-Val; 3 – (*R,S*)-Ala; 4 – (*S*)-Lys; 5 – (*S*)-i-Leu; 6 – (*S*)-Glu; 7 – Gly.

In comparison with the previous method, this method enables increasing almost three times the effective capacity of the resin in the aldehyde form for the concomitant amino acids. Apparently, this is due to elimination of copper salts. Also, in this case, there is the possibility of separating (*S*)-valine and (*S*)-isoleucine from other related amino acids (see Figure 9.4).

The advantage of this method over the previous one is also less stability of free forms of Schiff base compared to copper complexes, which reduces the required amount of eluent for decomposition of complexes and liberation of concomitant to (*S*)-proline amino acids (almost three times), excluding alcohol from the eluent composition, thereby reducing the potential for aldehyde leaching from resin's surface.

In the case of salicyl aldehyde during the elution of concomitant amino acids, its partial exclusion from the surface of the resin (10%) is observed. In case of 5-sulphosalicyl aldehyde resin during elution of concomitant to (*S*)-proline amino acids, aldehyde particles are not washed out from the surface of the resin, and its original shape is fully recovered, and the resin without additional regeneration can be reused (50–100 cycles according to spectrophotometric studies).

As carriers, different anion exchange resins (EDE-**10p**, AV-**17**, Amberlite IRA-**400**) containing as a counterion ionized salicyl aldehyde, 5-bromosalicyl aldehyde, or 5-sulfosalicyl aldehyde as well as polymeric resins (polystyrene-based phenol-formaldehyde resin) with covalently bound fragments of salicylaldehyde were tested [159]. Resins with various degrees of saturation with ionized salicylaldehyde were also used. According to the results of experiments, the effective separation of (*S*)-proline from concomitant amino acids is possible using EDE-**10p** and AV-**17** resins, as the counterions containing 5-sulfosalicyl aldehyde. Resins with covalently bound aldehyde groups appeared ineffective.

Studies have shown that in the process of formation of Schiff bases with amino acids, the aldehyde resin capacity (aldehyde on the resin surface) is used most effectively in the case of resin AV-**17** (~98%), compared with the EDE-**10p** resin (30–32%). IR spectroscopic study of the resin surface containing salicyl aldehyde and Schiff base of salicyl aldehyde with primary amino acids showed that the effectiveness of the AV-**17** resin was due to the content of its matrix having only quaternary ammonium groups as positively charged particles. The matrix of EDE-**10p** resin contains only 35% of quaternary ammonium groups and 60% of the primary and the other ammonium groups. According to IR spectroscopy, on a surface of the EDE-**10p** resin, about 60% of aldehyde fragments are bound to the matrix not by the ionic bonds through the ionized OH group of the aldehyde, but covalently through the carbonyl group of aldehyde, for example, in the form of a Schiff base with the primary amine groups of the resin. Such resins lose their ability to interact with amino acids, since their aldehyde groups are already bound to amino groups of the matrix.

Based on further studies in the case of using AV-**17** resin in the form of 5-sulpho-salicyl aldehyde an efficient separation of proline from the concomitant amino acids is observed at 50% aldehyde saturation of the resin. Zero activity of the resin at 100% saturation with 5-sulfosalicyl aldehyde particles is apparently due

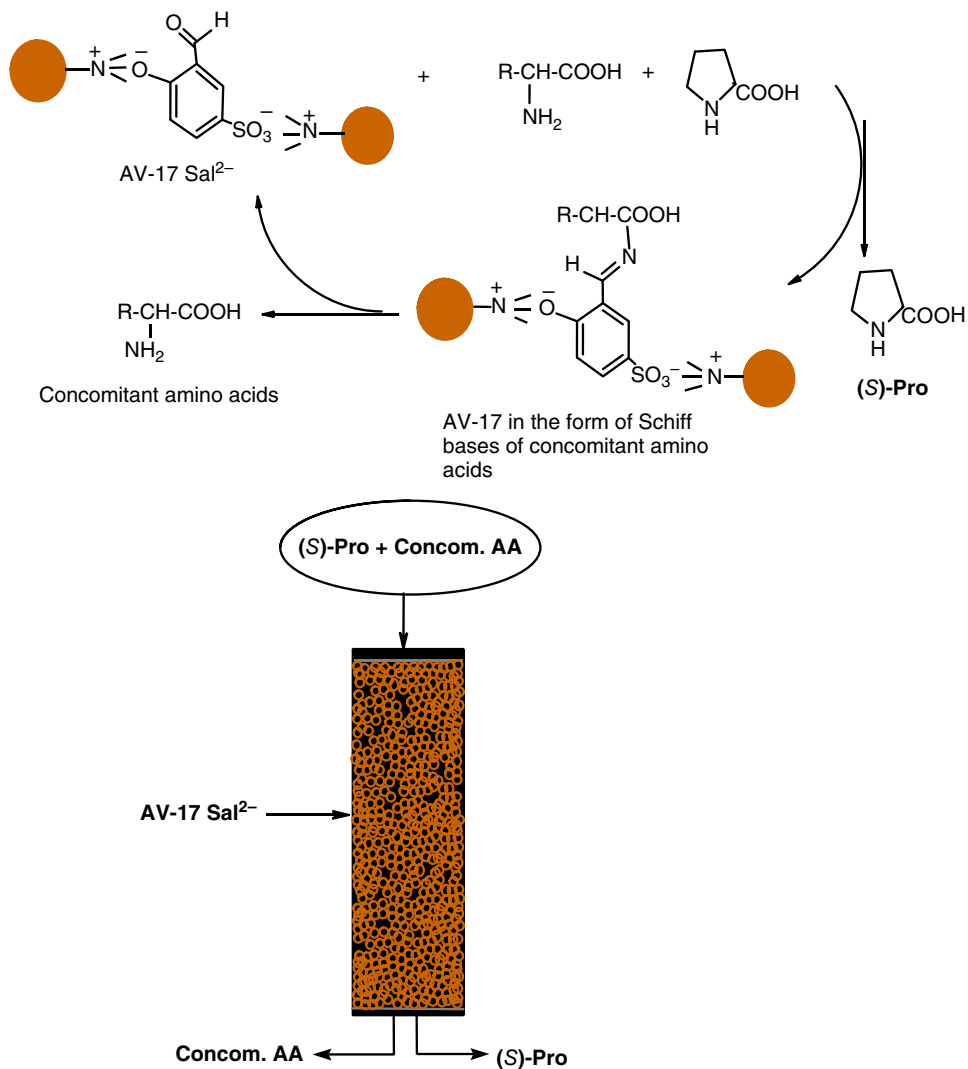


Figure 9.5 Separation scheme of (*S*)-proline from the amino acid mixture.

to the fact that in this case the aldehyde molecules bind with quaternary ammonium groups of the matrix only by the strong acidic SO³⁻ group. This form of the resin with undissociated α -OH group of aldehydes is inactive in reactions of Schiff base formation. Figure 9.5 shows an effective low-waste separation route of (*S*)-proline from the concomitant primary α -amino acids.

The effluent from the column solution, along with (*S*)-proline, also contains mineral salts, impurities, and colored pigments. To clean proline from these impurities, the eluent is passed through the serially connected ion exchange columns with anion and cation exchange resins in the OH⁻ and H⁺ forms, respectively.

The obtained (*S*)-proline solution has a pH value of 6.3, which corresponds to the isoelectric point of proline and facilitates its subsequent crystallization.

The developed method for obtaining (*S*)-proline was tested in experimental base of the Abovyan biochemical plant. For this purpose, after removal of the biomass, residual sugars and other ballast substances from fermentation solutions by decantation, separation, and ion exchange sorption and elution, the obtained solution of amino acid mixture was passed through three serially connected columns with AV-17 resins in 5-sulfosalicyl aldehyde form, AV-17 or EDE-10p in the OH⁻ form, and Ku-2-8 in H⁺ form. The prepared (*S*)-proline solution purified from concomitant amino acids and other associated trace impurities, crystallized from water–alcohol solution provides the desired product with high chemical (>99%) and optical (>99.9%) purities and in good chemical yield (~83–85% based on the initial amount of proline in the fermentation solution).

The (*S*)-proline, obtained by this method, was used for the synthesis of chiral auxiliary reagents of different generations, as well as for producing (*R*)-proline.

9.1.2

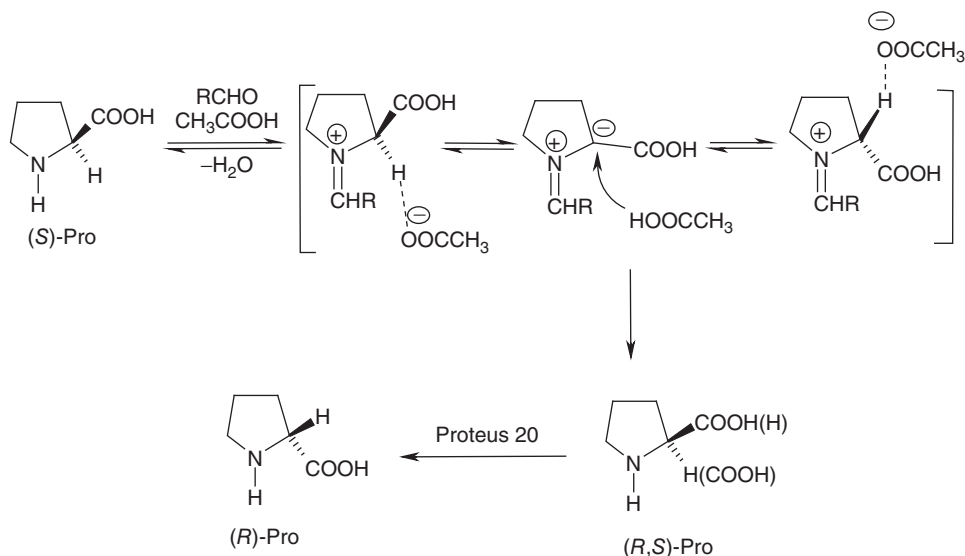
Preparation of (*R*)-Proline from (*S*)-Proline

Recently, much attention has been drawn to development of highly efficient methods for preparing racemic (*R,S*)-amino acids from optically active (*S*)-enantiomers. Research in this area is of particular interest for those natural amino acids, (*S*)-enantiomers of which are easily and inexpensively obtained by a microbiological method; on the other hand, the investigations are aimed at isolation of optically active (*R*)-enantiomers from their racemates. (*S*)-proline is among such amino acids and is produced microbiologically worldwide.

Today, synthesis of (*R*)-proline is composed of two stages. In the first stage, (*S*)-proline is racemized to (*S,R*)-proline, and (*R*)-proline is then isolated by microbiological degradation of (*S*)-isomer.

Conversion of (*S*)-proline to (*S,R*)-proline is carried out easily by a known method for racemization of amino acids in acetic acid in the presence of aldehydes [162] (see Scheme 9.50). Racemization proceeds fast and in high yield using salicylic or 5-sulfosalicyl aldehyde. The temperature also significantly affects racemization; thus, the best results are obtained at a 95–100 °C. Acetic, formic, and propionic acids are used as medium. Higher yield of racemization is observed in acetic acid. Under such conditions, complete racemization of (*S*)-proline (>98%) takes place, as shown by data of the specific rotation: $[\alpha]_D^{25} = 0-2^\circ$ (H₂O).

(*R*)-Proline was isolated from the obtained (*S,R*)-proline by microbiological degradation of (*S*)-isomer using “Proteus 20” strain of bacteria, which was selected in the “Scientific-Research Institute of Biotechnology.” In fermentation solution, as a result of (*S*)-proline utilization, other amino acid impurities related to (*R*)-proline with (*S*)-configuration appear (alanine, valine, glutamic acid), but their amount does not exceed 5% of the total amino acid content. From the



Scheme 9.50

resulting culture liquid, (*R*)-proline was isolated by the above-described method to obtain (*S*)-proline using an anion exchange resin AV-17 in 5-sulfosalicylic aldehyde form. Overall yield of (*R*)-proline based on starting (*S*)-proline amount is 38–40%. The physicochemical analysis results (^1H NMR, elemental analysis, polarimetric measurements) confirm the structure and absolute configuration of the synthesized (*R*)-proline. Specific rotation value is $[\alpha]_D^{25} = +49^\circ$ to $+52^\circ$ ($c = 2.5$; 1 N HCl) and chiral GLC analysis results indicate high optical purity of the product (>98%).

The obtained (*R*)-proline was used for the synthesis of chiral auxiliary (*R*)-2-*N*-(*N'*-benzylprolyl)aminobenzophenone.

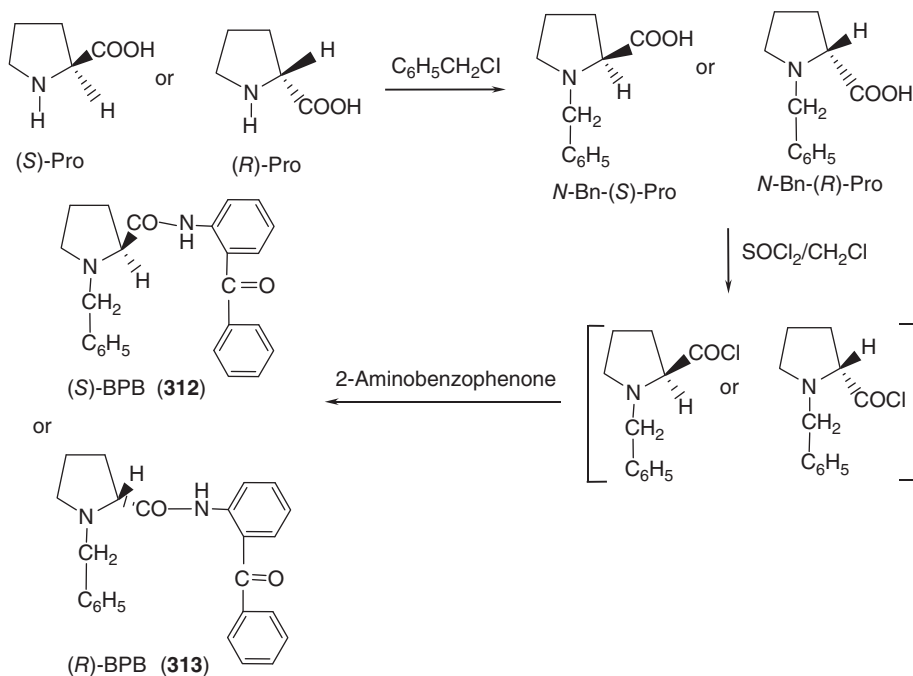
9.1.3

Synthesis of Chiral Auxiliary Reagents and Ni^{II} Complexes of their Schiff Bases with Amino Acids

The first chiral auxiliary reagents that have been prepared and tested in asymmetric synthesis reactions of amino acids are chiral carbonyl derivatives of natural amino acid (*S*)-proline or its *N*-substituted analogs with 2-aminobenzaldehyde, 2-aminoacetophenone, and 2-aminobenzophenone. Studies have shown that in the structures of Ni^{II} complexes of Schiff bases of amino acids, chiral auxiliary based on *N*-benzylproline and 2-aminobenzophenone (BPB) has the highest enantioselectivity. It has been shown that in the absence of a benzyl group in the pyrrolidone moiety, regardless of the size of the substituent at the $-\text{C}=\text{N}-$ bond, zero enantioselectivity is observed in reactions of amino acid moiety conversion. However, in the case of chiral auxiliary reagents containing *N*-benzylproline, increase in

stereoselectivity is observed during synthesis of amino acids with increasing sizes of the substituents at the aldimine carbon atom of the (at the $\text{C}=\text{N}$ bond) complexes: ee is $\sim 50\%$ in the case of 2-aminobenzaldehyde (BPBA), $\sim 75\%$ in the case of 2-amino-acetophenone (BPA), and $\sim 90\%$ in the case of 2-aminobenzophenone (BPB) ligands.

Chiral auxiliary (*S*)-2-*N*-(*N'*-benzylprolyl)aminobenzophenone (BPB) is obtained by reacting *N*-benzyl-(*S*)-proline with 2-aminobenzophenone in CH_2Cl_2 [163] (see Scheme 9.51).



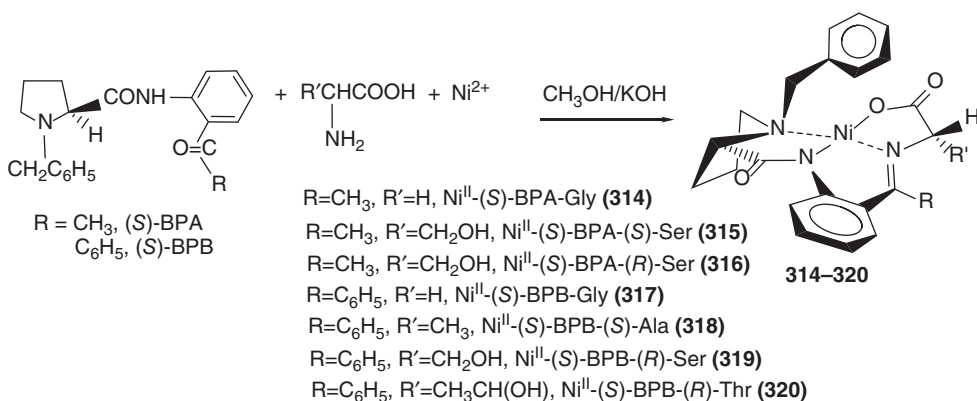
Scheme 9.51

Further improvement of this method allowed increasing the yield of the final product and simplifying the process technology. Using 1.2- to 1.5-fold excess of hydrochloride of *N*-benzylproline chloroanhydride at the step of its condensation with 2-aminobenzophenone in CH_2Cl_2 and conducting the reaction with cooling to -30°C allows the synthesis in one (organic) phase, without using aqueous buffer solution [164], and also improves the yield of the desired product (*S*)-BPB (**312**) from 60% to 85%. By a similar scheme, from (*R*)-proline (*R*)-2-*N*-(*N'*-benzylprolyl)-aminobenzophenone [(*R*)-BPB] (**313**) was synthesized. Spectral analyses results (^1H NMR, elemental analysis, and polarimetric measurements) of the synthesized samples of chiral reagents **312** and **313** unequivocally confirm the structures shown in Scheme 8.35.

As expected, polarimetric measurement results ($[\alpha]_D^{25}$, ORD curves) of chiral reagents (*S*)-BPB and (*R*)-BPB in absolute values coincide and have the opposite sign of rotation.

Use of 2-aminoacetophenone, instead of 2-aminobenzophenone, allows, by the same scheme, synthesizing (*S*)-2-*N*-(*N'*-benzylpropyl) aminoacetophenone (BPA).

From the obtained chiral auxiliary reagents BPA and BPB, Ni^{II} complexes of their Schiff bases with amino acids (Gly, Ala, Ser, Thr) were synthesized. Syntheses were carried out by reacting the corresponding amino acids with the chiral reagents and $\text{Ni}(\text{NO}_3)_2$ in CH_3OH in the presence of a base [128, 129, 165]. Moreover, the complexation reactions of glycine and alanine in quantitative yields take place in $\text{CH}_3\text{OH}/\text{KOH}$, and for β -hydroxy- α -amino acids (Ser, Thr) – in $\text{CH}_3\text{OH}/\text{NaOH}$ environment (see Scheme 9.52).



Scheme 9.52

Unlike other amino acids, complexes of β -hydroxy- α -amino acids are preferably produced in the form of (*S,R*)-diastereomers containing (*R*)-serine (**319**) and (*R*)-threonine (**320**); and alanine complexes, similar to other amino acids, are preferably produced in the form of (*S,S*)-diastereomer containing a fragment of (*S*)-alanine.

Figure 9.4 shows the structure of (*S,S*)-diastereomer of the serine complex on the basis of X-ray analysis (Struchkov, Batsanov, INEOS RAS) [129]. As can be seen from Figure 9.6, the ion of the metal is coordinated with the ionized carboxyl and amide groups, nitrogen atoms of pyrrolidone fragment, and Schiff base. Chelate rings are distorted, and the phenyl group of *N*-benzylproline fragment is oriented above the coordination plane of the metal.

A characteristic feature of these complexes containing (*S*)-amino acid is the axial orientation of side alkyl group of the amino acid and, accordingly, equatorial orientation of its α -hydrogen.

The resulting complexes are easily isolated from the reaction mixture by precipitation from water (15-fold excess of water) and purified from trace contaminants of other isomer by crystallization from acetone. Complex **315** was isolated from

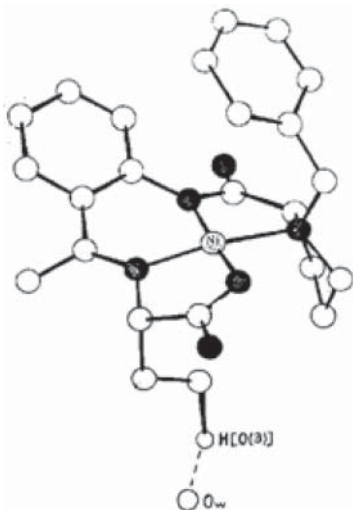
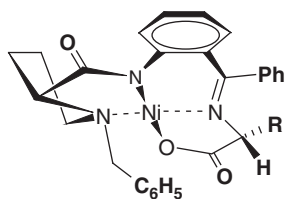


Figure 9.6 Structure of $\text{Ni}^{\text{II}}\text{-(S)-BPA-(S)-Ser}$ (**315**) complex according to XRD.

the mixture of diastereomeric complexes **315** and **316** by chromatography on SiO_2 ($\text{CH}_3\text{OH}/\text{CH}_3\text{Cl}=1/3$).

The structures and absolute configuration of the synthesized complexes **314**–**320** were established using ^1H NMR and electronic spectra, elemental analysis, ORD curves, and specific rotation.

By a similar scheme using chiral reagent (*R*)-BPB (**313**), Ni^{II} ion complexes with Schiff base of glycine (**321**), (*R*)-alanine (**322**), and (*S*)-serine (**323**) [166–168] were synthesized.



$\text{R}=\text{H}$, $\text{Ni}^{\text{II}}\text{-(R)-BPB-Gly}$ (**321**)
 $\text{R}=\text{CH}_3$, $\text{Ni}^{\text{II}}\text{-(R)-BPB-(R)-Ala}$ (**322**)
 $\text{R}=\text{CH}_2\text{OH}$, $\text{Ni}^{\text{II}}\text{-(R)-BPB-(S)-Ser}$ (**323**)

Spectral data of glycine complex **321** and (*R,R*)-diastereomer of alanine complex **322** coincide with the data of glycine complex **317** and (*S,S*)-diastereomer of alanine complex **318**, respectively. Spectral data of (*R,S*)-diastereomer of (*S*)-serine complex (**323**) coincide with the data of (*S,R*)-diastereomer of the complex of the same amino acid (**319**), and their polarimetric parameters have the opposite sign of rotation. Based on polarimetric data, it follows that the synthesized (*R,R*)- and (*R,S*)-diastereomers of Ni^{II} complexes of Schiff bases of amino acids with chiral auxiliary BPB are mirror images of the corresponding (*S,S*)- and (*S,R*)-diastereomers of the same amino acids. This is evidenced by their ORD curves (see Figure 9.7).

It should be noted that Ni^{II} complexes of Schiff bases of β -hydroxy- α -amino acids can be also prepared by aldol condensation of the corresponding complexes

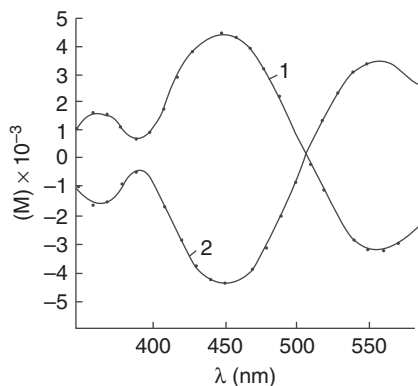


Figure 9.7 ORD curves of complexes in CH_3OH at 25°C 1 – $\text{Ni}^{\text{II}}\text{-(R)-BPB-(R)-Ala}$ (**322**); 2 – $\text{Ni}^{\text{II}}\text{-(S)-BPB-(S)-Ala}$ (**318**).

of glycine with formaldehyde or acetaldehyde, as was done by the group of Professor Belokon. This approach is particularly effective in the case of complexes of threonine and provides relatively high excess of diastereomers containing (*R*)-*threo* form.

In subsequent work, the production technology for serine complexes **319** and **323** has been improved. Determination of optimal process parameters (substrate concentration, ratio of substrate/reactant/base, reaction conditions – $T^\circ\text{C}$, time, stirring) allows obtaining diastereomerically pure (*R*)-serine complexes in a single step, avoiding the chromatographic step (or crystallization) of mixtures of (*S,S*)- and (*S,R*)-diastereomers.

Complexes of glycine and alanine were used as starting amino acid synthons for the asymmetric synthesis of more complex nonprotein α -amino acids and α -substituted α -amino acids. Complexes of (*R*)- β -hydroxy- α -amino acids (Ser, Thr) were used for preparation of chiral Ni^{II} complexes of Schiff bases of dehydroamino acids (dehydroalanine and dehydroaminobutyric acid) for their subsequent use as active dehydroamino acid synthons for the asymmetric synthesis of β -substituted α -amino acids.

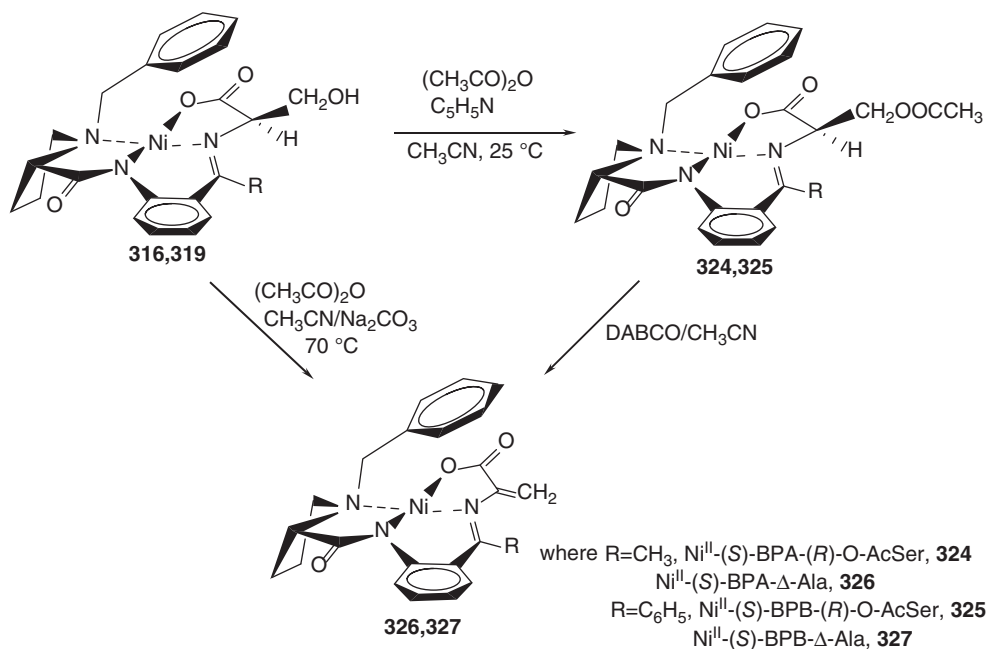
9.1.4

Preparation of Ni^{II} Complexes of Schiff Bases of Dehydroamino Acids

Dehydroamino acid complexes can be prepared by dehydration of complexes of β -hydroxy- α -amino acids (serine and threonine). However, the OH group of the amino acid moieties of these complexes is a difficult leaving group and its cleavage, as was shown in the example of salicylidene complexes of Co^{III} (see Chapter 3-6), is accompanied by retroaldol breakage (breaking of the C–C bond). In this connection, there is a need to replace the hydroxyl group of serine or threonine complexes by an easily leaving group, in particular, by an acetoxy group, as it occurs in the organism under the action of pyridoxal enzymes for subsequent α,β -elimination of the acetic acid moiety, resulting in complexes of dehydroamino acids.

9.1.4.1 Synthesis of Chiral Ni^{II} Complexes of Dehydroalanine

Complexes of dehydroalanine Schiff base with chiral auxiliaries (*S*)-BPA and (*S*)-BPB were prepared from the corresponding complexes of (*R*)-serine – Ni^{II} -(*S*)-BPA-(*R*)-Ser (**316**) and Ni^{II} -(*S*)-BPB-(*R*)-Ser (**319**) [169–171]. For this purpose, in the first stage, serine fragment of complexes **316** and **319** were *O*-acetylated with acetic anhydride in the presence of Na_2CO_3 in CH_3CN or in pyridine as a base, then the obtained acetyl derivatives were subjected to deacetoxylation when heated (α,β -elimination of acetic acid moiety from the *O*-acetylserine fragment) with the formation of dehydroalanine complexes (see Scheme 9.53).



Scheme 9.53

The resulting *O*-acetylated complexes **324** and **325**, like the initial serine complexes, are neutral diamagnetic substances readily soluble in chloroform. Structures of the obtained complexes are similar to the structure of starting complex of (*S*)-serine **315**, the absolute configuration of which is established by X-ray analysis (see Figure 9.6). The *O*-acetylation reaction of serine complexes is conveniently monitored by TLC [SiO_2 , $\text{CHCl}_3/\text{CH}_3\text{COCH}_3$ (3/1)], as acetylated complexes differ from initial serine complexes by R_f value.

The structures and absolute configuration of acetylated complexes **324** and **325** were confirmed by ^1H NMR, electronic spectra, and polarimetric measurements.

In Figure 9.8, ORD curves of (*R*)- and (*S*)-*O*-acetylserine complexes and of similarly constructed complex of (*S*)-serine (**315**) (for comparison) are presented. As can be seen from these curves, *O*-acetylation of the serine moiety does not

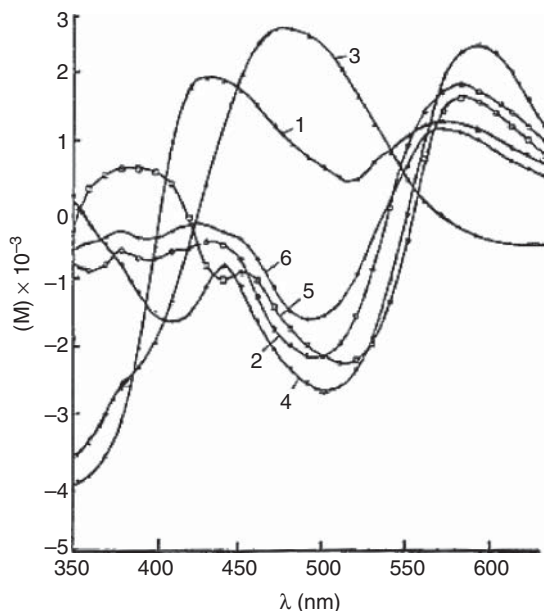


Figure 9.8 ORD curves of diastereomers in CH_3OH , 25°C 1 – $\text{Ni}^{\text{II}}\text{-(S)-BPA-(R)-O-AcSer}$ (**324**); 2 – $\text{Ni}^{\text{II}}\text{-(S)-BPA-(S)-O-AcSer}$; 3 – $\text{Ni}^{\text{II}}\text{-(S)-BPB-(R)-O-AcSer}$ (**325**); 4 – $\text{Ni}^{\text{II}}\text{-(S)-BPB-(S)-O-AcSer}$; 5 – $\text{Ni}^{\text{II}}\text{-(S)-BPA-}\Delta\text{-Ala}$ (**326**); 6 – $\text{Ni}^{\text{II}}\text{-(S)-BPB-}\Delta\text{-Ala}$ (**327**).

change the configuration of asymmetric centers in the complex. α -Carbon atoms of amino acid fragments are known to contribute to the value of the observed Cotton effects of amino acid complexes. For complexes having (*S*)-absolute configuration of α -carbon atom of the amino acid fragment, the Cotton effects in the range of 400–500 nm are negative; and for complexes having (*R*)-absolute configuration of α -carbon atom, they are positive. This difference in ORD curves will allow their use in future to determine the configuration of the α -carbon atom of amino acid moiety in the complexes of similar structure.

Cleavage of the acetic acid moiety from *O*-acetylserine complexes occurs in CH_3CN under the action of Na_2CO_3 or 1,4-diazabicyclooctane (*Dabco*) (see Scheme 9.52). The deacetoxylation reaction can be also easily monitored by TLC [$\text{CH}_3\text{Cl}_3/\text{CH}_3\text{COCH}_3$ (5/1)] following the disappearance of spots of the starting acetylated complexes. The reaction of acetic acid elimination from *O*-acetylserine complexes can be also monitored by ^1H NMR spectroscopy following the appearance of signals of vinyl hydrogens of dehydroalanine fragment at 4.1–4.9 and 5.8–5.9 ppm or the disappearance of protons signal of the acetoxy group at 2 and 2.2 ppm.

Dehydroalanine complexes **326** and **327** can be easily separated from the reaction mixture by chromatography on silica gel or by crystallization from acetone.

The structures of dehydroalanine complexes are determined by physicochemical methods of analysis. In electronic spectra, a shift of the absorption band from

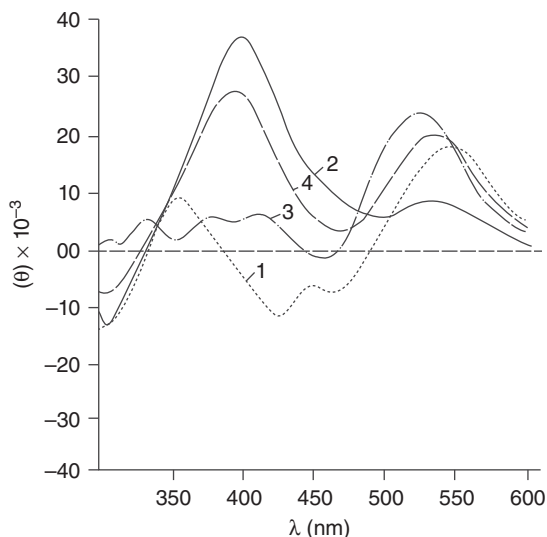


Figure 9.9 CD spectra of diastereomers in CH_3OH , 25°C 1 – $\text{Ni}^{\text{II}}\text{-(S)-BPA-}\Delta\text{-Ala}$ (**326**); 2 – $\text{Ni}^{\text{II}}\text{-(S)-BPA-(R)-Ser}$ (**316**); 3 – $\text{Ni}^{\text{II}}\text{-(S)-BPA-(S)-Ser}$ (**325**); 4 – $\text{Ni}^{\text{II}}\text{-(S)-BPA-Gly}$ (**314**).

403 nm in the initial *O*-acetyl derivatives (**324**, **325**) to 428 and 440 nm in the acetic acid elimination products (**326** and **327**) was observed, as would be expected with the appearance of a conjugated system of Schiff base of dehydroalanine (the same long-wavelength shift is observed in octahedral bissalicylidene complexes of dehydroaminobutyric acid with the Co^{3+} ion). Finally, the spectra of circular dichroism (CD) (see Figure 9.9) and ORD curves (see Figure 9.8) of dehydroalanine complexes differ from spectra of the starting complexes of (*R*)-serine and (*S*)-serine, as expected, due to the disappearance of the asymmetric center of amino acid fragment of these complexes.

It should be noted that stable complexes of Schiff bases of dehydroalanine with transition metal ions were obtained for the first time.

Elimination of acetoxy ion is accompanied by a side process, the nature of which could not be established. In the case of (*R*)-acetylserine complexes (**324**, **325**), the specific weight of this reaction is low ($\sim 5\%$); in the case of complexes of (*S*)-acetylserine, it is high ($\sim 30\%$).

The rate of elimination under the action of *Dabco* base was determined spectrophotometrically by the increase of absorbance at 435 nm. Measurements were carried out in the initial sections of the kinetic curve when the side reaction could be disregarded. The rate of the process is in conformity with the laws of general base catalysis, and the rate constant for elimination of CH_3COOH from *O*-acetylserine fragment in the case of (*R*)-acetylserine complex (**324**) is 70 times higher than in the case of the (*S*)-acetylserine complex under *Dabco* catalysis in CH_3CN .

It can be assumed that acetoxy group cleavage is accompanied by a larger decrease in intramolecular steric strain in the case of (*R*)-acetylserine complex

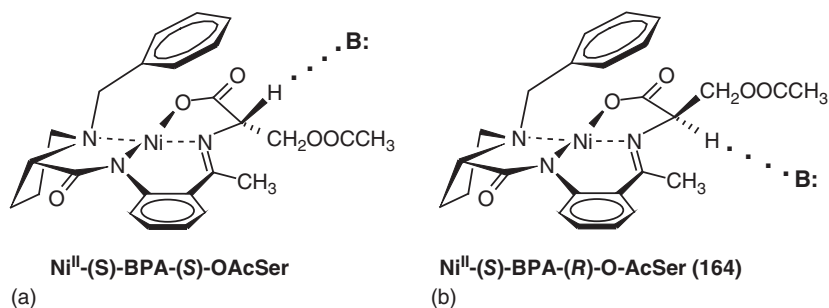


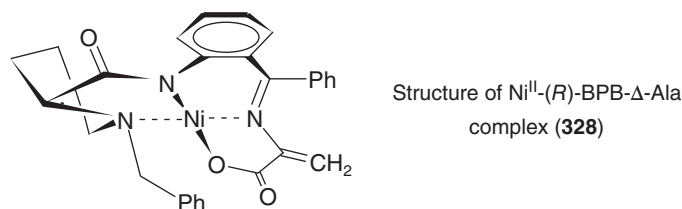
Figure 9.10 Isolation of α -proton of *O*-acetylserine fragment in the complexes of Schiff bases of (*S*)-BPA with (*S*)-*O*-acetylserine (a) and (*R*)-*O*-acetylserine (**324**) (b).

than in the case of (*S*)-acetylserine complex, since in this type of complexes the (*R*)-amino acids have greater energy than the (*S*)-amino acids [165].

However, apparently, the kinetic factors also play an important role. It is possible that under the influence of the pyrrolidine moiety of the macrocyclic ligand, induced by chiral distortion of chelate rings, α -proton of the amino acid fragment occupies a more axial position in the case of complexes of (*R*)- β -hydroxy- α -amino acids (see Figure 9.10b) than in the case of complexes of (*S*)- β -hydroxy- α -amino acids (see Figure 9.10a).

According to Danatan's hypothesis about the stereoelectronic control of the reaction, it will increase the rate of α -H amino acid fragment separation, consequently increasing the rate of β -elimination of the acetic acid moiety from acetylserine complexes in the case of amino acids of (*R*)-absolute configuration.

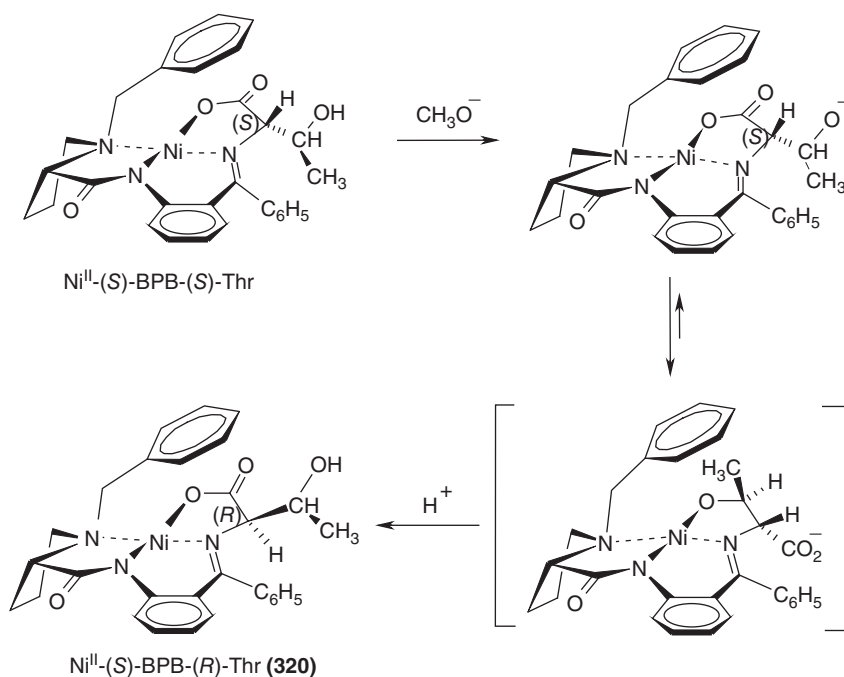
Similarly, from complex **323**, a complex of dehydroalanine Schiff base with chiral auxiliary reagent (*R*)-2-*N*-(*N'*-benzylprolyl)aminobenzophenone – Ni^{II}-(*R*)-BPB- Δ -Ala (**328**) was obtained [172].



Complex **328** was isolated from the reaction mixture by crystallization from acetone. Elemental analysis, ¹H NMR spectra, and electronic spectra are in good agreement with the corresponding data of complex **327**; and the data of the molecular rotation ($[M]^{25}$) and ORD curves in absolute value coincide with the data of complex **327**, but have the opposite sign of rotation. This implies that synthesized complex **328** is a mirror antipode of complex **327**. The synthesized dehydroalanine complexes **326**–**328** have been involved in asymmetric synthesis of β -substituted α -amino acids.

9.1.4.2 Synthesis of Chiral Ni^{II} Complexes of Dehydroaminobutyric Acid

Dehydroaminobutyric acid complexes can be synthesized by dehydration of threonine moiety of Ni^{II} -(*S*)-BPB-(*R*)-Thr complex (**320**), which is easily obtained by both complexation method (see Scheme 9.52) and condensation of glycine complex (**317**) with acetaldehyde in the presence of a strong base – sodium methylate [173, 174]. It has been shown that with an increase of medium basicity, ionization of β -hydroxyl group of the threonine moiety and intramolecular rearrangement of the complex occur, resulting in displacement of a carboxyl group from the metal coordination sphere by ionized hydroxyl group, which occupies its place. In the formed new complex due to spatial constraints, the preferred location of carboxylic and β -methyl groups of the amino acid moiety turns out to be in opposite sides of the coordination plane, which ensures stability and, consequently, a large excess of (*R*)-threo form of the β -hydroxy- α -amino acid (see Scheme 9.54).



Scheme 9.54

By analogy with salicylidene complexes of Co^{III} , dehydration of the threonine fragment in this complex is also accompanied by retroaldol breakage (breaking of the C–C bond); in this connection, the hydroxyl group of threonine is replaced by the easy leaving acetoxy group.

Attempts were made at trifluoroacetylation of threonine fragment of complex **320** with trifluoroacetic anhydride followed by elimination of trifluoroacetic acid moiety. However, elimination of the trifluoroacetic acid from trifluoroacetylated complexes led to the formation of initial complex **320**. Attempts to replace the

hydroxyl group of the threonine moiety by the tosyl group using tosyl chloride were also unsuccessful. In the reaction mixture, either initial complex **320** was re-formed or epimerization of (*R*)-threonine complex to (*S*)-threonine complex occurred. The attempts to replace the hydroxyl group of the threonine moiety by chlorine under the action of SOCl_2 followed by elimination of HCl were also unsuccessful.

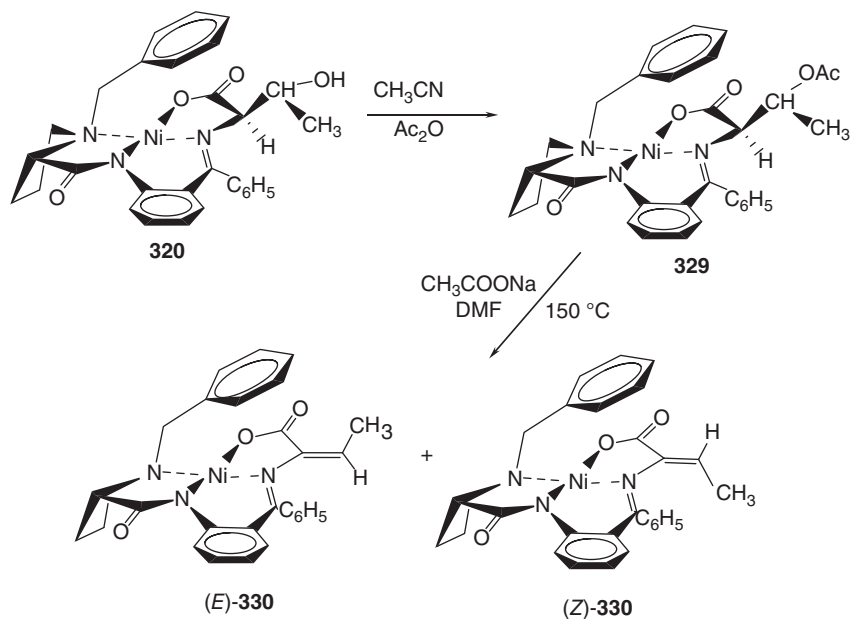
In connection with this, the version of O-acetylation of the threonine moiety of complex **320** followed by α,β -elimination of the acetic acid moiety was used. For this reason, various options of acetylation of threonine moiety of complex **320** were investigated: (i) in CH_2Cl_2 , in the presence of $\text{CH}_3\text{COONa}/\text{CH}_3\text{COOH}$ by acetic anhydride; (ii) in CH_3CN , in the presence of CH_3COONa by acetic anhydride; (iii) in DMF, in the presence of pyridine by acetic anhydride followed by adding CH_3COONa at 50°C for elimination; and (iv) in CH_3CN by acetic anhydride, followed by removal of CH_3CN from the reaction mixture after acetylation and elimination of acetic acid moiety in DMF under the action of CH_3COONa . Best results were obtained in the fourth version of acetylation and elimination of acetic acid moiety.

Acetylation of the hydroxyl group of the threonine moiety in complex **320** is easily accomplished by the action of acetic anhydride in acetonitrile to form an O-acetylserine complex **329** (see Scheme 9.55). Elimination of acetic acid moiety from the acetylserine fragment of $\text{Ni}^{\text{II}}\text{-(S)-BPB-(R)-OAcThr}$ complex (**329**) takes place under the action of sodium acetate in dimethylformamide (DMF) at 150°C to form complexes of (*Z*)- and (*E*)-dehydroaminobutyric acid (**330**) in a total yield of 50% (see Scheme 9.55). The reaction of O-acetylation and deacetoxylation can be easily monitored by TLC [SiO_2 , $\text{CHCl}_3/\text{CH}_3\text{COOC}_2\text{H}_5$ (3/1) or $\text{CHCl}_3/\text{CH}_3\text{COCH}_3$ (5/1)], as the initial threonine, intermediate O-acetylthreonine, and final deacetoxylation complexes differ by R_f values.

The (*E*)- and (*Z*)-isomers of dehydroaminobutyric acid complex can be easily separated on silica gel using benzene/acetone solvent system. The ratio of (*E*)- to (*Z*)-isomeric dehydroamino-butyric acid complexes in the reaction medium after their chromatography on SiO_2 was determined spectrophotometrically and it was (*E*)-**330**/*(Z)*-**330** = 5/1. The deacetoxylation reaction of $\text{Ni}^{\text{II}}\text{-(S)-BPB-(R)-OAcThr}$ complex (**329**) is also convenient to monitor by ^1H NMR following the disappearance of singlet signals of methyl protons of acetoxy group at 1.96 ppm or appearance of doublet signals of methyl protons of dehydroaminobutyric acid fragment of complexes (*E*)-**330** and (*Z*)-**330** at 1.65 and 0.84 ppm, respectively. Complexes of acetylthreonine (**329**) and (*E*)- and (*Z*)-dehydroaminobutyric acid (**330**) were subjected to chromatography and their structure and absolute configuration were determined by spectral methods.

Assignment of the (*E*)- and (*Z*)-configuration to isomers of dehydroaminobutyric acid complex was performed by ^1H NMR spectroscopy and X-ray structural analysis.

A significant difference in the chemical shifts of signals of the methyl protons of dehydroaminobutyric acid fragment of these complexes in ^1H NMR spectra was observed. In the isomer with the highest R_f value on SiO_2 , there is a signal



Scheme 9.55

at 1.65 ppm, typical of chemical shift of methyl group protons at the $\text{C}=\text{C}$ bond [175]. The methyl group signal of the dehydroaminobutyric fragment of bis-[*N*-salicylidenedehydroaminobutyrate]cobaltate (III) sodium complex (**31**, see Chapter 5), as in the case of (*Z*)- and (*E*)-isomers, is observed in the range of 2.15–2.2 ppm.

It is interesting to note that in the case of square-planar complex of Ni^{II} ion **330**, a similar signal for the second isomer (with a lower R_f value) appears at 0.84 ppm. Such a strong shift to the strong fields shows a significant magnetic shielding of the protons of the methyl group of this isomer due to the magnetic anisotropy of the phenyl substituent at the $\text{C}=\text{N}$ bond (see Figure 9.11) that is a strong argument in favor of the (*Z*)-configuration isomer with low R_f value on SiO_2 [174].

Conclusive evidence of the accuracy of such an assignment is based on the X-ray diffraction (XRD) analysis of the isomer having the greatest mobility on silica gel. As can be seen in Figure 9.12, this complex comprises a fragment of dehydroaminobutyric acid of (*E*)-configuration [174].

The structure of the complex (bond lengths, values of valence angles, and magnitude of distortion of chelate rings) is close to the structures earlier found for other complexes of this type [129]. The nickel atom has a slightly distorted square-planar coordination; changes from O(1) N(1) N(2) N(3) correspond to 0.10 Å for O(1) and N(2), 0.10 Å for N(1) N(3), and 0.05 Å for the Ni. Benzyl group has a conventional *endo*-orientation (i.e., rotated to the Ni atom), and proline heterocycle has $\text{C}\sigma$ -envelope conformation. Of particular interest is the chelate

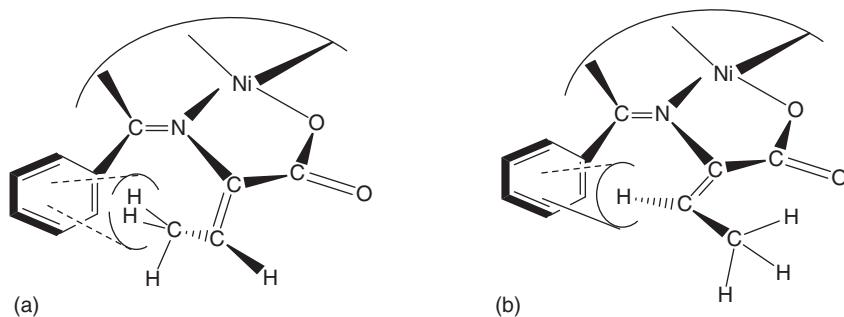


Figure 9.11 Magnetic anisotropy of the phenyl group at the C-N bond in (Z)-330 (a) and (E)-330 (b) complexes.

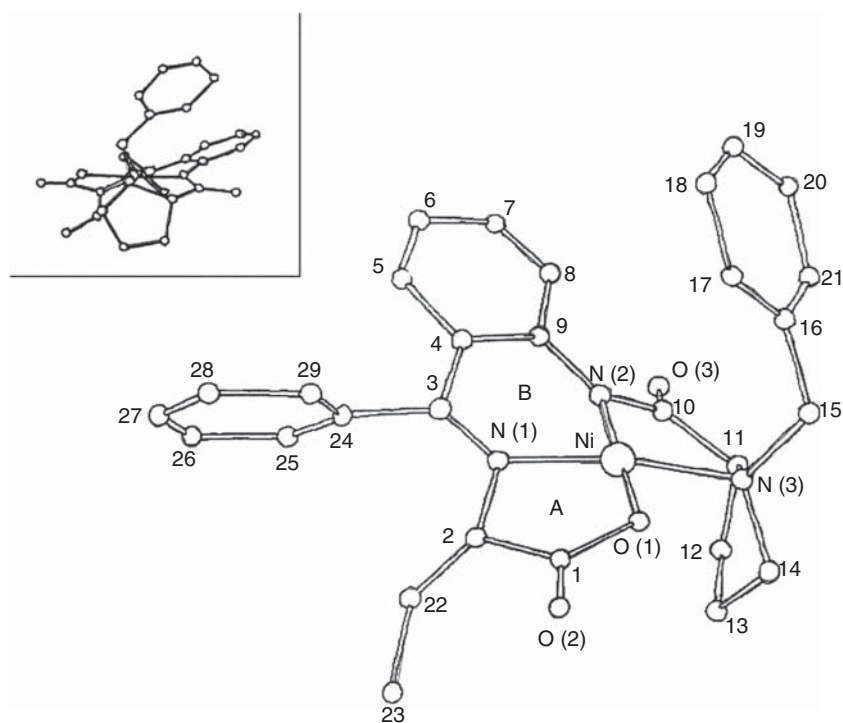


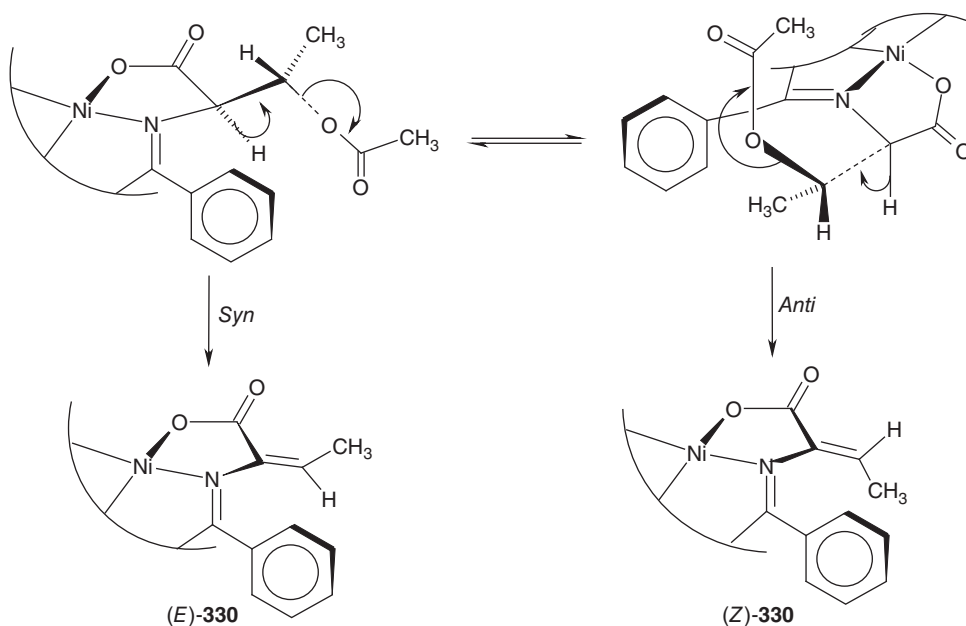
Figure 9.12 The structure of complex (E)-330 based on X-ray structural analysis.

ring, built by dehydroaminobutyric acid fragment. This metallocycle has λ -chiral conformation of the envelope with a flap of N(1) atom for $0.45\text{\AA}$ from the actually planar fragment of NiO(1) C(1) C(2). There is some twisting of the double bond C=C of dehydroaminobutyric fragment, so the torsion angle C(1) C(2) C(22) C(23) is 11° . However, the length of the C=C bond, equal to $1.35\text{\AA}$, is typical of

a double carbon–carbon bond, such as in salicylidene dehydroaminobutyric acid complexes with Co^{3+} ion. The phenyl ring at the $\text{C}=\text{N}$ bond is inclined relative to the plane of this bond (the dihedral angle $\text{N}(1) \text{C}(3) \text{C}(24) \text{C}(29)$ equals to 66°), and selectively shields the *re-re* side of the $\text{C}=\text{C}$ moiety of dehydroaminobutyric acid.

Larger excess of (*E*)-dehydroaminobutyric acid complex [(*E*)-330] compared with the (*Z*)-330 complexes in the product of elimination is a consequence of the kinetic factors, which is confirmed by specific experiments, according to which, under the action of diazabicyclooctane (*Dabco*), a thermodynamic equilibrium between the (*E*)- and (*Z*)-isomers is established in acetonitrile. Under equilibrium conditions, the ratio of these isomers is equal to 1/1.

After determination of the structure of dehydroaminobutyric acid isomers, the stereochemistry of elimination of acetic acid moiety from the acetylthreonine fragment, resulting in formation of (*E*)- and (*Z*)-isomers of dehydroaminobutyric acid, was investigated [173]. It has been shown that the elimination of acetic acid moiety from acetylthreonine complex by means of the base primarily occurs as a *syn* process to form an isomer of (*E*)-configuration. Since the equilibrium ratio of (*E*)- and (*Z*)-isomers is close to 1/1, only the kinetic factors rather than the difference in energies of the end isomers can explain the observed preference of elimination. The reason for the preference of *syn* elimination is the relatively high steric hindrances of *anti* elimination due to the nonbinding steric interaction between the CH_3 -group of acetylthreonine fragment and the phenyl substituent at the $\text{C}=\text{N}$ bond, occurring in the transient state of this process, as shown in Scheme 9.56.



Scheme 9.56

Ni^{II} complexes of dehydroaminobutyric acid (*E*)-**330** and (*Z*)-**330** were used as initial dehydroamino acid synthons for the asymmetric synthesis of optically active β -substituted derivatives of α -aminobutyric acid.

9.2

Stoichiometric Asymmetric Synthesis of α -Amino Acids

This section illustrates the results of research on asymmetric C-alkylation reactions of glycine and alanine in Ni^{II} complexes of their Schiff bases with chiral auxiliary BPB, leading to the formation of more complex nonprotein α -amino acids and their α -methyl substituted analogs. Moreover, depending on the absolute configuration of chiral constituent of the auxiliary reagent, alkylation is directed toward the asymmetric formation of amino acids of (*S*)- or (*R*)-absolute configuration.

9.2.1

Synthesis of α -Substituted (*S*)- α -Amino Acids

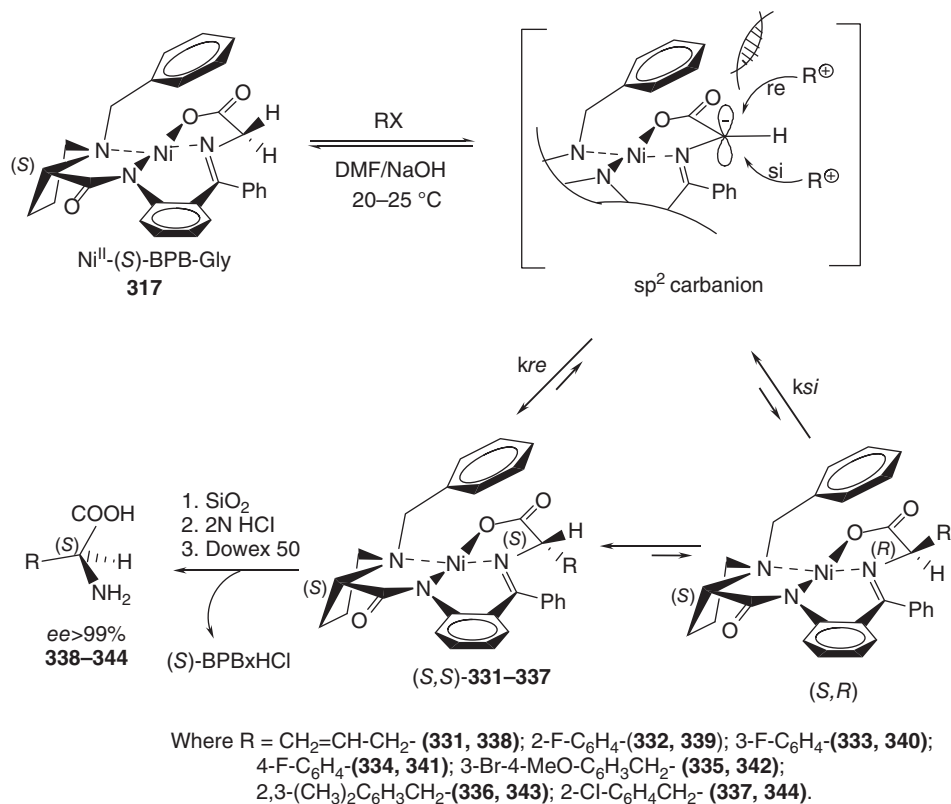
To perform asymmetric synthesis of nonprotein (*S*)- α -amino acids, square-planar Ni^{II} ion complexes of glycine and alanine Schiff bases with chiral auxiliary reagent (*S*)-BPB (**317**, **318**) [6, 123, 125, 176–178] were used as starting amino acid synthons. C-alkylation of a glycine moiety of **317** complex by alkyl halides under conditions of base catalysis resulted in the diastereoselective synthesis of (*S*)- α -amino acids (see Scheme 9.57).

Several solvents – CH_3CN , THF, and DMF – and bases – KOH, NaOH, and Na_2CO_3 – were tested, but the best results were obtained with DMF in the presence of NaOH. The progress of the reaction was monitored by TLC [SiO_2 , $\text{CHCl}_3/\text{CH}_3\text{COCH}_3$ (3/1)] following the disappearance of traces of the initial complex **317** and establishment of a thermodynamic equilibrium between the (*S,S*)- and (*S,R*)- diastereoisomers of the alkylation products.

Alkylation of complex **317** proceeds with the formation of a mixture of (*S,S*)- and (*S,R*)-diastereoisomeric complexes of the reaction products with high excess of (*S,S*)-diastereoisomer containing amino acid of (*S*)-absolute configuration. The formation of **331**–**337** complexes is a kinetically and thermodynamically controllable process. The stereoselectivity of synthesis is defined by both the relative rate of attack of the alkylating agent on the prochiral carbanion from *re* or *si* side of the plane of the Schiff base (kinetic stereoselectivity) and thermodynamic stability of the formed diastereoisomers (thermodynamic stereoselectivity).

Diastereoisomers of alkylation products are easily chromatographed on SiO_2 in the $\text{CHCl}_3/\text{CH}_3\text{COCH}_3$ (3/1) solvent system.

The absolute configuration of α -carbon atom of the amino acid moiety of the diastereoisomeric complexes was established by polarimetric measurements at 589 nm (Na-line). It has been shown that complexes of (*S*)- α -amino acids



Scheme 9.57

at 589 nm wavelength have a positive sign of rotation and the complexes of (*R*)- α -amino acids a negative sign. The positive value of the optical rotation sign of major diastereoisomers of alkylated complexes (**331–337**) indicates their (*S,S*)-absolute configuration with the content of (*S*)- α -amino acids.

The ratio of (*S,S*)- and (*S,R*)-diastereoisomers of alkylation products can be determined by ^1H NMR analysis of their mixture (before chromatography) by the ratio of the values of integrals of methylene proton signals of *N*-benzylproline moiety in the range of 2.55–4.40 ppm and by chiral GLC analysis of amino acids mixture isolated from acid hydrolysate of a mixture of diastereomeric complexes by ion exchange method.

The results are shown in Table 9.2. As follows from the table, on average the stereoselectivity of syntheses reaches 80% within 3 h.

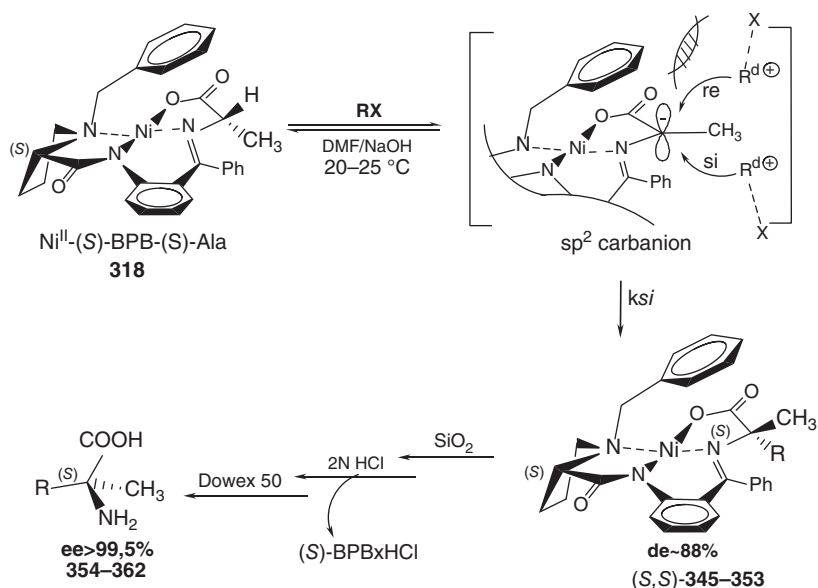
By C-alkylation of Ni^{II} complex of alanine **318** with alkylhalides, stoichiometric asymmetric synthesis of α -substituted α -amino acids was performed [6, 123, 125, 178]. These alkylation reactions also effectively proceeded under base catalysis

Table 9.2 The results of C-alkylation of glycine moiety of **317** complex by alkylhalides in DMF/NaOH at 25 °C

No.	Alkylating agent	Resulting complex	(<i>S,S</i>)/(<i>S,R</i>)/bisproduct (%) ^{a)}	Chemical yield (%) ^{b)}
1	CH ₂ =CH-CH ₂ Cl	331	89.8/10.12	85
2	2-F-C ₆ H ₄ CH ₂ Br	332	80.24/9.01/14.74	94
3	3-F-C ₆ H ₄ CH ₂ Br	333	95.08/4.36/0.55	95
4	4-F-C ₆ H ₄ CH ₂ Br	334	77.44/7.20/15.26	83
5	3-Br-4-OMe-C ₆ H ₃ CH ₂ Br	335	92.06/7.94	90
6	C ₆ H ₅ CH ₂ OC ₆ H ₄ CH ₂ Br	336	88.2/11.8	88
7	2-Cl-C ₆ H ₄ CH ₂ Br	337	90.7/9.3	93

a) Defined by chiral GLC analysis.

b) Overall chemical yield at alkylation step.



where R = CH₂=CH-CH₂ (**345**, **354**); CH₃CH₂ (**346**, **355**); CH₃CH₂CH₂ (**347**, **356**); (CH₃)₂CH (**348**, **357**); 3,4-Cl₂-C₆H₃CH₂ (**349**, **358**); 2-F-C₆H₄-CH₂ (**350**, **359**); 3-F-C₆H₄CH₂ (**351**, **360**); 4-F-C₆H₄CH₂ (**352**, **361**); C₆H₅CH₂OC₆H₄CH₂ (**353**, **362**).

Scheme 9.58

in DMF in the presence of NaOH at 45 °C (see Scheme 9.58). The course of the alanine alkylation reaction can be also conveniently monitored by TLC [SiO₂, CHCl₃/CH₃COCH₃ (3/1)] following the disappearance of traces of initial complex **318** and the appearance of traces of diastereomeric complexes of alkylation products.

As a result of alkylation of diastereomeric alanine complex, a mixture of (*S,S*)- and (*S,R*)-diastereoisomers of complexes of alkylation products are formed, with a high excess of the diastereoisomer containing the amino acid of (*S*)-absolute configuration.

In this case, the stereoselectivity of synthesis is only a kinetically controllable process (formation of carbanion in alkylation products is excluded) and is determined by the relative rate of attack of the alkylating agent on the prochiral sp^2 carbanion from *re* or *si* side of the Schiff base plane (kinetic selectivity).

The major diastereoisomers of alkylation products **345**–**353** were isolated by column chromatography [SiO_2 , 3×20 cm, $CHCl_3/CH_3COCH_3$ (3/1)] and characterized by physicochemical methods of analysis.

The absolute configuration of α -carbon atom of amino acid moiety of the obtained diastereoisomeric complexes was also determined by polarimetric measurements. The positive value of optical rotation of synthesized major diastereoisomeric complexes **345**–**353** at 589 nm wavelength shows their (*S,S*)-absolute configuration with the content of (*S*)- α -amino acids.

The ratio (*S,S*)- and (*S,R*)-diastereoisomers of alkylation products was determined by chiral GLC analysis of a mixture of amino acids recovered after acid decomposition of the diastereoisomeric mixture of complexes and ion exchange separation. The results are shown in Table 9.3.

After decomposition of major diastereoisomeric complexes of α -amino acids **331**–**337** and α -substituted α -amino acids **345**–**353** in methanol under the action of 2 N HCl, the target optically active amino acids were isolated from the hydrolysates by standard methods [176–178]. The amino acids were

Table 9.3 Alkylation results of Ni^{II} -(*S*)-BPB-(*S*)-Ala complex (**318**) with alkylhalides in DMF/NaOH.

No.	Alkylating agent	<i>T</i> (°C)	Resulting complex	(<i>S,S</i>)/(<i>S,R</i>) (%) ^{a)}	Chemical yield (%) ^{b)}
1	$CH_2=CH-CH_2Cl$	25	345	88.04/11.96	87
2	$CH_2=CH-CH_2I$	45	–	92.34/7.66	86
3	CH_3CH_2Br	25	346	85.2/14.8	80
4	–	45	–	88.5/11.5	83
5	$CH_3(CH_2)Br$	25	347	87.07/12.93	91
6	–	45	–	94.37/5.63	92
7	$(CH_3)_2CHBr$	25	348	86.9/13.1	81
8	–	45	–	88/12	84
9	$3,4-Cl_2-C_6H_3CH_2Cl$	25	349	90.12/9.8	75
10	–	45	–	90.4/7.6	68
11	$4-F-C_6H_4CH_2Br$	25	350	86.4/13.6	91.6/8.4
12	–	45	–	89.5/10.5	92.4/7.6

a) Defined by chiral GLC analysis.

b) Overall chemical yield at alkylation step.

demineralized with cation exchange resin Dowex-50 $\times$ 8 or Ku-2 $\times$ 8 in H^+ form (sorption and elution with 5% NH_4OH solution), concentrated *in vacuo* and crystallized from water–alcohol solutions. Auxiliary reagent was regenerated at that with full retention of the initial optical activity, and can be used repeatedly. Enantiomeric purity of the synthesized amino acids was determined by chiral GLC or HPLC analyses.

Thus, based on amino acid synthons of Ni^{II} complexes of Schiff bases of glycine and alanine with chiral auxiliary (*S*)-BPB, asymmetric syntheses of the following important optically active nonprotein (*S*)- α -amino acids were performed: α -allylglycine, 2-fluorophenylalanine, 3-fluorophenylalanine, 4-fluorophenylalanine, 3-bromo-4-methoxyphenylalanine, 3,4-dimethyl phenylalanine, 2-chlorophenylalanine, α -allylalanine, 2-amino-2-methylbutyric acid, 2-amino-2-methylvaleric acid, 2-amino-2,3-dimethylvaleric acid, 3,4-dichloro- α -methylphenylalanine, 2-fluoro- α -methylphenylalanine, 3-fluoro- α -methylphenylalanine, 4-fluoro- α -methylphenylalanine, and *p*-O-benzyl- α -methyltyrosine. Polarimetric characteristics of the synthesized (*S*)- α -amino acids are presented in Table 9.4.

Diastereoselectivity of syntheses averages 90% and the enantiomeric purity of the obtained amino acids exceeds 98%. This approach provides an opportunity for the synthesis of a wide variety of optically active nonprotein (*S*)- α -amino acids and the development of a universal technology for their small tonnage production.

Table 9.4 Chiroptic characteristics of synthesized nonprotein (*S*)- α -amino acids.

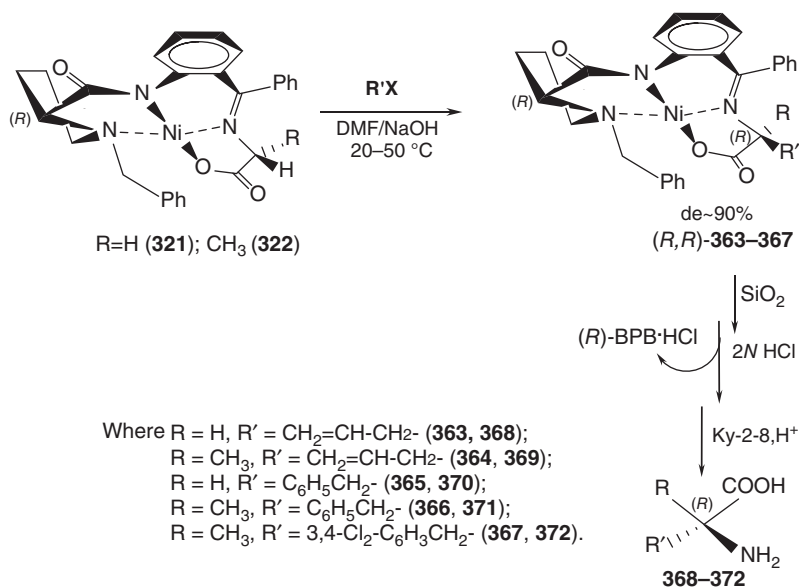
No.	Name of amino acids	Chiroptic characteristics	
		$[\alpha]^{25}_D$	ee (%)
1	(<i>S</i>)- α -Allylglycine (338)	$-38.1^\circ (c = 4; H_2O)$	99
2	(<i>S</i>)-2-Fluorophenylalanine (339)	$-14.3^\circ (c = 0.025; H_2O)$	98
3	(<i>S</i>)-3-Fluorophenylalanine (340)	$-27.0^\circ (c = 0.025; H_2O)$	98
4	(<i>S</i>)-4-Fluorophenylalanine (341)	$-26.9^\circ (c = 0.028; H_2O)$	98
5	(<i>S</i>)-3-Bromo-4-methoxyphenylalanine (342)	$+34.3^\circ (c = 0.03; H_2O)$	98
6	(<i>S</i>)-3,4,4-Dimethyl phenylalanine (343)	$+8.25^\circ (c = 0.4; 1\ N\ HCl)$	99
7	(<i>S</i>)-2-Chlorophenylalanine (344)	$-1.13^\circ (c = 0.5; 1\ N\ HCl)$	99
8	(<i>S</i>)- α -Allylalanine (354)	$-14.4^\circ (c = 1.3; 1\ N\ HCl)$	99
9	(<i>S</i>)-2-Amino-2-methylbutyric acid (355)	$+11.80^\circ (c = 1; H_2O)$	98
10	(<i>S</i>)-2-Amino-2-methylvaleric acid (356)	$+19.75^\circ (c = 1; H_2O)$	98
11	(<i>S</i>)-2-Amino-2,3-dimethylvaleric acid (357)	$-1.45^\circ (c = 0.91; H_2O)$	98
12	(<i>S</i>)-3,4-Dichloro- α -methylphenylalanine (358)	—	97
13	(<i>S</i>)-2-Fluoro- α -methylphenylalanine (359)	$-14.8^\circ (c = 0.34; H_2O)$	98
14	(<i>S</i>)-3-Fluoro- α -methylphenylalanine (360)	$-21.7^\circ (c = 0.27; H_2O)$	99
15	(<i>S</i>)-4-Fluoro- α -methylphenylalanine (361)	$-17.3^\circ (c = 0.15; H_2O)$	97
16	(<i>S</i>)- <i>p</i> -O-Benzyl- α -methyltyrosine (362)	$6.92^\circ (c = 2.1; CF_3COOH)$	99

9.2.2

Synthesis of α -Substituted (*R*)- α -Amino Acids

It can be assumed that the use of chiral auxiliary (*R*)-2-[*N*-(*N'*-benzyl)propyl]amino] benzophenone (*R*)-BPB (**313**) in asymmetric reactions of amino acids instead of (*S*)-BPB allows carrying out asymmetric synthesis of optically active α -substituted (*R*)- α -amino acids. By analogy with the procedure for the synthesis of (*S*)- α -substituted α -amino acids (see Section 9.2.1), the asymmetric C-alkylation of glycine and alanine in chiral Ni^{II} complexes of their Schiff bases with (*R*)-BPB (**321**, **322**) by alkyl halides was investigated [179, 180].

Benzyl bromide, 3,4-dichlorobenzyl bromide, and allyl chloride were used as alkylating agents. Condensation of complexes **321** or **322** with alkyl halides was performed in DMF in the presence of finely ground NaOH at both ambient temperature and upon heating to 45–50 °C (see Scheme 9.59).



Scheme 9.59

As a result of alkylation of glycine and alanine complexes, a mixture of (*R,R*)- and (*R,S*)-diastereomeric complexes is formed with a large excess of diastereomers of (*R,R*)-absolute configuration containing (*R*)- α -allylglycine (**363**), (*R*)- α -allylalanine (**364**), (*R*)-phenylalanine (**365**), (*R*)- α -methyl-phenylalanine (**366**), and (*R*)-3,4-dichloro- α -methylphenylalanine (**367**). The alkylation reaction of glycine and alanine complexes can be conveniently monitored by TLC, since by R_f values on SiO_2 both initial complexes with alkylation products and their (*R,R*)- and (*R,S*)-diastereoisomeric complexes [$\text{CHCl}_3/\text{CH}_3\text{COCH}_3$ (3/1) or $\text{CHCl}_3/\text{CH}_3\text{COOC}_2\text{H}_5$ (1/3)] can be distinguished.

The structure and absolute configuration of the alkylated complexes were studied by physicochemical methods of analysis. As expected, the (*R,R*)- and (*R,S*)-diastereomers of alkylated complexes differed from each other only by the

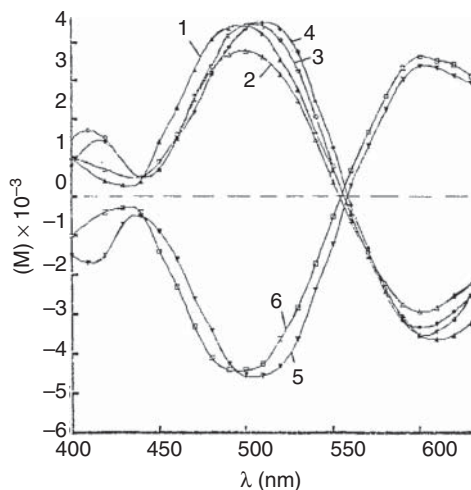


Figure 9.13 ORD curves of complexes in CH_3OH at $T = 25^\circ\text{C}$ 1 – (*R,R*)-**363**; 2 – (*R,R*)-**364**; 3 – (*R,R*)-**367**; 4 – (*R,R*)-**366**; 5 – (*S,S*)-**345**; 6 – (*S,S*)-**349**.

chemical shifts of signals of the α -H amino acid fragment in ^1H NMR spectra; the data of elemental analysis and electronic spectra were practically identical.

To determine the absolute configuration of alkylated complexes, their ORD curves were recorded and compared with ORD curves of the corresponding (*S,S*)-diastereomers – Ni^{II} complexes of the same amino acids of (*S*)-configuration with the chiral reagent (*S*)-BPB (see Figure 9.13).

ORD curves of main fractions of synthesized complexes with smaller R_f value on SiO_2 (**363**–**367**) are mirror images of corresponding ORD curves of (*S,S*)-diastereoisomers. The data of their molecular rotation in their absolute value coincide and have the opposite sign of rotation. It follows from this that the main fractions resulting from the alkylation of glycine and alanine complexes, based on the chiral auxiliary (*R*)-BPB, are diastereomeric complexes of (*R,R*)-absolute configuration.

The ratio of (*R,R*)- and (*R,S*)-alkylated diastereoisomeric complexes was determined by chiral GLC analysis. The results are shown in Table 9.5.

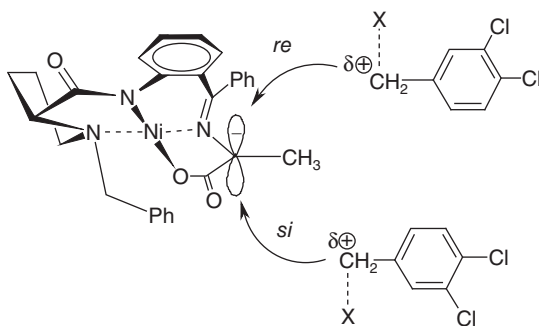
As seen from the table, the highest stereoselectivity is observed during synthesis of 3,4-dichloro- α -methylphenylalanine (**367**); the excess of (*R,R*)-diastereomer in this case is more than 96%. High enantioselective effects in alkylation of these complexes is the result of the steric nonbinding interaction between the phenyl group of *N*-benzylproline moiety and a bulky alkylating radical on the *si* side of prochiral carbanion preventing the attack of alkylating agent on prochiral carbanion exactly from this side of the plane.

This is due to the slowing of C-alkylation reaction from the *si* side of prochiral carbanion compared to the reaction from the *re* side with formation of the (*R,R*)-diastereomer in a large excess. Such regularity has an even greater effect on alkylation of alanine with the more bulky 3,4-dichlorobenzyl chloride (see Figure 9.14) [179].

Table 9.5 Results of glycine and alanine alkylation in complexes **321** and **322** by alkyl halides

Starting RX complex	$(R,R)/(R,S)$ (%) ^{a)}	Amino acid		Yield (%) ^{b)}
		Name	$[\alpha]_D^{25}$	
321 CH ₃ I	93.4/6.8	(<i>R</i>)-Ala	4.2° (<i>c</i> = 5; 1 N HCl)	87
321 CH ₂ =CHCH ₂ Br	92.4/7.6	(<i>R</i>)- α -AllylGly	+34.8° (<i>c</i> = 0.55; H ₂ O)	79
322 C ₆ H ₅ CH ₂ Br	94.2/5.8	(<i>R</i>)- α -MePhe	+4.2° (<i>c</i> = 0.5; 1 N HCl)	83
322 CH ₂ =CHCH ₂ Br	92.2/7.8	(<i>R</i>)- α -AllylGly	+14.4° (<i>c</i> = 1.3; 1 N HCl)	79
322 3,4-Cl ₂ C ₆ H ₃ CH ₂ Cl	>96	(<i>R</i>)- α -Me-3,4-Cl ₂ Phe	+4.96 (<i>c</i> = 1; H ₂ O)	65

a) Enantiomeric excess (ee) was determined by enantiomeric GLC analysis.

b) Chemical yield was calculated based on amounts of starting complexes **321** and **322**.**Figure 9.14** Steric shielding from the *si* side of prochiral carbanion during alanine alkylation in complex **322** with 3,4-dichlorobenzyl chloride.

Decomposition of complexes **363**–**367** and isolation of target (*R*)- α -substituted α -amino acids **368**–**372** were conducted by the conventional procedure in CH₃OH under the action of HCl. Chiral auxiliary (*R*)-BPB was regenerated at that in quantitative chemical yield (>94%) and complete retention of the starting optical purity.

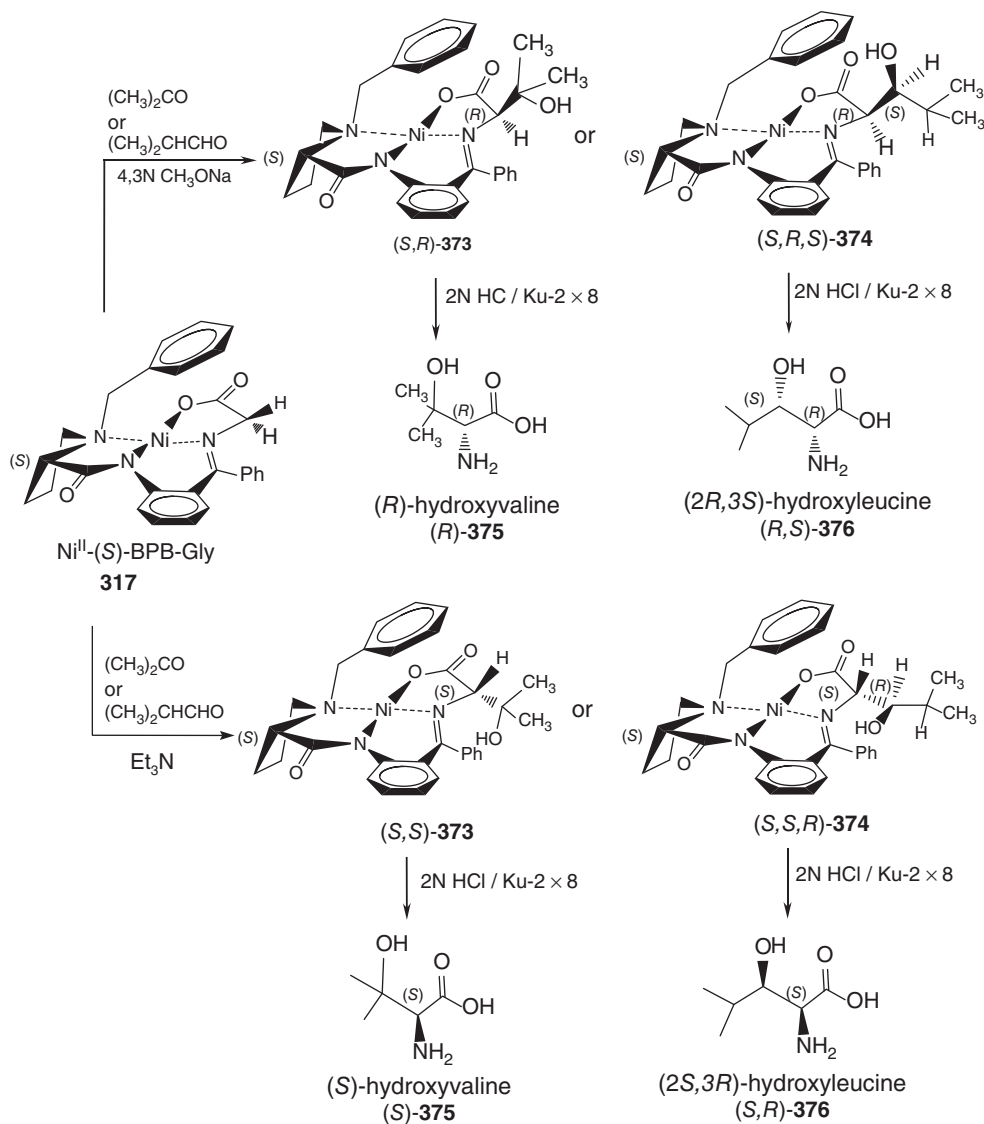
The resulting amino acids with (*R*)-absolute configuration **368**–**372** were recrystallized from water–alcohol solutions and characterized by spectral methods of analysis. All spectral data of the isolated (*R*)- α -amino acids unambiguously confirm their structure and absolute (*R*)-configuration. Optical purity of the synthesized samples was additionally determined by GLC-enantiomeric analysis in the form of isopropyl esters of *N*-trifluoroacetyl derivatives on a chiral phase [181]. Results are presented in Table 9.5.

9.2.3

Diastereoselective Synthesis of β -Hydroxy- α -Amino Acids

Earlier, in the example of serine and threonine synthesis, it was shown that during the aldol condensation of glycine moiety of Ni^{II} complex of its Schiff base

with chiral auxiliary (*S*)-BPB in the presence of a strong base (CH_3ONa), the (*R*)-form of β -hydroxy- α -amino acid was preferably formed, while in the presence of a weak base (Et_3N) – the (*S*)-form was formed (see Section 9.1). This approach was applied for the asymmetric synthesis of nonprotein β -hydroxy- α -amino acids, in particular in the case of hydroxyvaline and hydroxyisoleucine, using as alkylating agents acetone and *iso*-propyl aldehyde, respectively (see Scheme 9.60) [129, 182].



Scheme 9.60

Table 9.6 Results of aldol condensation of glycine complex **317**.

No.	Name of amino acids	de (%) ^{a)}	Chiroptic characteristics		Chemical yield (%) ^{b)}
			(α) ²⁵ _D	ee (%) ^{a)}	
1	(<i>S</i>)-Hydroxyvaline; (<i>S</i>)- 375	88.5	+11.1° (<i>c</i> = 0.64; 6 N HCl)	>98	62
2	(<i>R</i>)-Hydroxyvaline; (<i>R</i>)- 375	87.8	11.08° (<i>c</i> = 0.64; 6 N HCl)	>98	58
3	(2 <i>S</i> ,3 <i>R</i>)-Hydroxyleucine; (<i>S</i> , <i>R</i>)- 376	90.8	+19.15° (<i>c</i> = 2.0; 6 N HCl)	>98.5	54
4	(2 <i>R</i> ,3 <i>S</i>)-Hydroxyleucine; (<i>R</i> , <i>S</i>)- 376	88.8	−19.12° (<i>c</i> = 2.0; 6 N HCl)	>99	57

a) Optical purity of crystals and diastereoselectivity according to chiral GLC and HPLC analyses.

b) Chemical yield at the stages of the aldol condensation and separation of amino acids.

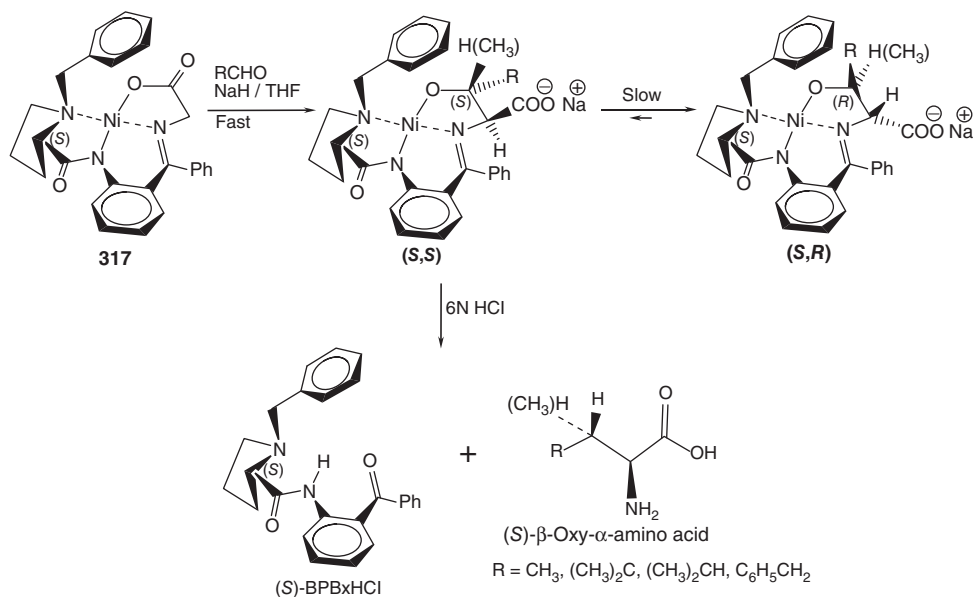
Conducting aldol condensation reaction in 4.3 N CH₃ONa, diastereomeric complexes of (*R*)-hydroxyvaline [(*S*,*R*)-**373**] and (2*R*,3*S*)-hydroxyleucine [(*S*,*R*,*S*)-**374**] were formed in excess; and in the presence of triethylamine, diastereomeric complexes of (*S*)-hydroxyvaline [(*S*,*S*)-**373**], and (2*S*,3*R*)-hydroxyleucine [(*S*,*S*,*R*)-**374**] were preferably formed. After acid decomposition of a mixture of diastereomeric complexes and ion-exchange demineralization of target amino acids, optically active (*S*)- and (*R*)-hydroxyvalines (**375**) and (2*R*,3*S*)- and (2*S*,3*R*)-hydroxyleucines (**376**) with an optical purity ee >98 % were prepared by one recrystallization from aqueous ethanol.

The stereoselectivity of asymmetric aldol condensation reactions was determined by chiral HPLC analysis of amino acids isolated from an acid hydrolysate mixture of diastereomeric complexes by ion exchange method (prior to crystallization). The results are shown in Table 9.6.

The conditions of kinetic and thermodynamic stereoselectivities in aldol condensation reaction were studied. It is shown that in thermodynamic equilibrium between the diastereomers, *syn*-(*R*)- β -hydroxy- α -amino acid is preferably formed, while initially under kinetic control *syn*-(*S*)- β -hydroxy- α -amino acid is formed (see Scheme 9.61).

Under experimental conditions, it is difficult to stop the reaction at the stage of kinetically controlled stereoselectivity. The product, within several minutes, passes to thermodynamically controlled through the reactions of cleavage and C–C bond formation

It could be assumed that conducting the reaction in aprotic solvents with relatively low dielectric constant, which undoubtedly is the most convenient condition for catalytic reactions, will increase the basicity of the intermediate aldol adduct with ionized hydroxyl group (possibly due to formation of the O–Ni bond) and at the same time reduce the rate of conversion between the diastereomeric complexes. Consequently, the separation of kinetically favorable aldol product of *syn*-(*S*)- β -hydroxy- α -amino acid will become possible.



Scheme 9.61

Proceeding from the above, aldol condensation reaction of complex **317** with aliphatic aldehydes, benzaldehyde, and acetone was carried out in THF at different temperatures [183]. To stop conversion between diastereomers, the reaction mixture was poured into a cold solution of acetic acid. The reverse order of AcOH addition in all cases led to the formation of large amounts of (*R*)-diastereomer.

Diastereomeric ratio of isolated complexes was determined by ¹H NMR or enantiomeric GLC analysis. CD spectra of the complexes were used to further determine the absolute configuration of α -carbon atom of the amino acid fragment. The optimal base for this reaction is NaH. In the case of *t*-BuOK and *t*-BuLi, the ratio of *syn*-(*S*)/*syn*-(*R*) products is reduced, for example, in the case of **374** from 60/1 to 7/1 and 5/1, respectively (see Table 9.7, No. 4,5). The effect of temperature is not so clearly manifested and has a negative impact on isobutyl aldehyde and *t*-butyl aldehyde and positive for acetaldehyde and benzaldehyde adduct (Table 9.7, No. 1–3 and 8, 9, 11). Interaction with acetone is the most sensitive to the reaction time, since after 7 min the ratio of (*S*)-**373**/(*R*)-**373** falls from 30/1 to 2/1 (see Table 9.7, No.13, 14).

9.2.4

The Asymmetric Synthesis of β -Substituted- α -Amino Acids

The chiral Ni^{II} complexes of Schiff bases of dehydroamino acids with an active electrophilic C=C bond are convenient synthons for incorporation of functional groups into β -position of amino acid moieties.

Table 9.7 Aldol reaction of carbonyl compounds with chiral glycine complex catalyzed by NaH in THF.^{a)}

No.	Aldehyde	<i>T</i> (°C)	Time (min)	(<i>syn</i> -2 <i>S</i>)/(<i>syn</i> -2 <i>R</i>) ^{b)}	Yield (%)	ee (<i>S</i>) (%), ^{c)} (yield (%)) ^{d)}
1	(CH ₃) ₂ CHCHO	16	10	60/1	96	95.5 (87)
2	(CH ₃) ₂ CHCHO	−5	35	7/1	75 ^{e)}	—
3	(CH ₃) ₂ CHCHO	−20	180	10/1	80 ^{e)}	—
4	(CH ₃) ₂ CHCHO	20	5	7/1/4	60 ^{f)}	—
5	(CH ₃) ₂ CHCHO	20	10	5/1/1	70 ^{f)}	—
6	(CH ₃) ₃ CCHO	20	13	10/1	80	81(62)
7	(CH ₃) ₃ CCHO	−12	75	5/1	78	—
8	CH ₃ CHO	−12	30	60/1	80	95(66)
9	CH ₃ CHO	0	15	6/1	80	—
10	CH ₃ CHO	20	30	—	—	—
11	C ₆ H ₅ CHO	−7	30	20/1	75	94 (55)
12	C ₆ H ₅ CHO	20	4	3/2	55	—
13	(CH ₃) ₂ CO	20	7	30/1	85	99 (80)
14	(CH ₃) ₂ CO	20	14	2/1	70	—

a) The substrate concentration in THF 0.18 M; molar ratio of substrate/RCHO/NaH = 1/2/1.

b) Analysis of the reaction mixture by ¹H NMR.

c) Analysis of amino acids by enantiomeric GLC.

d) Before crystallization of amino acid.

e) Yield is determined by weight after precipitation.

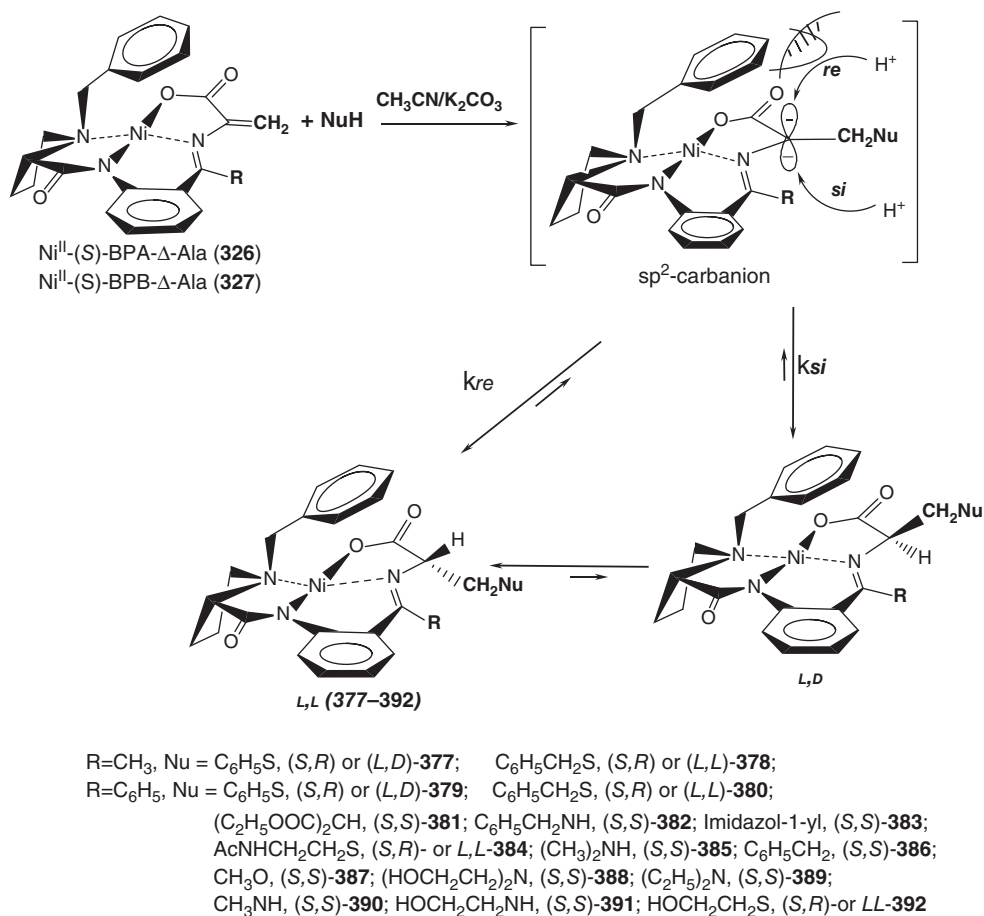
f) *t*-BuOK and *t*-BuLi used as bases.

Nucleophilic Michael addition to the dehydroamino acid moiety of complexes followed by separation of target amino acids can be used for the asymmetric synthesis of a wide range of optically active β -functionally substituted nonprotein α -amino acids of both (*R*)- and (*S*)-absolute configuration.

9.2.4.1 Asymmetric Addition of Nucleophiles to Chiral Dehydroalanine Complexes

Chiral complexes of dehydroalanine Ni^{II}-(*S*)-BPA- Δ -Ala (**326**) and Ni^{II}-(*S*)-BPB- Δ -Ala (**327**) readily undergo addition reactions with various nucleophiles in acetonitrile in the presence of a base (see Scheme 9.62)[170, 171, 184–189].

When free amines are used as nucleophiles, the addition reaction proceeds even in the absence of a base. The nucleophilic addition reaction can be conveniently monitored by TLC on SiO₂, as well as by ¹H NMR spectroscopy following the disappearance of signals of vinyl hydrogens of dehydroalanine or the appearance of signals of α -protons of amino acid fragments of addition products. Besides, diastereomeric complexes of addition products can be easily separated on SiO₂ in CHCl₃/CH₃COCH₃ (2/1) or CHCl₃/CH₃COOC₂H₅ (3/1) solvent system and differ from each other by the position of α -proton signals of amino acid moieties. This difference was used to determine the ratio of diastereomers derived from nucleophilic addition to dehydroalanine complexes by ¹H NMR and TLC.



Scheme 9.62

The initial product of the addition reaction is a mixture of two diastereomers in approximately equal amounts in the case of complex **326**, and in 70/30% ratio in favor of less mobile diastereomer on silica gel in the case of complex **327** (by ^1H NMR and TLC). Then, during the reaction, the amount of this diastereomer increases due to the thermodynamic equilibrium between the diastereomers. The diastereomeric equilibrium ratio is given in Table 9.8.

In the case of dehydroalanine complexes with 2-aminoacetophenone chiral reagent (**326**), the addition of nucleophiles in the example of benzyl mercaptan and thiophenol was carried out in the presence of Na_2CO_3 , pyridine, and in a biphasic system $\text{CH}_3\text{CN/K}_2\text{CO}_3/(\text{Bu})_4\text{N}^+(\text{TBA})$. The ratio of (*S,R*) (or *L,L*) and (*S,S*) (or *L,D*) diastereomers of the obtained complexes of *S*-substituted cysteines was 1/1 in the case of benzylmercaptan (**378**) and 2.6/1 in the case of thiophenol (**377**) addition, indicating a low asymmetric yield of addition reaction.

Table 9.8 Results of asymmetric addition of nucleophiles to dehydroalanine in chiral complexes with Ni^{II} ion.

No.	Starting complex	Nucleophile	Medium/base	Main product	Ratio of diastereomers (%) ^{a)}	
					L,L ^{b)}	L,D ^{b)}
1	326	$\text{C}_6\text{H}_5\text{SH}$	$\text{CH}_3\text{CN}/\text{K}_2\text{CO}_3$	377	78(<i>S,R</i>)	22(<i>S,S</i>)
2	–	$\text{C}_6\text{H}_5\text{CH}_2\text{SH}$	$\text{CH}_3\text{CN}/\text{K}_2\text{CO}_3$	378	55(<i>S,R</i>)	45(<i>S,S</i>)
3	–	$\text{C}_6\text{H}_5\text{SH}$	Biphasic system	377	73(<i>S,R</i>)	27(<i>S,S</i>)
4	327	$\text{C}_6\text{H}_5\text{SH}$	$\text{CH}_3\text{CN}/\text{K}_2\text{CO}_3$	379	93(<i>S,R</i>)	7(<i>S,S</i>)
5	–	$\text{C}_6\text{H}_5\text{CH}_2\text{SH}$	$\text{CH}_3\text{CN}/\text{K}_2\text{CO}_3$	380	94(<i>S,R</i>)	6(<i>S,S</i>)
6	–	$\text{CH}_2(\text{CO}_2\text{Et})_2$	$\text{CH}_3\text{CN}/\text{K}_2\text{CO}_3$	381	84(<i>S,S</i>)	16(<i>S,R</i>)
7	–	$\text{C}_6\text{H}_5\text{CH}_2\text{NH}_2$	$\text{CH}_3\text{CN}/\text{K}_2\text{CO}_3$	382	95(<i>S,S</i>)	5(<i>S,R</i>)
8	–	Imidazole	$\text{CH}_3\text{CN}/\text{K}_2\text{CO}_3$	383	95(<i>S,S</i>)	5(<i>S,R</i>)
9	–	$\text{AcNHCH}_2\text{CH}_2\text{SH}$	$\text{CH}_3\text{CN}/\text{K}_2\text{CO}_3$	384	93(<i>S,R</i>)	7(<i>S,S</i>)
10	–	$(\text{CH}_3)_2\text{NH}$	$\text{CH}_3\text{CN}/\text{K}_2\text{CO}_3$	385	94.0(<i>S,S</i>)	6.0(<i>S,R</i>)
11	–	CH_3OH	CH_3ONa	387	92(<i>S,S</i>)	8(<i>S,R</i>)
12	–	$(\text{HOCH}_2\text{CH}_2)_2\text{NH}$	CH_3CN	388	94(<i>S,S</i>)	6(<i>S,R</i>)
13	–	$(\text{CH}_3\text{CH}_2)_2\text{NH}$	CH_3CN	389	94(<i>S,S</i>)	6(<i>S,R</i>)
14	–	CH_3NH_2	$\text{CH}_3\text{CN}/\text{K}_2\text{CO}_3$	390	90(<i>S,S</i>)	10(<i>S,R</i>)
15	–	$\text{HOCH}_2\text{CH}_2\text{NH}_2$	CH_3CN	391	88(<i>S,S</i>)	12(<i>S,R</i>)
16	–	$\text{HOCH}_2\text{CH}_2\text{SH}$	$\text{CH}_3\text{CN}/\text{K}_2\text{CO}_3$	392	92(<i>S,R</i>)	8(<i>S,S</i>)

a) The ratio of diastereomers was determined based on ^1H NMR.b) The transition to nomenclature is for avoiding confusion as natural L-cysteine and its S-substituted derivatives in contrast to other amino acids should be assigned to (*R*)-rather than to (*S*)-configuration, according to Cahn–Ingold–Prelog's rule.

By analogy with alkylation of amino acid complexes, one would expect to see an increase in diastereomeric excess of (*S,S*)-diastereomers at the transition from the dehydroalanine complex based on (*S*)-BPA chiral reagent (**326**) to a complex with chiral-inducing reagent (*S*)-BPB (**327**).

Complexes **377–392** resulting from nucleophile addition were isolated from the reaction medium by crystallization from acetone or by silica gel chromatography and characterized by physicochemical methods of analysis. The data of these analyses are consistent with the expected structures.

To establish the absolute configuration of diastereomers of synthesized complexes, their ORD curves were recorded and compared with ORD curves of similarly structured complexes of (*S*)-serine **315** and (*R*)-serine **316**, the absolute configuration of which was established by X-ray analysis. Comparison of these data shows that the main fractions of synthesized complexes **377–392** with smaller R_f value on silica gel have L,L or (*S,S*) (for complexes of substituted cysteines (*S,R*)) absolute configuration.

Addition of nucleophiles occurs under base catalysis conditions with the formation of two possible diastereomers of (*S,S*)- and (*S,R*)-configuration. If the formation of equilibrium between the diastereomers is slow, then at the initial

steps of the reaction their kinetically controlled ratio can be fixed, which is determined by the relative rates of *re* and *si* attack of a proton on the intermediately formed α -carbanion of the amino acid fragment. During thermodynamic equilibrium between these diastereomers, a large excess of isomer of (*S,S*)-configuration (~70–95%) is formed (see Table 9.8).

Under conditions of slow epimerization of diastereomers (in the presence of pyridine and *Dabco*), kinetically controlled ratio of (*S,S*)- and (*S,R*)-diastereomers can be fixed by TLC, which is equal to 1.08/1 for benzylmercaptan and 1.1/1 in the case of thiophenol when dehydroalanine complex with (*S*)-BPA (**326**) is used. In the case of addition of thiophenol to the dehydroalanine complex with chiral reagent (*S*)-BPB (**327**), the ratio of (*S,S*)/(*S,R*) (or $L,L/L,D$) equals 2.7/1.

When conducting addition reaction of nucleophiles to dehydroalanine in acetonitrile under the influence of K_2CO_3 , the diastereoselectivity is largely a consequence of the thermodynamic equilibrium between the diastereoisomers. The ratio of the resulting (*S,R*) (or L,L) and (*S,S*) (or L,D) diastereoisomers when attaching thiols to complex **327** is equal to 93/7 for benzylmercaptan and 94/6 – for thiophenol.

However, using DMF as a medium significantly increases the concentration of the reactants due to the better solubility of complex **327** in DMF; at the same time, this creates difficulties in monitoring the progress of the reaction by TLC on SiO_2 , because the presence of DMF in samples distorts the TLC results.

The table shows that the best option for obtaining *S*-substituted *L*-cysteines is the use of complexes based on chiral-inducing agent (*S*)-BPB and carrying out the addition reaction of thiols in CH_3CN in the presence of K_2CO_3 . This option was used for the asymmetric addition of other nucleophiles to dehydroalanine in a chiral complex with Ni^{II} ion. During addition of benzylamine after establishment of thermodynamic equilibrium (by TLC data), the ratio of (*S,S*)/(*S,R*) diastereomers in the reaction mixture of complex **382** was 81/19. When catalytic amounts of NaOH were added to the reaction mixture and the temperature was maintained at 20 °C under argon for 12 h, the ratio of (*S,S*)/(*S,R*) diastereomers in the reaction mixture reached 95/5. However, during chromatography of diastereomers on SiO_2 and storing them, a partial epimerization is observed. This phenomenon is also observed in the case of other complexes of β -amino-containing amino acids. It is evident that the cause of the instability of these complexes is the presence of a basic aminoalkyl group in the side-chain radical of amino acid moiety; this aminoalkyl group serves as a general basic catalyst of the key stage of α -proton separation of the amino acid fragment.

Imidazole addition to dehydroalanine complex proceeds fairly smoothly to form complex **383**, which is stable to epimerization in diastereomers ratio of (*S,S*)/(*S,R*) = 95/5. Based on theoretical considerations, addition of imidazole to dehydroalanine would be expected to occur at both nitrogen atom and carbon. In the latter case, histidine would be formed. To determine the structure of the adduct, 1H NMR spectra of histidine and amino acid isolated from **383** adduct were compared.

It turned out that in the field of aliphatic protons, signals of the β -CH₂ and α -CH for histidine were very different by the values of chemical shifts, wherein the β -CH₂ signals were in a relatively strong field. Chemical shifts of β - and α -protons isolated from complex (*S,S*)-**383** amino acid were in a relatively weak field, which indicates the presence of an electron-withdrawing substituent attached to the β -CH₂ group. Along with this, in the field of aromatic protons in the ¹H NMR spectrum of histidine, there were two signals with the same intensity; at the same time, in the ¹H NMR spectrum of amino acid isolated from complex **383** in this region there were two multiplets with intensity of 1/2. These data evidently show that the isolated amino acid is an imidazole adduct to the C=C bond of the dehydroalanine moiety of complex **327** at the nitrogen atom forming the C–N bond (**383**).

In the case of malonic ester attachment, the ratio of the forming diastereomers of complexes **381** stops changing 30 min after the reaction starts. The products were chromatographed on a column with SiO₂ and four fractions were isolated in a ratio of 7.4/82/0.43/10.05 in accordance with the decrease in their mobility on the silica gel. By spectroscopic methods it was found that the fractions I and II were the (*S,R*)- and (*S,S*)-diastereoisomers of adduct **381**. ORD curve analysis showed that fraction I had (*R*)-absolute configuration of the α -carbon atom, and the second (main) fraction – (*S*)-absolute configuration of the α -carbon atom. The structure of fraction IV was determined by chromatography-mass spectrometry (GC-MS) after its decomposition and isolation of the amino acid, which appeared to be the Ni^{II} complex of a Schiff base of (*S*)-serine with (*S*)-BPB. The structure of fraction III could not be established due to the small amount of the sample. To provide regioselective addition of cystamine to dehydroalanine complex **327** at the sulfur atom, the amino group of cystamine was protected via *N*-acetylation by treatment with acetic anhydride in CH₃CN at room temperature under argon. In this case, acetylation proceeded at both the amino group and the thiol group. By selective removal of *S*-acetyl protection by the action of K₂CO₃ in methanol at room temperature *N*-acetylcystamine was formed. Attachment of *N*-acetylcystamine to the C=C bond of dehydroalanine in complex **327** resulted in a mixture of (*S,S*)- and (*S,R*)-diastereoisomers of complex **384**. The products were chromatographed on a column with SiO₂ and three fractions were isolated in a ratio of 10.1/2.5/87.3 in order of decreasing their mobility on the silica gel. Polarimetric data demonstrated that fraction II had (*S*)- or *D*-absolute configuration of the α -carbon atom [(*S,S*)-diastereomer]), and fraction III – (*R*)- or *L*-absolute configuration of the α -carbon atom [(*S,R*)-diastereomer]. *N*-Acetyl group of the resulting amino acid was removed after decomposition of complex **384** and isolation of *S*-(2-*N*-acetylaminoethyl)-*L*-cysteine amino acid. Based on ¹H NMR, fraction I was an oxidized by-product.

Attachment of methanol to complex **327** proceeded fairly smoothly, with the preferred formation of (*S,S*)-diastereomer of complex **387** with diastereomeric

purity >90%. Attachment of benzylmagnesium chloride to the double C=C bond of dehydroalanine moiety of complex **327** in THF resulted in the formation of the three fractions in a ratio of 77.9/4.37/17.7 in order of decreasing their mobility on the silica gel. ^1H NMR spectra and polarimetric measurements showed that fraction I was an adduct of benzylmagnesium chloride to dehydroalanine (**386**) and had an (*S*)-absolute configuration of the α -carbon atom. After decomposition of fractions II and III and isolation of amino acids, their identity was determined by GC-MS spectroscopy. They turned out adducts of water to complex **327** (complex of (*S*)-serine), and the organic magnesium compound (complex of 2-amino-4-phenylbutyric acid).

Adducts of diethanolamine, diethylamine, ethanolamine, and methylamine to **327** complex (**388–391**) do not undergo epimerization reaction, but they are partially subjected to oxidation (10%) on silica gel. Accordingly, the main (*S,S*)-diastereomers of these complexes are isolated from the reaction mixture by crystallization from acetone or acetonitrile, or target amino acids are isolated by direct acid decomposition of the reaction mixture (without chromatography) as hydrochlorides.

From the results in Table 9.8, it follows that the transition from aminoacetophenone complexes (**377**, **378**) of addition products to the complexes based on aminobenzophenone (**379–392**) leads to an increase in stereoselectivity of the synthesis on an average from 50% to 90%. Apparently, this is due to the increasing steric nonbinding interaction between the bulky substituent at the C=N bond and *endo*-CH₂X group of amino acid fragment in the case of (*R*)-configuration at the transition from complexes based on (*S*)-BPA to complexes based on (*S*)-BPB (see Figure 9.15).

Decomposition of major diastereomeric complexes of nucleophilic addition products **377–392** in methanol under the influence of 2 N HCl and isolation of target amino acids were performed by standard methods (see Scheme 9.63). The structure and absolute configuration of synthesized β -substituted α -amino acids were determined by physicochemical methods of analysis.

To determine the enantiomeric purity of the synthesized nonprotein α -amino acids, particularly of amino acids synthesized for the first time and those with unknown polarimetric parameters, chiral HPLC and GLC analysis methods were used. For GLC analysis, the amino acids were analyzed as *iso*-propyl esters of *N*-trifluoroacetyl derivatives. A representative HPLC chromatogram is presented in

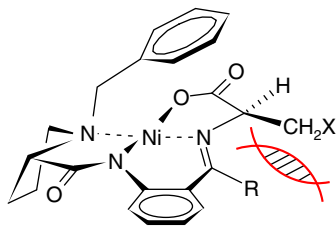
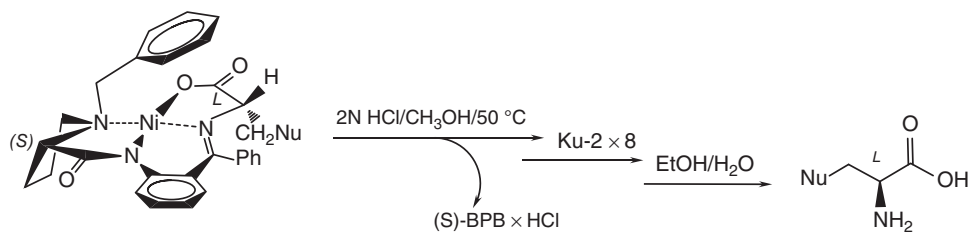
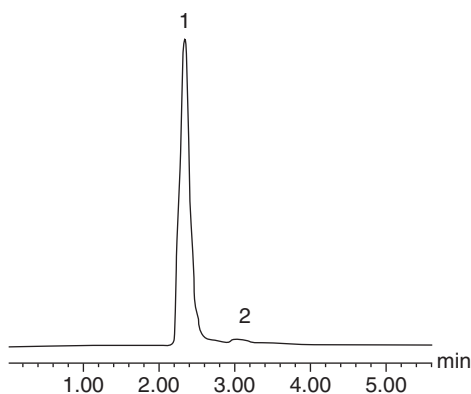


Figure 9.15 Steric nonbinding interaction in Ni^{II} complexes of Schiff bases of (*R*)- α -amino acids with chiral reagents (*S*)-BPA (*R*=CH₃) and (*S*)-BPB (*R*=C₆H₅).



Nu = C₆H₅S, (*R*) or *L*-**393**; C₆H₅CH₂S, (*R*) or *L*-**394**;
 (C₂H₅COO)₂CH, (*S*)-**395**; C₆H₅CH₂NH, (*S*)-**396**; Imidazol-1-yl, (*S*)-**397**;
 H₂NCH₂CH₂S (*R*) or *L*-**398**; (CH₃)₂N, (*S*)-**399**; C₆H₅CH₂-, (*S*)-**400**;
 CH₃O, (*S*)-**401**; (HOCH₂CH₂)₂N, (*S*)-**402**; (C₂H₅)₂N, (*S,S*)-**403**;
 CH₃NH, (*S*)-**404**; HOCH₂CH₂NH, (*S*)-**405**; HOCH₂CH₂S, (*R*)- or *L*-**406**

Scheme 9.63



No.	Isomer	Retention time	Area	% Area	Height
1	(<i>S</i>)	2.347	2,050,460	99.56	213,496
2	(<i>R</i>)	3.028	9512	0.44	648

Figure 9.16 Chiral chromatogram of (*S*)-hydroxyvaline.

Figure 9.16, which demonstrates high optical purity (*ee* >98%) of the obtained sample of (*S*)-hydroxyvaline.

Chiroptic characteristics $[\alpha]_D^{25}$ and chemical yields of synthesized nonprotein β -substituted α -amino acids are presented in Table 9.9.

The need to move to *D,L* nomenclature in case of substituted cysteines is due to the fact that according to Cahn–Ingold–Prelog's rule the natural *L*-cysteine, unlike other amino acids, should be assigned to (*R*)-rather than to (*S*)-configuration. To avoid confusion in presenting materials for this amino acid and its derivatives, *D,L*-nomenclature was used.

Table 9.9 Chiroptic data and chemical yields of β -substituted α -amino acids.

Name of amino acid	Chiroptic characteristics		Chemical yield (%) ^{b)}
	$[\alpha]_D^{25}$	ee (%) ^{a)}	
(<i>R</i>)- or L- <i>S</i> -Phenylcysteine (393)	+47.6° (<i>c</i> = 10; 6 N HCl)	>98	82
(<i>R</i>)- or L- <i>S</i> -Benzylcysteine (394)	−19.6° (<i>c</i> = 1.0; 6 N HCl)	>98	84
(<i>S</i>)-Glutamic acid (395)	+31.3° (<i>c</i> = 2; 6 N HCl)	79.8	80
(<i>S</i>)- β -(<i>N</i> -Benzylamino)alanine (396)	+29.67° (<i>c</i> = 1; 6 N HCl)	>98.0	61.0
(<i>S</i>)- β -Imidazolylalanine (397)	−2.2° (<i>c</i> = 10; 6 N HCl)	>98	78
(<i>S</i>)- β -(<i>N,N</i> -Dimethylamino)alanine $\times$ 2HCl $\times$ H ₂ O (399)	+16.6° (<i>c</i> = 1; 6 N HCl)	>98	84
(<i>R</i>)- or L- <i>S</i> -(2-Aminoethyl)cysteine (398)	−4.7° (<i>c</i> = 1; H ₂ O)	>96	65
(<i>S</i>)-Homophenylalanine (400)	+43° (<i>c</i> = 20; 1 N HCl)	~50	58
(<i>S</i>)- <i>O</i> -Methylserine (401)	+13° (<i>c</i> = 10; 6 N HCl)	>98	83
(<i>S</i>)- β -(<i>N,N</i> -Diethanolamine)alanine $\times$ HCl (402)	+28.9° (<i>c</i> = 1; 6 N HCl)	95.4	64
(<i>S</i>)- β -(<i>N,N</i> -Diethylamino)alanine $\times$ HCl (403)	+9.83° (<i>c</i> = 0.6; 1 N HCl)	97.5	74
(<i>S</i>)- β -(<i>N</i> -Methylamino)alanine $\times$ HCl (404)	+20.7° (<i>c</i> = 1; 6 N HCl)	86.2	78
(<i>S</i>)- β -(<i>N</i> -Ethanolamine)alanine $\times$ HCl (405)	+15.07° (<i>c</i> = 0.5; 6 N HCl)	85.6	75
(<i>R</i>)- or L- β -(<i>S</i> -Ethanolthio)alanine (406)	−12.39° (<i>c</i> = 0.5; 6 N HCl)	98	3
(<i>S</i>)- β -(<i>N</i> -Benzylamino)alanine $\times$ HCl (396)	+26.8° (<i>c</i> = 10; 6 N HCl)	>98	68

a) Enantiomeric excess (ee) was determined by chiral-HPLC and GLC analyses.

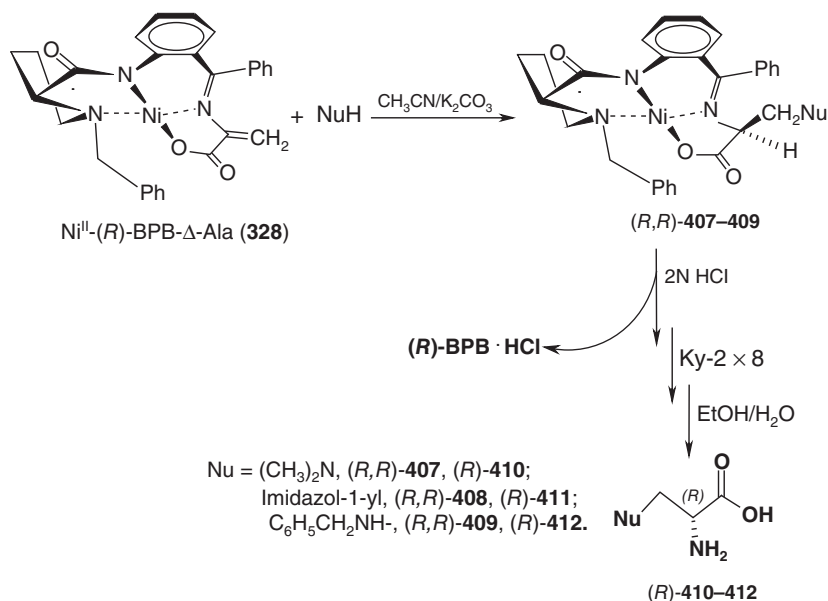
b) Chemical yield is calculated based on the amount of original complex **327**.

Since β -amino-substituted α -amino acids are subjected to partial racemization during isolation and lose optical purity, amino acids **399**, **402**–**405** were mostly isolated as hydrochlorides by crystallization from hydrochloric acid solutions.

Thus, by the addition of nucleophiles to the double C=C bond of dehydroalanine in a chiral Ni^{II} complex with its Schiff base and a chiral-inducing reagent (*S*)-BPB, a general method for the asymmetric synthesis of β -functionally substituted L- α -amino acids was developed. The method is versatile and allows obtaining optically active β -substituted-L- α -amino acids of different structures.

Similarly, a number of nucleophiles (imidazole, benzylamine, and dimethylamine) were added to dehydroalanine complex with a chiral reagent (*R*)-2-*N*-(*N'*-benzylpropyl)amino-benzophenone (**328**) [172, 190] (see Scheme 9.64).

As a result of nucleophilic addition in acetonitrile in the presence of K₂CO₃, mainly (*R,R*)-diastereoisomers of the complexes containing (*R*)- β -(*N,N*-dimethylamino)-alanine (**407**) [190], (*R*)- β -imidazolylalanine (**408**) [172], and (*R*)- β -(*N*-benzylamino) alanine (**409**) [190] were formed.



Scheme 9.64

Table 9.10 Results of nucleophilic addition to chiral complex **328** in $\text{CH}_3\text{CN/K}_2\text{SO}_3$.

Nucleophile	(<i>R,R</i>)/(<i>R,S</i>) of product (%) ^a	Amino acid	$[\alpha]_{\text{D}}^{25}$	Chemical yield (%) ^b
$(\text{CH}_3)_2\text{NH}$	94/6 (407)	(<i>R</i>)- β -(<i>N,N'</i> -Dimethylamino) alanine (410)	-20.6° (<i>c</i> = 1; 6 N HCl)	86
Imidazole	95/5 (408)	(<i>R</i>)- β -Imidazolyl alanine(411)	$+2.21^\circ$ (<i>c</i> = 10; 6 N HCl)	75
$\text{C}_6\text{H}_5\text{CH}_2\text{NH}_2$	94.5/5.5 (409)	(<i>R</i>)- β -(<i>N</i> -Benzylamino)alanine (412)	-29.5° (<i>c</i> = 1; 6 N HCl)	66

a) The ratio of (*R,R*)/(*R,S*) on the basis of ^1H NMR analysis.

b) Chemical yield at the stages of nucleophilic addition and elimination.

The ratio of (*R,S*)- and (*R,R*)-diastereoisomers of complexes **407–409** was determined by ^1H NMR. The results are shown in Table 9.10.

To determine the absolute configuration of diastereomers after their separation on SiO_2 , their ORD curves were recorded and compared with the ORD curves of complexes of the same amino acids of (*S*)-configuration with chiral reagent (*S*)-BPB (**385**, **382**) (see Figure 9.17).

Based on the obtained data, the diastereomers with lower R_f value on silica gel (main fractions **407–409**) have (*R,R*)-absolute configuration as their ORD curves are mirror images of respective ORD curves of (*S,S*)-diastereomeric complexes.

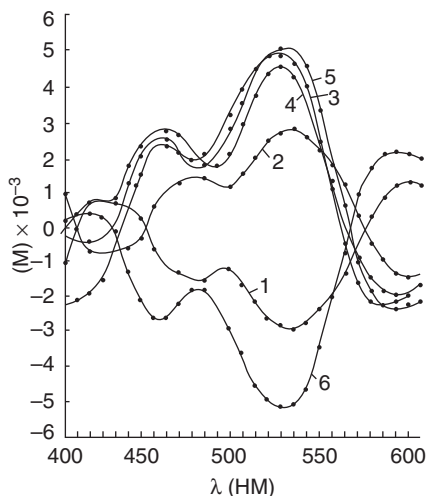


Figure 9.17 ORD curves of complex in CH_3OH , 25°C : 1 – (*S,S*)-**385**; 2 – (*R,R*)-**407**; 3 – (*R,R*)-**408**; 4 – (*R,R*)-**409**; 5 – (*R,R*)-**322**; 6 – (*S,S*)-**382**.

In complexes based on (*R*)-BPB chiral reagent, as shown in Scheme 9.64, the phenyl ring of the *N*-benzylproline fragment shields the amino acid fragment from the *si* side of the Schiff base plane, which hinders proton from joining the prochiral carbanion exactly from this side of the plane, resulting in thermodynamic destabilization of diastereoisomer of (*R,S*)-absolute configuration. Moreover, as in the case of complexes based on (*R*)-BPB chiral reagent, the stereoselectivity in these complexes in the initial stage of the reaction of nucleophiles addition is controlled by kinetic factors, and then, as the thermodynamic equilibrium between diastereoisomers is reached, the reaction is controlled by thermodynamic factors.

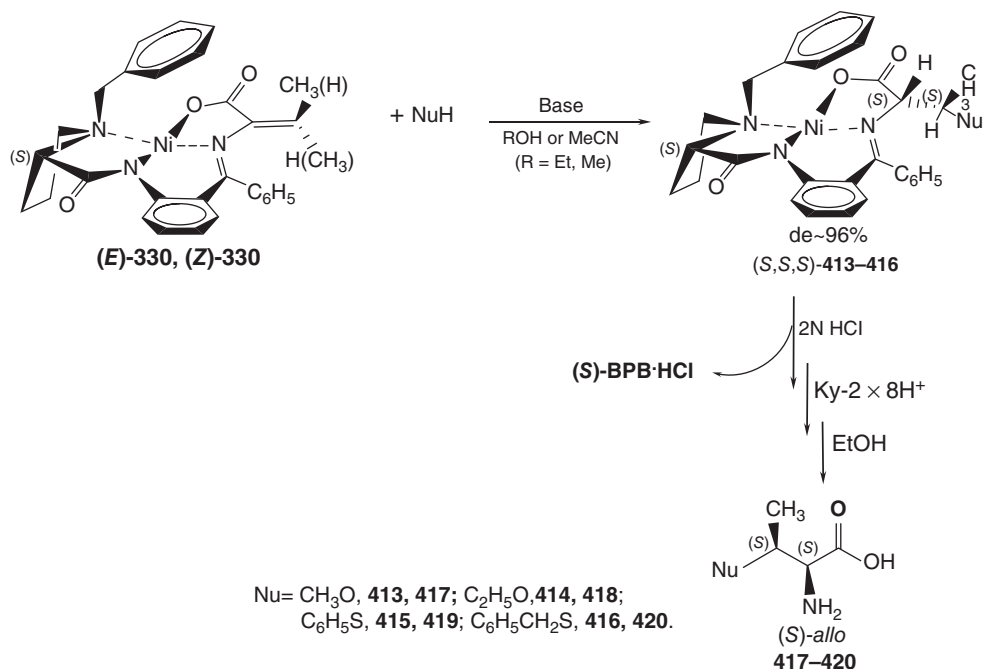
After acid decomposition of a mixture of diastereomeric complexes **407–409**, the optically active β -substituted α -amino acids of (*R*)-absolute configuration – (*R*)- β -(*N,N'*-dimethylamino)-alanine (**410**), (*R*)- β -imidazolylalanine (**411**), and (*R*)- β -(*N*-benzylamino)alanine (**412**) – were isolated according to traditional methods. Chemical yields and specific rotation data of the obtained amino acids are presented in Table 9.10.

The chiral reagent (*R*)-BPB, as well as its optical antipode (*S*)-BPB, in the stage of decomposition of complexes and isolation of amino acids is recovered in quantitative chemical yield (94–97%) and with full retention of its original chirality (optical purity).

9.2.4.2 Asymmetric Nucleophilic Addition to Chiral Complexes of Dehydroaminobutyric Acid

Chiral complexes of Ni^{II} ion with Schiff base of (*Z*)- and (*E*)-dehydroaminobutyric acid with auxiliary reagent BPB, having active electrophilic $\text{C}=\text{C}$ double bond and high enantioselective effects, are good starting synthons for the asymmetric

synthesis of optically active β -substituted derivatives of α -aminobutyric acid by addition of nucleophiles. Scheme 9.65 illustrates the addition reaction of alcoholate- and thiolate-ions to the double C=C bond of dehydroaminobutyric acid in Ni^{II} complex of its Schiff base with (*S*)-BPB (**330**). The reaction proceeds in the medium of corresponding alcohols in the case of the alcoholate-ions, and in CH_3CN – in the case of addition of thiolate ions [173, 174].



Scheme 9.65

The progress of coupling reaction is conveniently monitored by TLC on SiO_2 using chloroform-acetone (2/1) as an eluent. The obtained diastereomerically pure complexes were decomposed by hydrochloric acid and target enantiomerically pure amino acids were isolated by ion-exchange method. The structures of synthesized enantiomerically pure complexes **413–416** and isolated β -substituted derivatives of α -aminobutyric acid **417–420** were determined by physicochemical methods of analysis. The ratio of diastereoisomers after establishment of thermodynamic equilibrium was determined by ^1H NMR, as diastereomeric complexes containing amino acids of (*S*)- and (*R*)-absolute configuration of α -carbon atom differ by the position of α -proton signals of the amino acid fragment.

The results are shown in Table 9.11. Enantiomeric purity of isolated amino acids was determined by chiral HPLC and GLC analyses.

The absolute configuration of α -carbon atom of the amino acid fragment was determined by analysis of ORD curves of their complexes. The negative

Table 9.11 Results of nucleophilic addition of dehydroaminobutyric acid to the double C=C bond in chiral complexes (Z)-**330** and (E)-**330**.

Starting complex	NuH	The excess (de) of the main diastereomer	Amino acid		
			Amino acid, configuration	Chemical yield (%) ^{a)}	ee (%) ^{b)}
(E)- 330	CH ₃ OH	>98, (S,S,S)- 413	O-MeThr (417) 2L,3L or (2S,3S)	78	>99
(Z)- 330	CH ₃ OH	~96, (S,S,S)- 413	O-MeThr (417) 2L,3L or (2S,3S)	80	>99
(E)- 330	C ₂ H ₅ OH	>94, (S,S,S)- 414	O-EtThr (418) 2L,3L or (2S,3S)	79	>99
(Z)- 330	C ₂ H ₅ OH	>94, (S,S,S)- 414	O-EtThr (418) 2L,3L or (2S,3S)	76	>99
(E)- 330	C ₆ H ₅ SH	>92, (S,R,S)- 415	S-PhCys(419) 2L,3L or (2S,3R)	65	>98
(E)- 330	C ₆ H ₅ CH ₂ SH	>92, (S,R,S)- 416	S-BnCys (420) 2L,3L or (2S,3R)	67	>98

a) Chemical yield is calculated based on the amount of original complex **330**.

b) ee (enantiomeric purity) of synthesized amino acids based on chiral HPLC and GLC analyses.

Cotton effects of ORD curves of major diastereomeric complexes **413–416** at 450–500 nm indicate L-absolute configuration of α -carbon atom of their amino acid fragments. The configuration of β -carbon atom was determined by ¹H NMR chemical shift value of β -methyl group of an amino acid moiety of complexes. By analogy with threonine complex, in ¹H NMR spectra of **413–416** complexes, the presence of proton signals of the methyl group in strong fields is an argument in favor of conjoint *allo*-arrangement of α - and β -asymmetric carbon atoms of the amino acid fragment. The characteristic difference between ¹H NMR spectra of complexes containing amino acids of *threo* and *allo* L-configuration (threonine, O-methylthreonine, O-ethylthreonine, S-benzylcysteine, S-phenylcysteine) is observed in chemical shifts of methyl proton signals. These signals appear in the range of 1.05–1.0 ppm for complexes of L-*allo*-amino acids and for complexes of L-*threo*-amino acids they are in the range of 1.8–1.9 ppm.

The phenomenon can be explained by analysis of complex structures. As previously shown [138, 166], the isopropyl group of the (S)-valine fragment in similarly constructed complexes is rigidly fixed in a space with the *pro-S* methyl group located under the Ni^{II} ion.

This leads to magnetic deshielding of the group protons due to magnetic anisotropy of Ni atom and to a simultaneous shift of their signal toward the low-field region (to 1.9 ppm). The location of the methyl group under the metal ion, as shown in Figure 9.18, is possible only in the case of threonine (*threo* form), and it is impossible for steric reasons for allothreonine and other synthesized *allo*-isomers of aminobutyric acid derivatives.

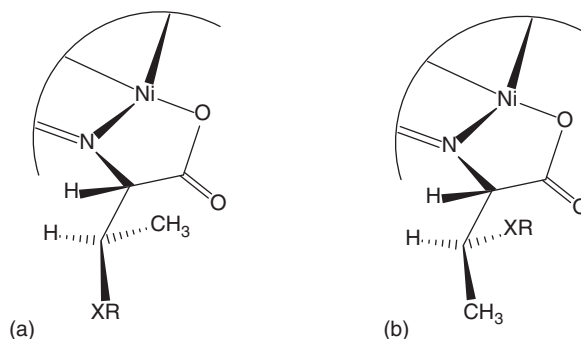


Figure 9.18 The spatial arrangement of the side chain of the amino acid fragment of complexes: (a) *L*-threo-configuration; (b) *L*-allo-configuration.

From this it follows that the main diastereomeric complexes obtained from nucleophilic addition of alcoholate- and thiolate-ions to the $C=C$ bond of chiral complexes of dehydroamino-butyric acid [(*Z*)-**330** and (*E*)-**330**] have 2*L*, 3*L*-absolute configuration of the amino acid moiety.

Based on Table 9.11 data, regardless of (*E*)- or (*Z*)-configuration of the original dehydro-aminobutyric acid complex, the main end product of addition reaction is amino acid of *L*-allo-configuration.

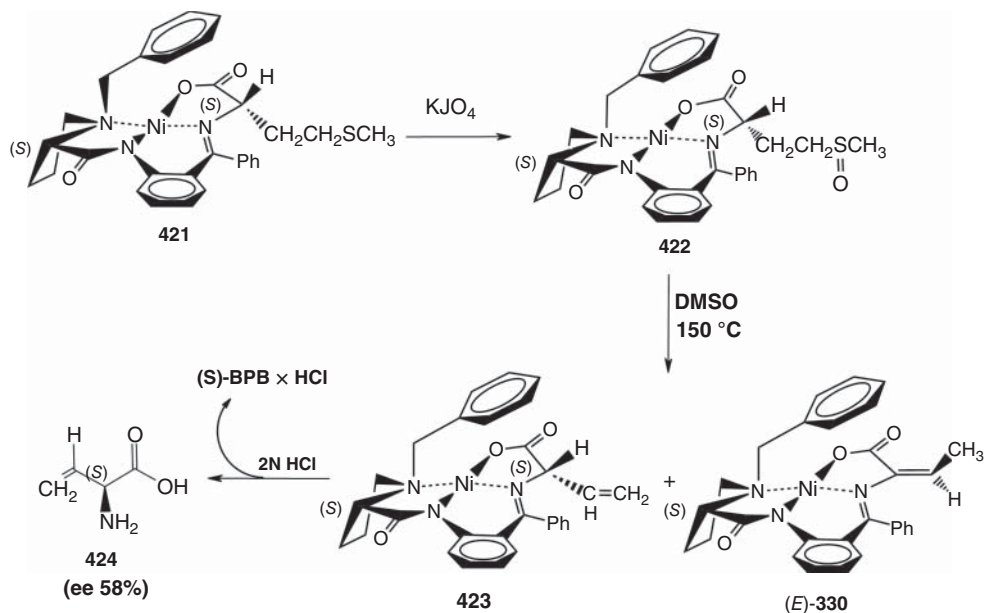
In reaction products, trace amounts of complex impurities containing *D*-amino acids or *L*-amino acids of *threo*-configuration (up to 5%) were detected. Only with addition of methanol, solely one diastereoisomer of *L*-allo-configuration is formed (based on TLC and ^1H NMR).

Nucleophile attachment is accompanied by side reactions, mainly formation of threonines (up to 5%), presumably because of attachment of the water available in the reaction mixture; and in case of thiol attachment, formation of important nonprotein amino acid complex of *L*-vinylglycine up to 18% is observed.

On the other hand, attempts to convert dehydroaminobutyric acid complexes [(*Z*)-**330** or (*E*)-**330**] to a vinylglycine complex by treating with solid sodium or sodium phenolate in acetonitrile have failed. Such a vinylglycine complex was synthesized according to Scheme 9.66 on the basis of racemic methionine [174, 191]. For this purpose, according to the standard procedure of complexation, at the first step chiral Ni^{II} complex of Schiff base of (*S*)-methionine with auxiliary reagent (*S*)-BPB is produced (**421**).

Methionine complex is oxidized with periodic acid to the corresponding sulfoxide complex **422** using a procedure that is similar to the one described in [192, 193]. Further, complex **422** by heat treatment (200°C) in dimethylsulfoxide (DMSO) is converted to vinylglycine complex (**423**), which is obtained in a mixture with (*E*)-dehydroaminobutyric acid complex [(*E*)-**330**]. After purification of the complex on SiO_2 and decomposition with hydrochloric acid, the target amino acid – (*S*)-vinylglycine (**424**) – is released.

Enantiomeric GLC analysis of (*S*)-vinylglycine shows that this amino acid during its isolation partially racemizes (58% ee). Spectral parameters of complex **423**



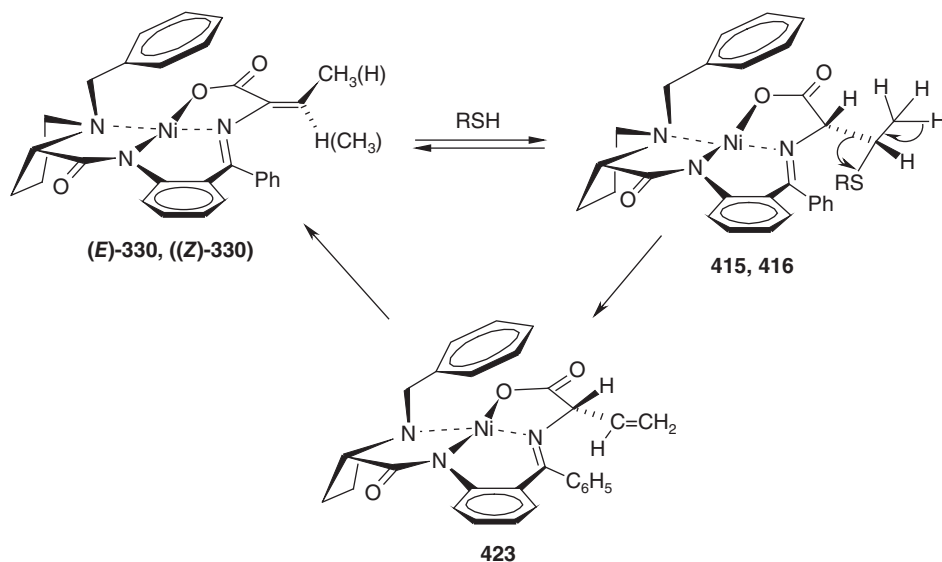
Scheme 9.66

and the by-product obtained in the process of attachment of benzylmercaptan to the dehydroaminobutyric acid complex containing a fragment of (S) -vinylglycine turned out identical.

Thus, attachment of strong nucleophiles to the double $\text{C}=\text{C}$ bond of chiral complexes of dehydroaminobutyric acid **330** leads to the formation of diastereomeric complexes of β -substituted derivatives of α -aminobutyric acid of *L*-*allo*-configuration. One might imagine that under the experimental conditions between the isomers equilibrium is established at a rate exceeding the rate of the nucleophiles' attachment to the activated double bond of dehydroaminobutyric acid complexes. Consequently, the thermodynamic effects associated with the difference in energy of diastereomeric complexes containing (S) - and (R) -, as well as *threo*- and *allo*-isomers of β -substituted aminobutyric acid, are responsible for the observed high diastereoselective effects. Confirmation of this assumption is the identical results of attachment of nucleophiles to the $\text{C}=\text{C}$ bond of (E) - and (Z) -dehydroaminobutyric acid. It is obvious that an alternative mechanism, according to which the kinetic control is responsible for the steric result of the reaction, cannot explain why the nucleophilic attack on the two different in their structure isomers leads to the same result. Figure 9.18 shows that orientation of the side chain of the amino acid substituent in the space provided by rigid steric nonbinding interaction with the phenyl substituent at the $\text{C}=\text{N}$ bond is such that the alkyloxy or alkylthioxy groups are located directly under the metal ion in the case of *allo*-isomer, whereas for a *threo*-isomer the methyl group is located under the metal ion. The thermodynamic preference of the diastereoisomer containing *L*-allothreonine derivative is a possible consequence

of a larger volume of the methyl group as compared to the methoxy, ethoxy, phenylthio, and benzylthio groups. This is reflected in the relative conformational energies of these substituents in a series of cyclohexane derivatives, and hence less steric nonbinding interaction of metal ion and *endo*-hydrogens of the proline moiety with a side-chain substituent of the amino acid moiety in the case of *allo*-isomer. However, we cannot exclude the possibility of some interaction between the metal ion and the oxygen or sulfur atom, providing additional stabilization to the *allo*-isomer. Because of conformation of the side chain of the serine moiety in the crystal of Ni^{II} complex of Schiff base of (*S*)-serine with (*S*)-BPB [129], the oxygen atom of the hydroxyl group of serine is located under the metal ion; and though the distance between them is close to the sum of the radii of van der Waals atoms, it is possible that there is a weak interaction (not exceeding $1.2 \text{ kcal mol}^{-1}$) that provides the observed side-chain conformation. As the size of the attached nucleophile in a series of methoxy, ethoxy, phenylthio, and benzylthio substituents increases, the interaction of metal-heteroatom of the side substituent of amino acid cannot fully compensate for the steric effects. In the process of ethanol, thiophenol, and benzylmercaptan attachment to dehydroaminobutyric acid, formation of complexes of significant amount of isomers of *threo*-series is observed.

The appearance of relatively large amounts (up to 10%) of the complex, containing vinyl-glycine as a by-product when thiophenol and benzylmercaptan are attached to the dehydroaminobutyric acid complexes (**330**), cannot be explained in the absence of a nucleophile under the reaction conditions. The reason for its formation may be elimination of the thiol from the *S*-substituted- β -methylcysteine complex (**415**, **416**) by Scheme 9.67.



Scheme 9.67

The driving force behind this elimination can be the significant steric strain, observed in both original complexes (*E*)-**330** and (*Z*)-**330**, and the addition products of thiols to dehydroamino-butyric acid complexes **415**, **416**.

The developed method allows the synthesis of important and difficult to access derivatives of α -aminobutyric acid of *L-allo* absolute configuration based on the simplest α -amino acid glycine. At the same time, the initial chiral auxiliary reagents are regenerated in quantitative chemical yields and retention of the original chirality.

We can assume that the use of similarly structured complexes of dehydroaminobutyric acid based on chiral auxiliary (*R*)-BPB allows conducting the asymmetric synthesis of β -substituted derivatives of α -aminobutyric acid of *D-allo*-configuration.

9.2.5

Asymmetric Synthesis of All Possible Stereoisomers of 4-Aminoglutamic Acid

This section reports on the asymmetric synthesis of all possible stereoisomers of 4-amino-glutamic acid – an important component of many physiologically active peptides and other pharmaceuticals.

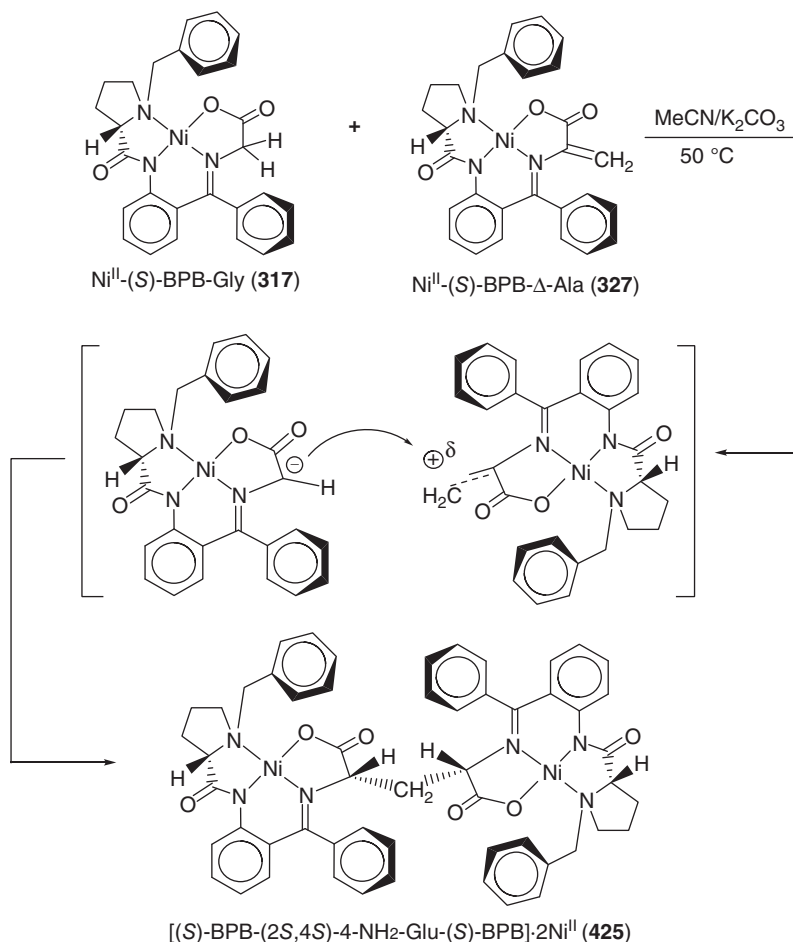
As indicated above, the C=C double bond of dehydroalanine in square-planar Ni^{II} ion complexes of its Schiff bases with chiral carbonyl compounds of (*S*)- and (*R*)-BPB (**327**, **328**) has sufficient electrophilicity for attachment of nucleophiles under base catalysis with the formation of β -substituted α -amino acids (see Section 9.2.4). In the similarly constructed complexes of α -amino acids (**317**, **321**), the amino acid moieties have high CH-acidity, which enabled asymmetric synthesis of α -substituted α -amino acids by their C-alkylation with electrophilic halides (see Section 9.2.3). It has been shown that the chiral reagent (*S*)-BPB induces (*S*)-absolute configuration at the newly formed asymmetric carbon atom, and the chiral agent (*R*)-BPB – (*R*)-absolute configuration.

Taking into account high enantioselective effects as well as high electrophilicity of dehydroalanine and nucleophilicity of glycine moieties in Ni^{II} complexes of their Schiff bases with the chiral auxiliaries (*S*)- and (*R*)-BPB, asymmetric condensation of glycine complexes (**317**, **321**) with dehydroalanine complexes (**327**, **328**) in all possible options was carried out [194, 195].

Condensation of complexes occurs in high yields in CH_3CN in the presence of K_2CO_3 at 25–50 °C. Condensation reaction of Ni^{II} -(*S*)-BPB-Gly (**317**) and Ni^{II} -(*S*)-BPB- Δ -Ala (**327**) complexes is presented in Scheme 9.68.

The progress of the asymmetric condensation reaction can be conveniently monitored by TLC on SiO_2 in the CH_3COCH_3 – CHCl_3 (1:3) or CHCl_3 – $\text{CH}_3\text{COOC}_2\text{H}_5$ (1:3) solvent system following the disappearance of traces of the starting dehydroalanine complex **327** since glycine complex **317** is taken in excess. The condensation results in dimeric complexes containing 4-aminoglutamic acid fragment (4- NH_2Glu) as a binding link.

The reaction proceeds under base catalysis via intermediate formation of planar carbanion of glycine moiety, and its condensation with dehydroalanine



Scheme 9.68

complex occurs preferably from the *si* side of the Schiff base plane to form a (*S,S,S,S*)-diastereoisomer of the dimeric complex comprising 4-aminoglutaric acid of (*2S,4S*)-absolute configuration (**425**).

Since during chemical conversion processes of amino acid fragments of these complexes the configuration of the asymmetric carbon atom of proline moiety does not change (see Section 9.2), formation of three diastereoisomers of the dimeric complex could be expected. The total content of other diastereoisomers of the dimeric complex in the reaction mixture does not exceed 3–5%, which indicates high stereoselectivity of synthesis of the dimeric complex of (*S,S,S,S*)-absolute configuration (*de* > 90%). After completion of the condensation reaction and removal of the base, the main diastereoisomer is directly crystallized from the mixture with high diastereomeric purity (*de* > 90%).

Similarly, condensation of $\text{Ni}^{\text{II}}\text{-(S)-BPB-Gly}$ (**317**) and $\text{Ni}^{\text{II}}\text{-(R)-BPB-}\Delta\text{-Ala}$ (**328**), $\text{Ni}^{\text{II}}\text{-(R)-BPB-Gly}$ (**321**), and $\text{Ni}^{\text{II}}\text{-(S)-BPB-}\Delta\text{-Ala}$ (**327**), $\text{Ni}^{\text{II}}\text{-(R)-BPB-Gly}$ (**321**), and $\text{Ni}^{\text{II}}\text{-(R)-BPB-}\Delta\text{-Ala}$ (**328**) complexes was conducted.

Condensation of complexes **321** and **328** occurs preferably on the *re* side of the Schiff base plane, which leads to the formation of (*R,R,R,R*)-diastereoisomer of the dimeric complex of 4-aminoglutaric acid (**426**). In this case, the chiral centers of (*R*)-proline moieties of two complexes induce (*R*)-absolute configuration in the newly formed asymmetric centers of 4-aminoglutaric acid moiety of the dimeric complex in positions 2 and 4.

During condensation of glycine and dehydroalanine complexes based on chiral reagents with different absolute configurations (**317** and **328**, **321** and **327**), chiral centers of the opposite absolute configuration in positions 2 and 4 of 4-aminoglutaric acid fragment (*S,S,R,R*)-**427** are induced in the formed dimeric complex.

Structures of diastereoisomers of dimeric complex of 4-aminoglutaric acid (**425**–**427**) were investigated and determined by spectral methods of analysis (see Figure 9.19).

Diastereomeric excess of individual stereoisomers of the dimeric 4- NH_2Glu complex was determined by ^1H NMR analysis of their mixtures (before crystallization). The results are presented in Table 9.12.

In ^1H NMR spectra, the equivalency of chemical shifts of methylene proton signals of the amino acid fragment of dimeric complexes **425** and **426** suggests that the C_2 and C_4 carbon atoms of 4-aminoglutaric acid in these dimeric complexes have the same configuration – either (*2S,4S*) or (*2R,4R*). Unequivocal establishment of the absolute configuration of 4-aminoglutaric acid in synthesized dimeric complexes **425**–**427** became possible with the help of polarimetric measurements.

Comparison of CD spectrum of dimeric complex **425** with the CD spectrum of previously obtained similarly constructed dimeric complex of (*2S,3S*)-diaminosuccinic acid, the absolute configuration of which was established by X-ray analysis [124], indicates the (*2S,4S*)-absolute configuration of the amino acid fragment of this diastereoisomer – (*S,S,S,S*) (see Figure 9.20), which is

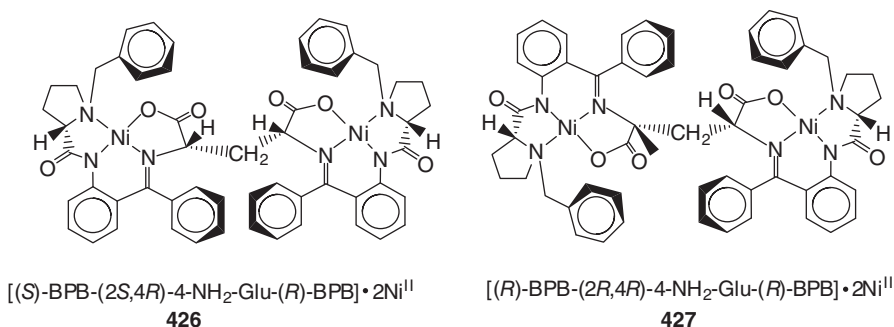


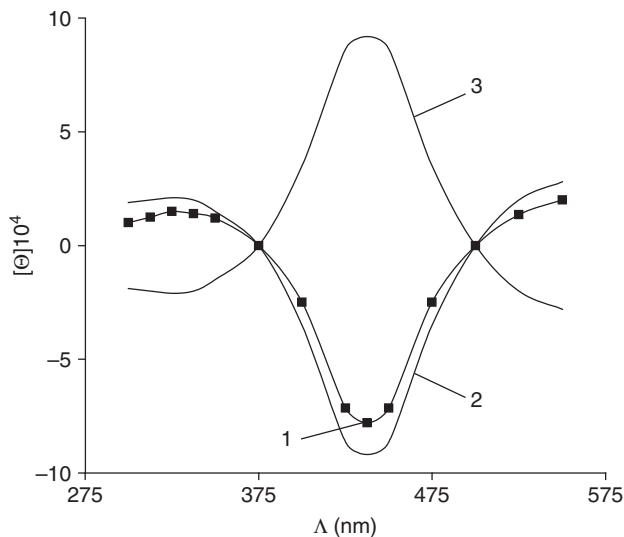
Figure 9.19 Structure of dimeric complexes **426** and **427**.

Table 9.12 The results of asymmetric condensation of glycine and dehydroalanine complexes in CH_3CN in the presence of K_2CO_3 at 25°C .

Starting complex		Time (h)	Dimeric complex			
Nucleophile	Electrophile		Main diastereo-isomer	ee (%) ^{a)}	$[\alpha]_D^{20}$ (CH_3OH)	Chemical yield (%) ^{b)}
$\text{Ni}^{\text{II}}-(S)\text{-BPB-Gly}$ (317)	$\text{Ni}^{\text{II}}-(S)\text{-BPB-}\Delta\text{-Ala}$ (327)	44–48	(<i>S,S,S,S</i>)	≥ 96	117.6°	90
$\text{Ni}^{\text{II}}-(S)\text{-BPB-Gly}$ (317)	$\text{Ni}^{\text{II}}-(R)\text{-BPB-}\Delta\text{-Ala}$ (328)	12–14	(<i>S,S,R,R</i>)	≥ 94	0°	95
$\text{Ni}^{\text{II}}-(R)\text{-BPB-Gly}$ (321)	$\text{Ni}^{\text{II}}-(S)\text{-BPB-}\Delta\text{-Ala}$ (327)	12–14	(<i>R,R,S,S</i>)	≥ 94	0°	94
$\text{Ni}^{\text{II}}-(R)\text{-BPB-Gly}$ (321)	$\text{Ni}^{\text{II}}-(R)\text{-BPB-}\Delta\text{-Ala}$ (328)	44–48	(<i>R,R,R,R</i>)	≥ 96	-119.3°	93

a) The diastereomeric excess (de) based on ^1H NMR.

b) Chemical yield of crystals of dimeric complex.

**Figure 9.20** The spectra of circular dichroism (CD) of complexes in CH_3OH at 25°C : 1 – Ni^{II} complex of Schiff base of (*S*)-BPB, and (2*S*,3*S*)-diaminosuccinic acid; 2 – complex 425; 3 – complex 427.

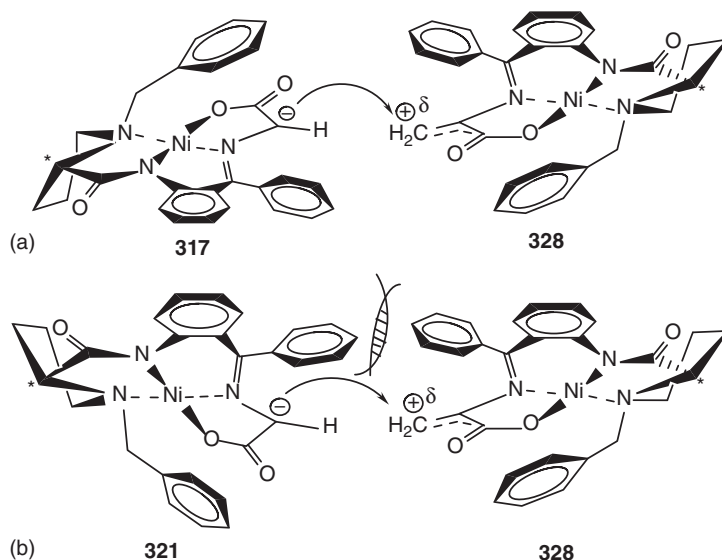


Figure 9.21 Steric hindrances during condensation of complexes **321** and **328** (b) that is weakly expressed in the case of condensing complexes **317** and **328** (a).

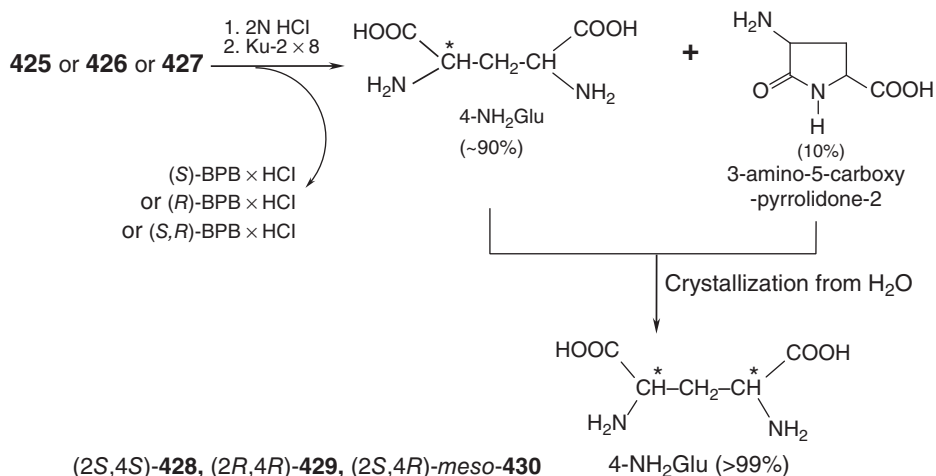
confirmed by similar negative Cotton effects in the CD spectra of these complexes in the range of 375–500 nm wavelength.

Mirror image of CD spectrum of complex **427** relative to the CD spectrum of complex **425**, as well as their identical R_f values on SiO_2 , indicate the (*R,R,R*)-absolute configuration of complex **427** with a content of (2*R*,4*R*)-4- NH_2 Glu fragment.

A zero value of specific rotation of dimeric complex **426** indicates its (*S,S,R,R*) absolute configuration with the content of (2*S*,4*R*)-*meso*-4- NH_2 Glu moieties. In this case, in the process of condensation of complexes, the chiral centers of (*S*)-proline and (*R*)-proline moieties of starting complexes induce (*S*)- and (*R*)-absolute configuration at C_2 and C_4 atoms of 4- NH_2 Glu fragment of dimeric complex **427**.

Studies have shown that during condensation of complexes containing chiral reagents of opposite configuration (**317** and **328** or **321** and **327**) the rate of condensation is about four to five times greater than the rates of condensation of the complexes containing chiral reagents of the same configuration (**317** and **327** or **321** and **328**). This is explained by spatial factors caused by the relatively high steric nonbonding interactions between the bulky phenyl substituents at the $\text{C}=\text{N}$ bond of two complexes in the case of their similar configuration (see Figure 9.21).

Individually pure stereoisomers of 4-aminoglutamic acid were isolated from diastereoisomeric complexes **425**–**427** by standard methods (see Scheme 9.69).



Scheme 9.69

Based on TLC and ^1H NMR spectra of the isolated reaction products along with 4-amino-glutamic acid, there is about 10% of cyclization product, which is 3-amino-5-carboxypyrrolidone-2; and this can be easily removed by crystallization of the mixture from aqueous solution.

The structure and absolute configuration of isolated 4-aminoglutaric acid stereoisomers (**428**–**430**) were determined by methods of physicochemical analysis. Results are presented in Table 9.13.

Equal in absolute value and opposite in sign, the results of the specific rotation of amino acids **428** and **429** indicate their (2S,4S)- and (2R,4R)-absolute configuration, respectively, and the zero value of the specific rotation of amino acid **430** indicates its (2S,4R)-*meso* absolute configuration.

Thus, by condensation of electrophilic dehydroalanine and nucleophilic glycine complexes of Ni^{II} ion with Schiff base of chiral auxiliary reagents (S)- and (R)-BPB, it became feasible to carry out the asymmetric synthesis of all possible stereoisomers of important nonprotein amino acid 4-aminoglutaric acid. Undoubtedly, this approach can be used for the asymmetric synthesis of stereoisomers of other derivatives of 4-aminoglutaric acid.

Table 9.13 The specific rotation and chemical yields of the synthesized stereoisomers of 4-aminoglutaric acid.

No.	Name of amino acid	Specific rotation, $[\alpha]_{\text{D}}^{20}$	Chemical yield (%)
1	(2S,4S)-4-NH ₂ Glu (428)	+4.25° ($c = 0.1$; 2 N HCl)	71
2	(2S,4R)- <i>meso</i> -4-NH ₂ Glu (430)	0° ($c = 0.1$; 2 N HCl)	80
3	(2R,4R)-4-NH ₂ Glu (429)	−4.60° ($c = 0.1$; 2 N HCl)	75

9.2.6

Asymmetric Synthesis of Heterocyclic-Substituted α -Amino Acids

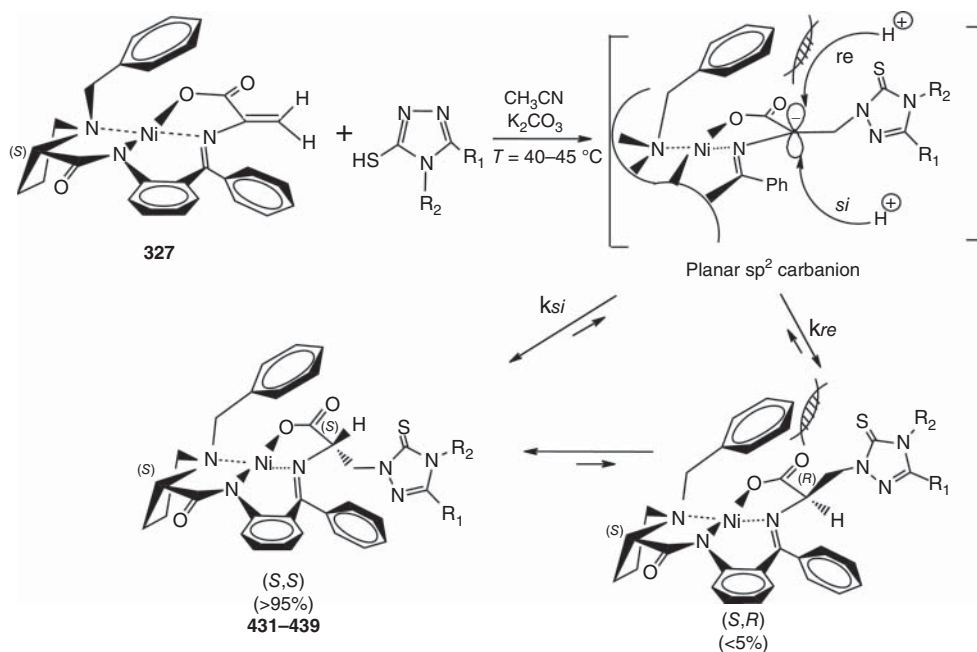
Analysis of literature data on screening biomedical properties of nonprotein amino acids and peptides indicates that optically active amino acids and peptides containing heterocyclic substituents in the side-chain radical can potentially have the greatest activity (antiviral, anticancer, radioprotective, etc.) [196, 197]. Unfortunately, the number of known heterocyclic amino acids is very small. The literature describes a limited number of heterocyclic-substituted α -amino acids, but synthesized in the form of optically inactive racemates. However, like other nonprotein α -amino acids, heterocyclic-substituted α -amino acids and peptides on their basis are also physiologically and pharmacologically active only in the form of one optically active enantiomer.

This section is dedicated to the asymmetric synthesis of optically active β -heterocyclic-substituted α -amino acids containing various substituted triazoles and thiodiazoles in the side-chain radical. Methods are based on the use of chiral Ni^{II} complexes of Schiff bases of dehydroamino acids (dehydroalanine and dehydroaminobutyric acid) as starting electrophilic synthons, the synthesis of which is described above (see Section 9.1)

9.2.6.1 Addition of Heterocyclic Nucleophiles to Dehydroalanine Chiral Complexes

Asymmetric addition of heterocyclic thiols to the double $\text{C}=\text{C}$ bond of dehydroalanine complex $\text{Ni}^{\text{II}}-(S)\text{-BPB-}\Delta\text{-Ala}$ (**327**) easily occurs in CH_3CN medium in the presence of K_2CO_3 at room temperature (see Scheme 9.70) [198–205]. 5-Mercapto-1,2,4-triazoles containing different aliphatic and aromatic substituents in positions 3 and 4 of the triazole ring were used as heterocyclic thiols. Unlike aliphatic thiols, addition of almost all heterocyclic thiols to dehydroalanine complex takes place under atmospheric oxygen, without formation of any side oxidized complexes, and the rate of addition reaction increases approximately threefold with heating to 45–50 °C without formation of any by-products.

The progress of the addition reaction in this case is also conveniently monitored by TLC on SiO_2 [$\text{CHCl}_3\text{--CH}_3\text{COCH}_3$ (3 : 1)] following the disappearance of the traces of starting complex **327**. Synthesized diastereomeric complexes of β -heterocyclic-substituted alanines differ from each other by their R_f values on SiO_2 , which was used to determine the ratios of diastereomers by spectrophotometry in the range of 320- to 340-nm wavelengths after their separation by preparative chromatography on SiO_2 . The ratio of diastereomers was also determined by ^1H NMR spectroscopy (by the ratio of signal integrals of $\alpha\text{-H}$ and CH_2 protons of benzyl group of *N*-benzylproline moiety diastereoisomeric complexes at 3.8–4.4 and 2.5–2.7 ppm, respectively) and by chiral HPLC analysis of the amino acids mixture derived from an acid hydrolysate of a mixture of diastereomeric complexes isolated by ion exchange method (before chromatography of diastereomeric complexes). Equilibrium ratios and chemical yields in the stage of



Where $R_1 = \text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$, $R_2 = \text{C}_6\text{H}_5$ (**431**);
 $R_1 = \text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$, $R_2 = \text{CH}_2\text{-CH=CH}_2$ (**432**);
 $R_1 = \text{C}_3\text{H}_7$, $R_2 = \text{C}_6\text{H}_5$ (**433**);
 $R_1 = \text{C}_3\text{H}_7$, $R_2 = \text{CH}_2\text{-CH=CH}_2$ (**434**);
 $R_1 = \text{CH}_2\text{CH}_2\text{CH(OH)CH}_2\text{OCH}_2\text{CH}_2\text{CH(CH}_3)_2$, $R_2 = \text{C}_6\text{H}_5$ (**435**);
 $R_1 = \text{CH}_2\text{CH}_2\text{CH(OH)CH}_2\text{OCH}_2\text{CH}_2\text{CH(CH}_3)_2$, $R_2 = \text{CH}_2\text{-CH=CH}_2$ (**436**);
 $R_1 = o\text{-OCH}_3\text{-C}_6\text{H}_4$, $R_2 = \text{CH}_2\text{-CH=CH}_2$ (**437**);
 $R_1 = o\text{-ClC}_6\text{H}_4$, $R_2 = \text{CH}_2\text{-CH=CH}_2$ (**438**);
 $R_1 = \text{CH}_2\text{CH}_2\text{CH(OH)C}_5\text{H}_{11}$, $R_2 = \text{CH}_2\text{-CH=CH}_2$ (**439**);

Scheme 9.70

asymmetric addition of heterocyclic nucleophiles to complex **327** are shown in Table 9.14.

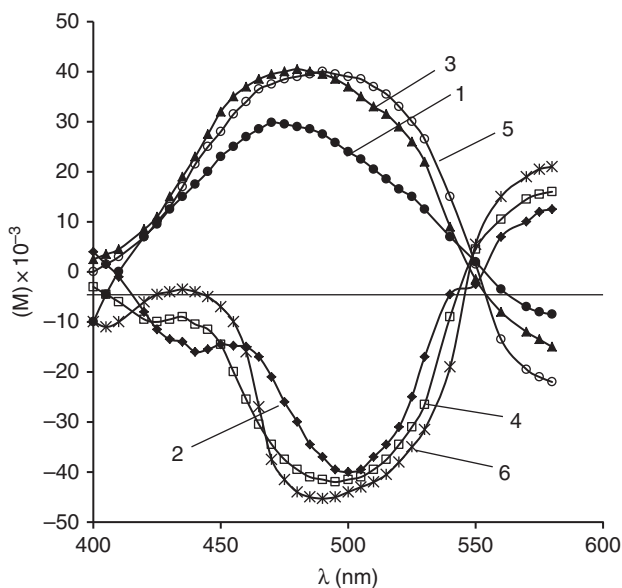
The absolute configurations of major diastereomeric complexes of synthesized heterocyclic substituted alanine (**431–439**) were determined by spectropolarimetric methods. For this, ORD curves of all major fractions with lower R_f values on SiO_2 were recorded and compared with ORD curves of previously obtained similarly constructed complexes of (*S*)- β -phenyl- α -alanine and (*R*)- β -phenyl- α -alanine. ORD curves of diastereomeric complexes of some heterocyclic-substituted alanines are shown in Figure 9.22. The ORD curves of diastereomeric complexes of other heterocyclic-substituted alanine have similar shapes.

From the comparison of the ORD curves it is obvious that all major stereoisomers of addition adducts to complex **327** have (*S*)-absolute configuration of the β -heterocyclic substituted alanine fragment, as evidenced by the presence of the same negative Cotton effect in the range of 400–550 nm in the ORD spectra of

Table 9.14 Results of asymmetric addition of heterocyclic thiols of 1,2,4-triazole series to chiral complex **327** at 45–50 °C.

$ \begin{array}{c} \text{N} \quad \text{N} \\ \diagup \quad \diagdown \\ \text{R}_1 \quad \text{SH} \\ \\ \text{N} \\ \\ \text{R}_2 \end{array} $		Time (h)	Ratio of diastereoisomers (%) ^a		Chemical yield (%) ^b
R ₁	R ₂		(S,R)	(S,S)	
HOCH ₂ CH ₂ CH ₂	C ₆ H ₅	2	94.5	4.5	≥90
HOCH ₂ CH ₂ CH ₂	CH ₂ –CH=CH ₂	2	97.2	2.8	≥82
C ₃ H ₇	C ₆ H ₅	2	96.2	3.8	≥89
C ₃ H ₇	CH ₂ –CH=CH ₂	1	95.1	4.9	≥90
(CH ₃) ₂ CHCH ₂ CH ₂ OCH ₂ (OH)- CHCH ₂ CH ₂	C ₆ H ₅	2.5	96.8	3.2	≥88
(CH ₃) ₂ CHCH ₂ CH ₂ OCH ₂ (OH)- CHCH ₂ CH ₂	CH ₂ –CH=CH ₂	1.5	96.2	3.8	≥89
<i>o</i> -CH ₃ O–C ₆ H ₄	CH ₂ –CH=CH ₂	2	97.0	3.0	≥90
<i>o</i> -Cl–C ₆ H ₄	CH ₂ –CH=CH ₂	2	96.5	3.5	≥88
C ₅ H ₁₁ (OH)CHCH ₂ CH ₂	CH ₂ –CH=CH ₂	3	97.4	26	≥84

- a) The averaged ratio of diastereoisomers based on ¹H NMR (mixture of diastereomeric complexes) and HPLC of isolated amino acids (before crystallization).
 b) Chemical yield of diastereomeric complexes mixture at the step of condensation of heterocyclic thiols to complex **327**.

**Figure 9.22** ORD curves of complexes in CH₃OH, 25 °C 1 – Ni^{II}-(S)-BPB-(R)-Phe; 2 – Ni^{II}-(S)-BPB-(S)-Phe (**380**); 3 – (S,S)-**437**; 4 – (S,R)-**437**; 5 – (S,S)-**438**; 6 – (S,R)-**438**.

diastereoisomeric complexes **431–439** and $\text{Ni}^{\text{II}}\text{-(S)-BPB-(S)-Phe}$ complex (**380**) (Section 9.2.4.1). Positive Cotton effects in the ORD spectra of the secondary fractions with a higher R_f value on SiO_2 and a complex of (*R*)-Phe indicate the (*S,R*)-absolute configuration of these complexes.

Addition of heterocyclic nucleophiles to complex **327** proceeds under base catalysis conditions and, in general, is a thermodynamically controlled process. During the initial steps of the reaction (5–10 min after the addition of nucleophiles), the excess of main (*S,S*)-diastereomers with lower R_f value on SiO_2 is ~87–90%. Then, gradually, the thermodynamically less stable (*S,R*)-diastereomer is converted to the more stable (*S,S*)-diastereomer, and in the equilibrium state the excess of the main diastereomeric complexes (**431–439**) reaches an average of 95%.

Lower thermodynamic stability of the diastereomer with (*S,R*)-absolute configuration, as was shown in the example of simple aliphatic α -amino acid complex, is due to the arrangement of more bulky heterocyclic radical of the amino acid moiety toward the phenyl group of *N*-benzylproline moiety. Such an arrangement is thermodynamically unfavorable due to steric nonbinding interaction between these moieties, which leads to an increase in steric strain and intramolecular energy of this diastereoisomer. Thermodynamically more favorable is the opposite arrangement of these groups in the Schiff base plane, which is observed in the case of the diastereoisomer with (*S,S*)-absolute configuration (see Figure 9.23). The increase in steric nonbinding interaction between the side-chain radical of the amino acid moiety and the phenyl group of the *N*-benzylproline moiety of the chiral reagent in the case of diastereoisomer with (*S,R*) absolute configuration explains the growth of stereoselectivity of syntheses of (*S,S*)-diastereomers at the transition from aliphatic thiols (de ~88–90%) to heterocyclic thiols of 1,2,4-triazole series (de ~92–94%).

The main diastereoisomeric complexes (**431–439**) were isolated from the mixture by preparative chromatography using SiO_2 .

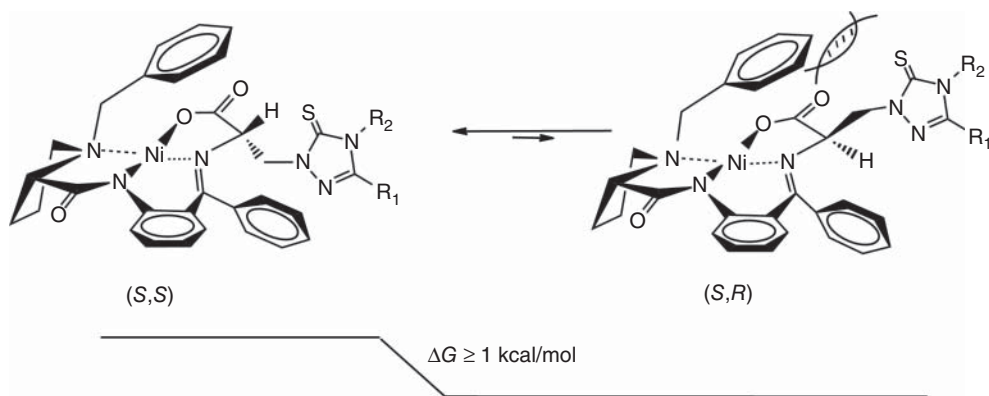
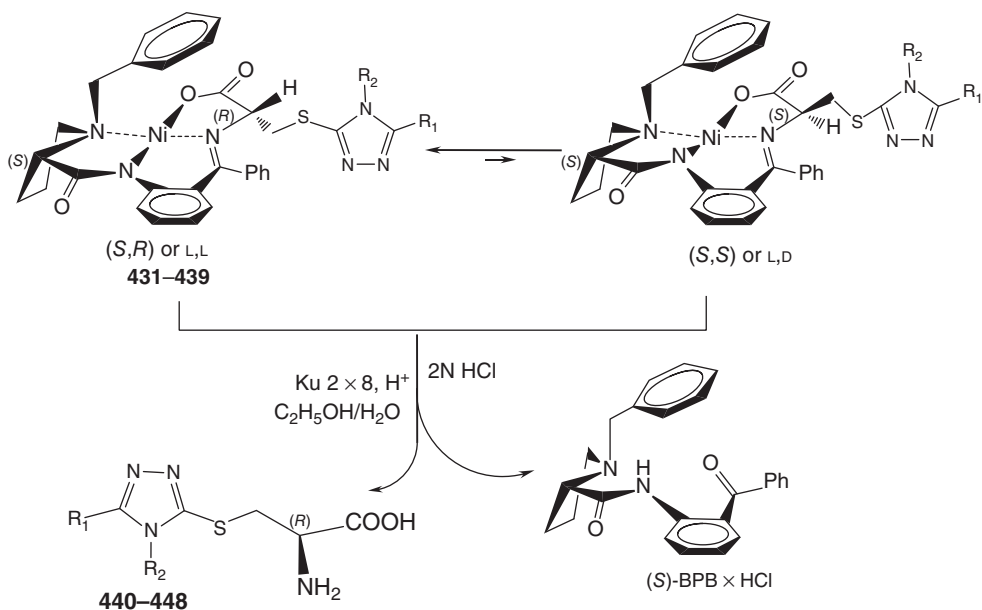


Figure 9.23 The thermodynamic equilibrium between the (*S,R*)- and (*S,S*)-diastereomers of Ni^{II} complexes of Schiff bases of β -heterocyclic substituted alanines.

Decomposition of complexes **431–439** and isolation of heterocyclic-substituted derivatives of (*S*)-alanine were carried out after the establishment of thermodynamic equilibrium between diastereoisomers by standard methods. The original chiral auxiliary reagent (*S*)-BPB is recovered in quantitative chemical yield (94–96%) and full retention of the original optical purity. The target heterocyclic-substituted amino acids were crystallized from a mixture of EtOH/H₂O (see Scheme 9.71).



Where $R_1 = \text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$, $R_2 = \text{C}_6\text{H}_5$ (**440**);
 $R_1 = \text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$, $R_2 = \text{CH}_2\text{-CH=CH}_2$ (**441**);
 $R_1 = \text{C}_3\text{H}_7$, $R_2 = \text{C}_6\text{H}_5$ (**442**);
 $R_1 = \text{C}_3\text{H}_7$, $R_2 = \text{CH}_2\text{-CH=CH}_2$ (**443**);
 $R_1 = \text{CH}_2\text{CH}_2\text{CH(OH)CH}_2\text{OCH}_2\text{CH}_2\text{CH(CH}_3)_2$, $R_2 = \text{C}_6\text{H}_5$ (**444**);
 $R_1 = \text{CH}_2\text{CH}_2\text{CH(OH)CH}_2\text{OCH}_2\text{CH}_2\text{CH(CH}_3)_2$, $R_2 = \text{CH}_2\text{-CH=CH}_2$ (**445**);
 $R_1 = \text{o-CH}_3\text{OC}_6\text{H}_4$, $R_2 = \text{CH}_2\text{-CH=CH}_2$ (**446**);
 $R_1 = \text{o-Cl-C}_6\text{H}_4$, $R_2 = \text{CH}_2\text{-CH=CH}_2$ (**447**);
 $R_1 = \text{CH}_2\text{CH}_2\text{CH(OH)C}_5\text{H}_{11}$, $R_2 = \text{CH}_2\text{-CH=CH}_2$ (**448**).

Scheme 9.71

Chiroptic data of synthesized β -heterocyclic substituted (*S*)-alanines (**440–448**) are presented in Table 9.15.

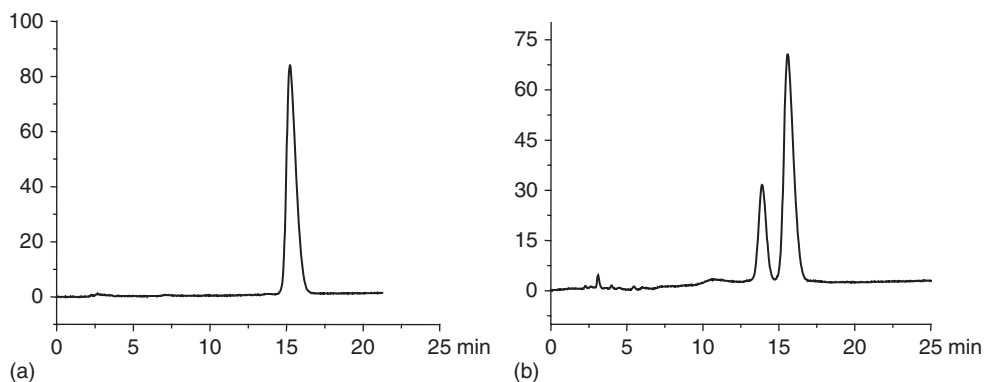
The enantiomeric purity of β -heterocyclic-substituted (*S*)-alanines (**440–448**) was determined by high-performance liquid chromatography (HPLC) using a chiral phase of Crownpak CR (+) type (see Figure 9.24).

Table 9.15 Chiroptic results and chemical yields of heterocyclic-substituted (S) -alanines.

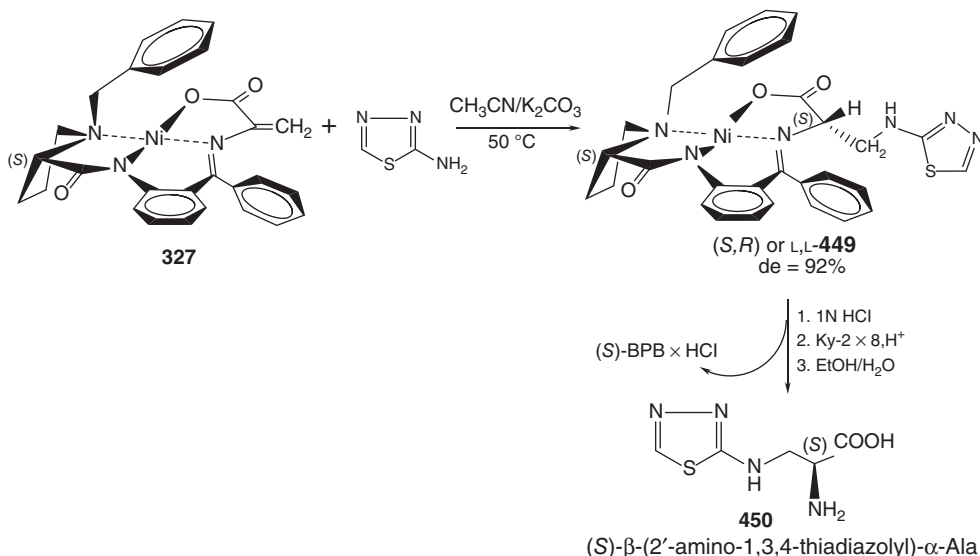
Name of amino acids	Chiroptic results		Chemical yield (%) ^{b)}
	$[\alpha]_D^{25}$	ee (%) ^{a)}	
(S)- β -[(3-hydroxypropyl)-4-phenyl-5-thioxo-1,2,4-triazol-1-yl]- α -alanine (440)	-22.31° ($c = 1$; 6 N HCl)	>99.5	86
(S)- β -[(3-hydroxypropyl)-4-allyl-5-thioxo-1,2,4-triazol-1-yl]- α -alanine (441)	-5.47° ($c = 1$; 6 N HCl)	>99.5	87
(S)- β -[3-propyl-4-phenyl-5-thioxo-1,2,4-triazol-1-yl]- α -alanine (442)	-24.00° ($c = 0.1$; 6 N HCl)	>99.5	88
(S)- β -[3-propyl-4-allyl-5-thioxo-1,2,4-triazol-1-yl]- α -alanine (443)	-5.00° ($c = 1$; 6 N HCl)	>99.5	84
(S)- β -[3-hydroxy-4'-isoamyloxybutyl)-4-phenyl-5-thioxo-1,2,4-triazol-1-yl]- α -alanine (444)	-17.00° ($c = 0.1$; 6 N HCl)	99.0	82
(S)- β -[3-hydroxy-4'-isoamyloxybutyl)-4-allyl-5-thioxo-1,2,4-triazol-1-yl]- α -alanine (445)	-4.50° ($c = 0.1$; 6 N HCl)	98.5	89
(S)- β -[(2-methoxyphenyl)-4-allyl-5-thioxo-1,2,4-triazol-1-yl]- α -alanine (446)	-5.00° ($c = 0.1$; 6 N HCl)	>99.5	85
(S)- β -[(2-chlorophenyl)-4-allyl-5-thioxo-1,2,4-triazol-1-yl]- α -alanine (447)	-2.00° ($c = 0.5$; 1 N HCl)	>99.5	80
(S)- β -[(3-hydroxyoctyl)-4-allyl-5-thioxo-1,2,4-triazol-1-yl]- α -alanine (448)	-4.00° ($c = 0.1$; 6 N HCl)	99.0	80

a) Chemical yield is calculated from the amount of original complex **327**.

b) Enantiomeric purity (ee) based on chiral GLC and HPLC.

**Figure 9.24** Chiral liquid chromatogram of amino acid (S)- β -[(3-hydroxypropyl)-4-allyl-5-thioxo-1,2,4-triazol-1-yl]- α -alanine (**441**) (Chiral phase-Crownpak CR (+), eluent-HClO₄, elution rate 0.4 ml min⁻¹, 20 °C). (a) Synthesized sample, (b) a mixture of (R)- and (S)-isomers.

Similarly, addition of 2-amino-1,3,4-thiadiazole to chiral complex of dehydroalanine **327** was performed and heterocyclic-substituted derivative of α -alanine – (*S*)- or β -(2'-amino-1,3,4-thio-diazolin)- α -alanine (**450**) was isolated (see Scheme 9.72).



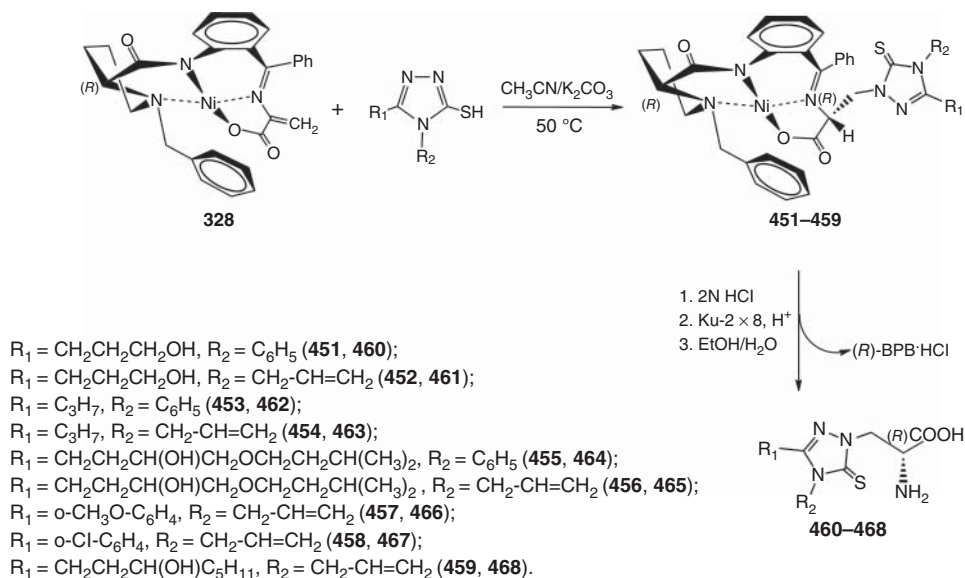
Scheme 9.72

The ratio of (*S,S*)- and (*S,R*)-diastereomers (de) and the absolute configuration of the amino acid moiety of the major diastereomeric complex adduct as well as the enantiomeric purity (ee) of the isolated amino acid were determined as described above for 1,2,4-triazole-containing amino acids (**440**–**448**): de of **449** at the coupling step is 92% and the ee of amino acid **450** is more than 99%.

A method for the asymmetric synthesis of β -heterocyclic-substituted derivatives of α -amino acids of *D*-absolute configuration by nucleophilic addition of substituted triazoles to the $\text{C}=\text{C}$ bond of dehydroalanine in Ni^{II} complex of its Schiff base with chiral auxiliary (*R*)-BPB (**328**) was also developed (see Scheme 9.73).

To determine the absolute configuration of the main diastereomeric complexes **451**–**459**, their ORD curves were recorded and compared with the ORD curves of diastereomeric complexes of the same amino acids with (*S,S*)-absolute configuration, constructed on the basis of chiral reagent (*S*)-BPB (see Figure 9.25).

From a comparison of ORD curves it follows that the main fractions of the products of nucleophilic addition with a lower R_f value on SiO_2 are diastereomers with (*R,R*)-absolute configuration, containing β -heterocyclic-substituted (*R*)-alanines. This is evidenced by mirror images of ORD curves of diastereomers of complexes **451**, **452**, and **456** and the corresponding diastereomers of (*S,S*)-absolute configuration synthesized from chiral reagent (*S*)-BPB (**431**, **432**, and **436**). A similar



Scheme 9.73

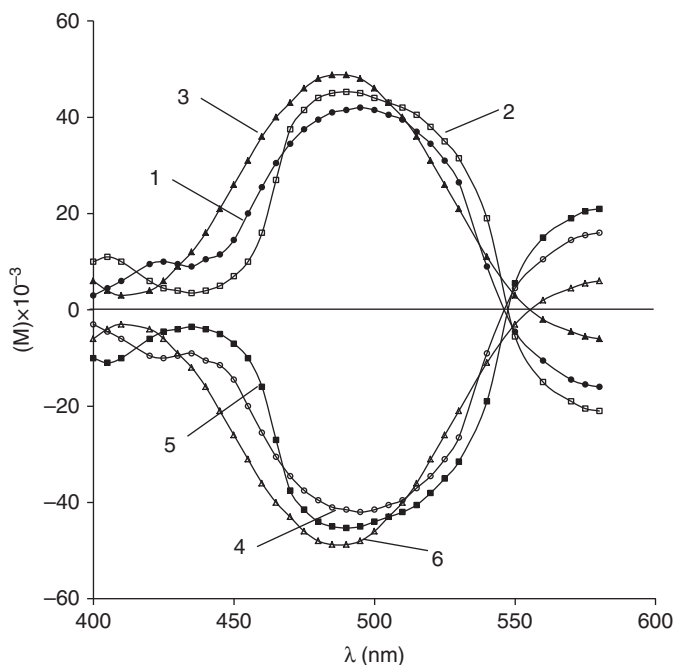


Figure 9.25 ORD curves of diastereoisomeric complexes of β -heterocyclic substituted alanines in CH_3OH (25 $^\circ\text{C}$) 1) **451**; 2) **452**; 3) **456**; 4) **431**; 5) **432**; 6) **436**.

pattern is observed for the ORD curves of diastereomeric complexes (**453–455**, **457–459**) and their antipodes (**433–435**, **437–439**).

The ratio of (*R,R*)- and (*R,S*)-diastereomeric complexes (de), the enantiomeric excess of isolated heterocyclic-substituted amino acids (ee), and the absolute configurations of their α -carbon atoms were determined similarly, as described above, for their optical antipodes.

As expected, all the data on diastereoselectivity (de) and the enantiomeric purity (ee) of isolated amino acids in absolute value coincide with corresponding data obtained using complex **327** as the starting dehydroamino acid synthon.

Addition of heterocyclic nucleophiles to the dehydroalanine chiral complex based on chiral auxiliary (*R*)-BPB is also a kinetically and thermodynamically controlled process.

Comparison of relative rotation data of the isolated β -substituted alanine samples (**460–468**) with the data of corresponding β -substituted (*S*)-alanines (**440–448**), the absolute configurations of which were established by chiral HPLC analysis, shows that β -heterocyclic-substituted cysteines **460–468** have an (*R*)-absolute configuration. This is evidenced by the same absolute value and opposite sign data of the specific rotation of these heterocyclic-substituted amino acids samples.

Thus, by addition of heterocyclic nucleophiles of triazole and thiodiazole series to the C=C bond of dehydroalanine in Ni^{II} complexes of its Schiff base with chiral auxiliary reagents (*S*)-BPB and (*R*)-BPB, a versatile method for the highly selective asymmetric synthesis of β -heterocyclic-substituted α -amino acids of both (*S*)- and (*R*)-absolute configuration has been developed.

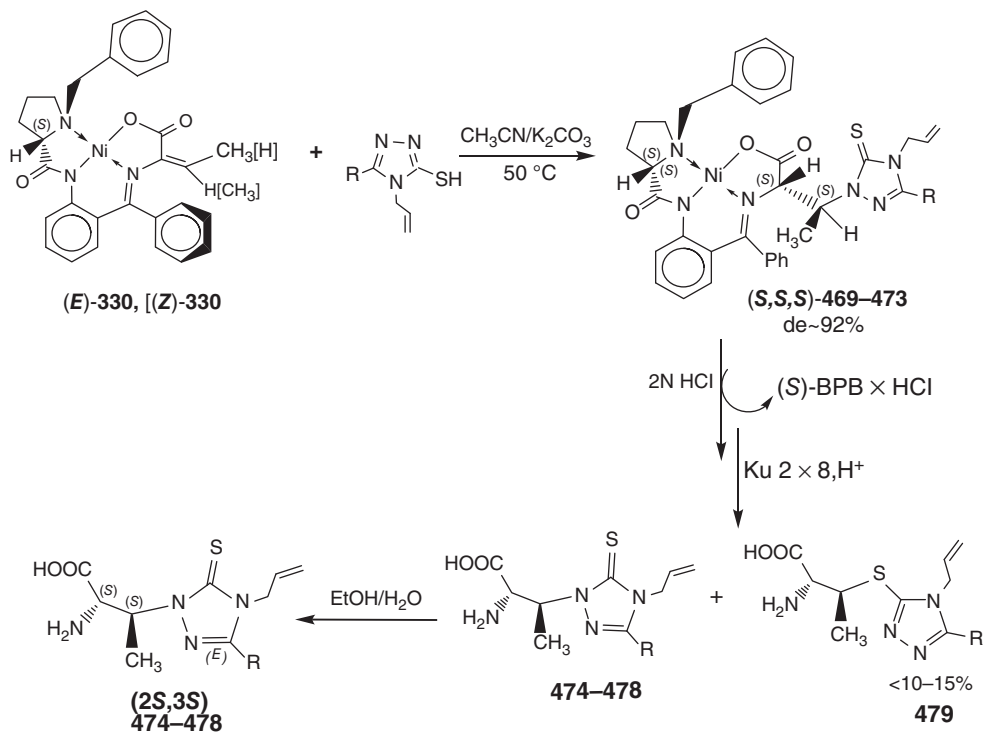
9.2.6.2 Asymmetric Synthesis of β -Heterocyclic-Substituted Derivatives of (2*S*,3*S*)- α -Aminobutyric Acid

This section describes asymmetric synthesis of optically active heterocyclic derivatives of α -aminobutyric acid containing 5-thioxo-4-allyl-1,2,4-triazole moieties with different aliphatic and aromatic substituents in position 3 of the triazole cycle [206, 207]. Asymmetric nucleophilic addition reactions of the corresponding 4-allyl-5-mercapto-1,2,4-triazoles to the electrophilic C=C bond of dehydroaminobutyric acid in Ni^{II} complexes of their Schiff base with chiral auxiliary (*S*)-BPB (**330**) (see Section 9.1.4.2) were studied. For this purpose, both individually pure complexes (*Z*)- and (*E*)-**330** and their mixtures after synthesis in the ratio of (*E*)-**330**/*(Z)*-**330** = 5/1 were used.

Previously, it was shown that (*E*)-**330** and (*Z*)-**330** complexes underwent Michael addition reaction with aliphatic nucleophiles, preferably forming diastereomeric complexes of β -substituted derivatives of α -aminobutyric acid with 2*L*,3*L*-*allo* absolute configuration (see Section 9.2.4.2). It was found that the addition of nucleophiles to the C=C bond of dehydroaminobutyric acid complexes was made difficult compared to the similarly constructed dehydroalanine complexes.

As heterocyclic nucleophiles 4-allyl-3-(3'-hydroxypropyl)-1*H*-1,2,4-triazol-5-thione, 4-allyl-3-(3'-hydroxy-4'-isoamyloxybutyl)-1*H*-1,2,4-triazol-5-thione, 4-allyl-3-(*o*-methoxyphenyl)-1*H*-1,2,4-triazol-5-thione, 4-allyl-3-(*o*-chlorophenyl)-1*H*-1,2,4-triazol-5-thione, and 4-allyl-3-(3'-hydroxyoctyl)-1*H*-1,2,4-triazol-5-thione were used.³⁾

Asymmetric addition of nucleophiles to the C=C bond of dehydroaminobutyric acid moiety of chiral (*E*)-**330** and (*Z*)-**330** complexes occurs in CH₃CN in the presence of K₂CO₃ at 50–60 °C (see Scheme 9.74).



Scheme 9.74

The addition reactions in the media of DMF/K₂CO₃, CH₃CN/NaOH, and CH₃CN/Na₂CO₃ were also investigated, but the best results in terms of yield and stereoselectivity were observed in the case of CH₃CN/K₂CO₃. The addition reaction is conveniently monitored by TLC [SiO₂, CHCl₃/CH₃COCH₃ (3/1) or CHCl₃/CH₃COOC₂H₅ (1/3)] following the disappearance of traces of starting complexes **330** and the establishment of thermodynamic equilibrium between

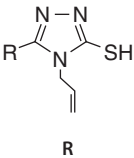
3) Nucleophiles were synthesized at the Department of Organic Chemistry, Yerevan State University.

the diastereomer adducts, since the original complexes and addition products differ from each other by their R_f values. The process of thermodynamic equilibrium establishment between the diastereoisomers can be also monitored by ^1H NMR, as diastereomers of complexes of β -heterocyclic-substituted derivatives of α -aminobutyric acid differ by the chemical shifts of the proton signals of α -H and β -CH₃.

TLC results indicate that the relative rate of addition of nucleophiles to the (*E*)-dehydro-aminobutyric acid complex markedly differs from the rate of addition to the (*Z*)-dehydro-aminobutyric acid complex. TLC and ^1H NMR revealed that in the initial stages of the addition reaction of heterocyclic nucleophiles, an excess of the main diastereomer was ~85–90%, which increased within several hours and reached the values shown in Table 9.16.

The minor diastereomeric complex was isolated by preparative TLC (fraction II by the R_f value) from product **469** before the establishment of thermodynamic equilibrium (after about 10 h at about 30% conversion of the starting complex), the contents of which relative to the main diastereomer was about 8%. Methods of polarimetric measurements and ^1H NMR attributed (*S,R,S*)-absolute configuration to the minor diastereomer. The amount of this diastereomer during the establishment of thermodynamic equilibrium decreased and after 120 h it was

Table 9.16 Results of asymmetric addition of substituted triazoles to chiral (*E*)-**330** and (*Z*)-**330** complexes in $\text{CH}_3\text{CN}/\text{K}_2\text{CO}_3$ at 50 °C.

Complex 330		Time	de (%) ^{a)}	Chemical yield (%) ^{b)}
(<i>E</i>)- 330	$\text{HO}-\text{CH}_2\text{CH}_2\text{CH}_2$	120 h	96	72
(<i>E</i>)- 330	$(\text{CH}_3)_2\text{CHCH}_2\text{CH}_2\text{OCH}_2\text{CH}(\text{OH})\text{CH}_2\text{CH}_2$	168 h	94	74
(<i>E</i>)- 330	$o\text{-CH}_3\text{O}-\text{C}_6\text{H}_4$	96 h	97	83
(<i>E</i>)- 330	$o\text{-Cl}-\text{C}_6\text{H}_4$	288 h	97	85
(<i>E</i>)- 330	$\text{C}_5\text{H}_{11}\text{CH}(\text{OH})\text{CH}_2\text{CH}_2$	168 h	86	75
(<i>Z</i>)- 330	$\text{HO}-\text{CH}_2\text{CH}_2\text{CH}_2$	40 days	96	50
(<i>Z</i>)- 330	$(\text{CH}_3)_2\text{CHCH}_2\text{CH}_2\text{OCH}_2\text{CH}(\text{OH})\text{CH}_2\text{CH}_2$	~50 days	90	40
(<i>Z</i>)- 330	$o\text{-CH}_3\text{O}-\text{C}_6\text{H}_4$	32 days	97	50
(<i>Z</i>)- 330	$o\text{-Cl}-\text{C}_6\text{H}_4$	~80 days	97	30
(<i>Z</i>)- 330	$\text{C}_5\text{H}_{11}\text{CH}(\text{OH})\text{CH}_2\text{CH}_2$	~60 days	80	30
(<i>E</i>) + (<i>Z</i>)- 330	$\text{HO}-\text{CH}_2\text{CH}_2\text{CH}_2$	200 h	96	63
(<i>E</i>) + (<i>Z</i>)- 330	$(\text{CH}_3)_2\text{CHCH}_2\text{CH}_2\text{OCH}_2\text{CH}(\text{OH})\text{CH}_2\text{CH}_2$	250 h	92	50
(<i>E</i>) + (<i>Z</i>)- 330	$o\text{-CH}_3\text{O}-\text{C}_6\text{H}_4$	200 h	97	60
(<i>E</i>) + (<i>Z</i>)- 330	$o\text{-Cl}-\text{C}_6\text{H}_4$	200 h	97	55
(<i>E</i>) + (<i>Z</i>)- 330	$\text{C}_5\text{H}_{11}\text{CH}(\text{OH})\text{CH}_2\text{CH}_2$	250 h	80	40

a) de (%) based on ^1H NMR results.

b) Yield of a mixture of diastereomeric complexes.

2–3%. Thus, based on the above data it is obvious that the addition of the heterocyclic nucleophiles to chiral (*E*)-**330** and (*Z*)-**330** complexes is both a kinetically (in the early stages of reaction) and thermodynamically controlled process. Such stereochemistry was also previously observed in the study of the addition reaction of simple aliphatic nucleophiles to chiral complexes of dehydroaminobutyric acid (see Section 9.2.4.2).

After completion of the addition reaction, the main diastereomeric complexes of adducts (*S,S,S*)-**469–473** were chromatographed [SiO_2 , 25×25 cm, $\text{CHCl}_3/\text{CH}_3\text{COOC}_2\text{H}_5$ (1:3)] and their structures determined using modern spectral analysis methods. As a result of the addition of nucleophiles, a mixture of diastereomeric complexes with high excess of the diastereomer of (*S*)-absolute configuration of the newly induced chiral centers in positions 2 and 3 of aminobutyric moieties is formed.

The absolute configuration of α -carbon atom of the amino acid fragment of the diastereomeric complexes was determined on the basis of the sign of optical rotation at 589 nm, as was previously done for similarly constructed complexes of other α -amino acids.

The absolute configuration of β -carbon atom of the amino acid fragment of complexes **469–473** was determined by ^1H NMR by chemical shift values of their β -methyl protons signals. As was previously shown in an example of similarly constructed complexes of β -aliphatically substituted derivatives of α -aminobutyric acid, in the case of (*2S,3S*)-*allo* absolute configuration of the amino acid moiety, chemical shift of β - CH_3 proton signals is in relatively strong fields, and in the case of (*2S,3R*)-configuration – in weak fields. The same difference in the chemical shifts of signals of β -methyl protons of the amino acid moiety was also observed in ^1H NMR spectra of diastereomeric complexes **469–473**, which implies that they have amino acid moieties of (*S*)-*anti* or (*2S,3S*)-*allo* absolute configuration [207]. The difference in chemical shifts is explained by the spatial arrangement of the CH_3 -group of aminobutyric moiety in the coordination sphere of the metal ion (see Figure 9.26), and the shift of the methyl proton signal toward weak fields in ^1H NMR spectra, presumably, is due to the influence of the magnetic anisotropy of Ni^{2+} ion, located directly above the CH_3 -group of the amino acid moiety in the case of (*2S,3R*)-*threo* absolute configuration.

Unfortunately, attempts to assess the diastereoselectivity (*de*) of synthesis by chiral HPLC or GLC methods after decomposing the mixture of diastereomeric complexes and isolating the heterocyclic derivatives of α -aminobutyric acid turned out unsuccessful. Previously, for aliphatic- and heterocyclic-substituted derivatives of α -aminobutyric acid, the *de* was determined by chiral HPLC analysis (see Section 9.1.4.2). The ratio of diastereoisomers of complexes **469–473** was determined by ^1H NMR analysis of the diastereomeric mixture of synthesized complexes and isolated heterocyclic amino acids. Because of the complexity of ^1H NMR spectra, it was not possible to determine the diastereomers for all nucleophilic addition products based on the ratio of the signal integrals of aromatic protons in the range of 8–9 ppm and the ratio of the signal integrals of the methylene protons of the benzyl group of *N*-benzylproline moiety in the

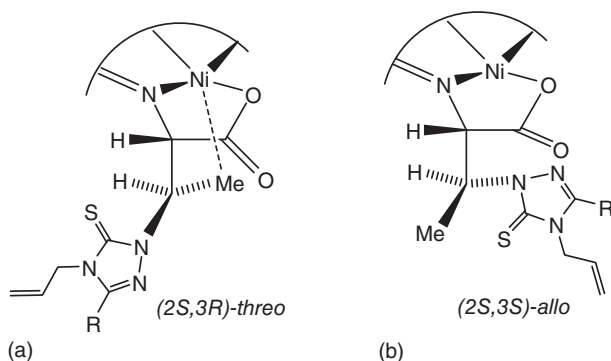


Figure 9.26 The spatial arrangement of the side group of the amino acid moiety in diastereomeric complexes **469–473**.

range of 3.5–3.55 and 4.5–4.6 ppm (as was done for the similarly constructed complexes of simple aliphatic amino acids). The most accurate results were noted during determination of the ratio of the integrals of doublet signals of α -protons of stereoisomers of synthesized heterocyclic-substituted amino acids **474–478** in ^1H NMR spectra of their mixture, obtained after decomposition of a mixture of diastereomeric complexes and demineralization of amino acid (see Figure 9.27).

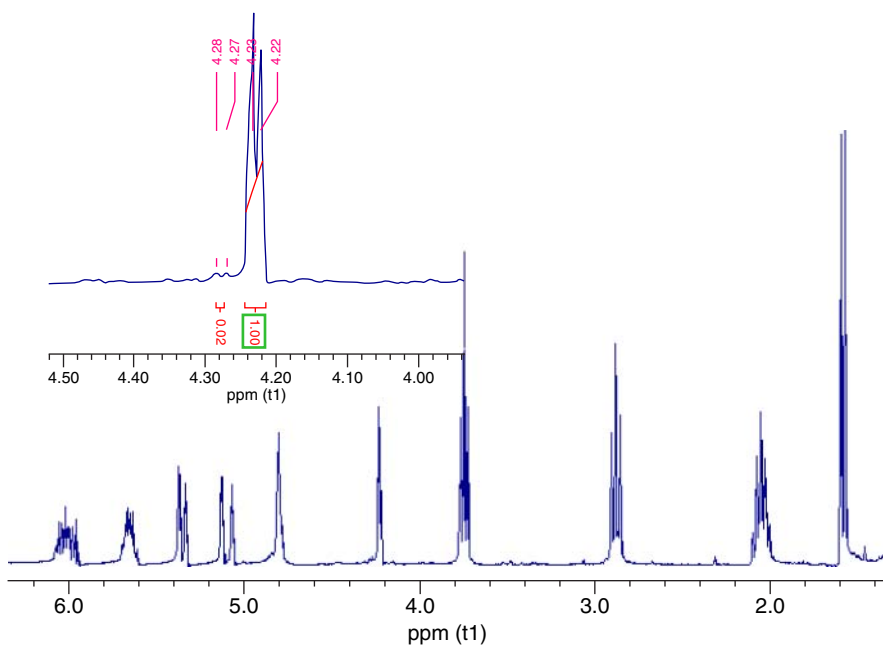


Figure 9.27 ^1H NMR spectrum of *(2S,3S)*-3-(4'-allyl-3'-hydroxypropyl-5-thioxo-1,2,4-triazol-1-yl)-2-aminobutyric acid (**474**) (before crystallization).

The results of nucleophilic addition of substituted triazoles to chiral (*E*)-**330** and (*Z*)-**330** complexes are presented in Table 9.16.

The addition reactions of substituted triazoles to both individually pure complexes (*E*)-**330** and (*Z*)-**330** and their mixture were also investigated. It was shown that regardless of the (*Z*)- or (*E*)-configuration of the dehydroaminobutyric acid fragment of starting complexes, the end main products of the triazole addition reaction were diastereomers containing heterocyclic amino acids of (*S*)-*anti* configuration.

As seen from Table 9.16, the rate of nucleophilic addition to complex (*E*)-**330** is about 5–10 times more than in the case of (*Z*)-**330** complex, which is apparently due to steric factors.

As was shown previously (see Section 9.2.4.2), in such systems, addition of nucleophiles preferably occurs from the *si* side of Schiff base plane, since the *re* side is shielded by the phenyl group of *N*-benzylproline moiety. Upon addition of nucleophiles to the dehydroaminobutyric acid complex of (*Z*)-configuration the *si* side of the Schiff base plane is additionally shielded by the methyl group of dehydroaminobutyric acid fragment.

Such shielding is absent in the case of triazoles' attachment to (*E*)-**330** complex, which provides the highest rate of nucleophiles addition to the C=C bond of dehydroaminobutyric acid with (*E*)-configuration (see Figure 9.28b)). Decomposition of a mixture of diastereomeric complexes **469**–**473** and isolation of target β -heterocyclic substituted (2*S*,3*S*)- α -aminobutyric acid derivatives were carried out by standard methods. Isolated amino acid mixtures (before crystallization) were studied by ^1H NMR and IR spectroscopy (Figure 9.28a). According to IR spectra, the isolated heterocyclic-substituted derivatives of α -aminobutyric acid **474**–**478** contain impurities of corresponding *S*-heterocyclic-substituted cysteines derivatives (**479**) – adducts of substituted triazoles to the C=C bond of complexes **330** at the sulphydryl group (~ 10 –15%).

This is evidenced by the presence of an absorption band in the range of 650 – 700 cm^{-1} in IR spectra of the isolated amino acid mixtures, typical of the –S–C– bond. After recrystallization from $\text{H}_2\text{O}/\text{C}_2\text{H}_5\text{OH}$ (1/1) mixture,

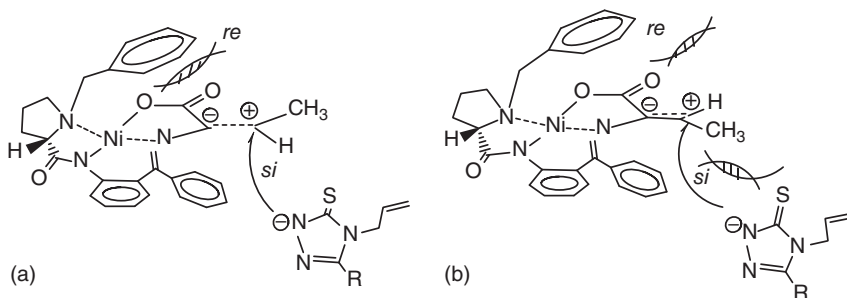


Figure 9.28 Additional steric hindrance of approaching heterocyclic nucleophiles to the C=C bond of dehydroaminobutyric moiety from the *si* side of Schiff base plane in the case of (*Z*)-**330** (b) complex; such shielding is absent in (*E*)-**330** (a) complex.

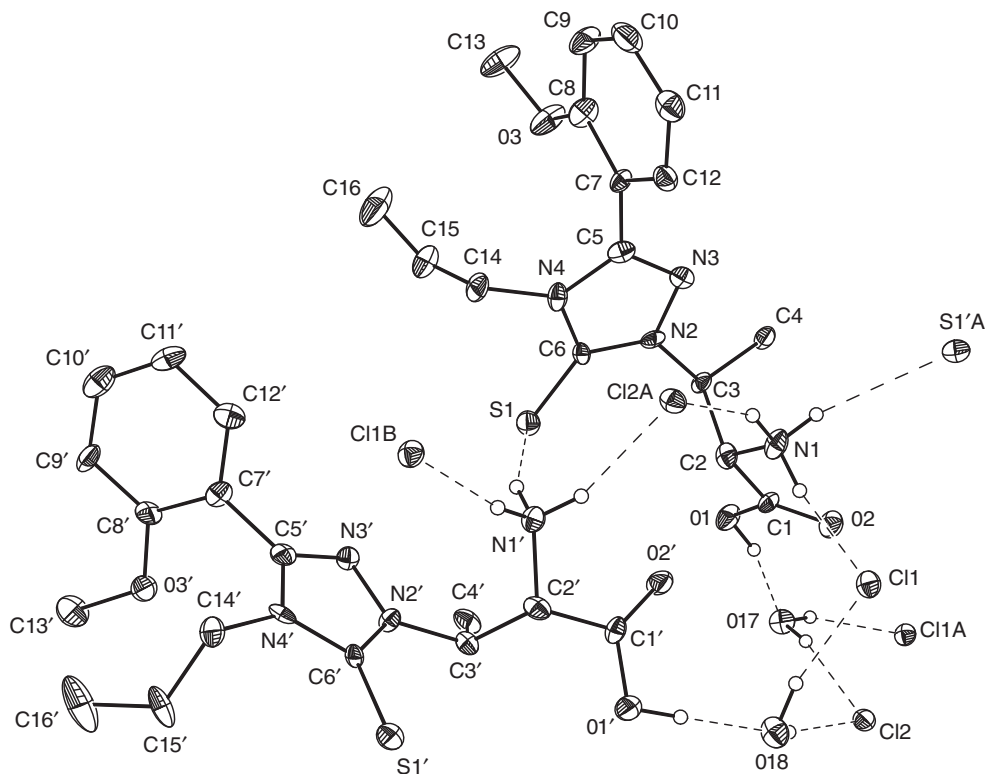


Figure 9.29 The molecular structure of heterocyclic-substituted amino acid **476** based on X-ray data.⁴⁾

individually pure β -heterocyclic-substituted derivatives of α -aminobutyric acid 474–478 were obtained.

The structures and absolute configurations of isolated amino acids were determined by physicochemical methods of analysis, including the XRD method. Figure 9.29 shows the molecular structure of **476** amino acid – (2*S*,3*S*)-3-(4'-allyl-3'-*o*-methoxyphenyl-5-thioxo-1,2,4-triazol-1-yl)-2-aminobutyric acid based on X-ray data.

The data clearly confirm the structures of synthesized heterocyclic-substituted amino acids **474–478** and their *(2S,3S)*-*allo* absolute configuration presented in Scheme 9.74.

Thus, a method for the asymmetric synthesis of heterocyclic derivatives of α -aminobutyric acid, based on addition of substituted triazoles to the C=C bond of chiral square-planar Ni^{II} complexes of Schiff base of dehydroaminobutyric acid, has been developed.

4) XRD analysis was performed by Khrustalev (XRD Laboratory; INEOS, Russian Academy of Sciences).

Five new β -heterocyclic-substituted derivatives of (2*S*,3*S*)-*allo*- α -aminobutyric acid were synthesized: (2*S*,3*S*)-3-(4'-allyl-3'-hydroxypropyl-5-thioxo-1,2,4-triazol-1-yl)-2-aminobutyric acid (**474**), (2*S*,3*S*)-3-(4'-allyl-3'-hydroxy-isoamyloxybutyl-5-thioxo-1,2,4-triazol-1-yl)-2-aminobutyric acid (**475**), (2*S*,3*S*)-3-(4'-allyl-3'-*o*-methoxyphenyl-5-thioxo-1,2,4-triazol-1-yl)-2-aminobutyric acid (**476**), (2*S*,3*S*)-3-(4'-allyl-3'-*o*-chlorophenyl-5-thioxo-1,2,4-triazol-1-yl)-2-aminobutyric acid (**477**), and (2*S*,3*S*)-3-(4'-allyl-3'-hydroxyoctyl-5-thioxo-1,2,4-triazol-1-yl)-2-aminobutyric acid (**478**).

The developed method is versatile and opens up the possibility of synthesis of a wide variety of new important optically active heterocyclic-substituted derivatives of (2*S*,3*S*)-*allo*- α -aminobutyric acid.

9.3

Asymmetric Synthesis of Precursors for PET Radiopharmaceuticals

Positron emission tomography (PET) [208] – the newest method of medical imaging (radionuclide diagnostics) – based on the use of radiopharmaceuticals labeled with radioisotopes (positron emitters), is currently the fastest growing area, which needs isotope-labeled amino acids with high optical purity.

PET is a noninvasive imaging technique based on the use of biologically relevant compounds labeled with short-lived positron-emitting radionuclides such as carbon-11, nitrogen-13, oxygen-15, and fluorine-18. In clinical applications, a very small amount of labeled compound (called *radiopharmaceutical* or *radio-tracer*) is introduced into the patient usually by intravenous injection and after an appropriate uptake period, the concentration of tracer in tissue is measured by the scanner.

The mode of PET lies in highly efficiently tracing the location of incredibly small amount of radioactive compound introduced into the human body. Typically, PET isotopes are produced at the place of study. This is associated with short survival of PET isotopes, which leaves little time to manufacture and delivery of radiopharmaceuticals. Selection of radiopharmaceuticals depends on the particular function of the body, which is scheduled for tracing. For example, to determine the intensity of cell work, isotope-labeled analog of glucose – ^{18}F -deoxyglucose – is used. To determine the rate of growth and reproduction of cells, especially for the detection of tumors, the most informative is the use of isotopically labeled amino acids with ^{11}C and ^{18}F . Because of isotopes' short half-life (half-life of ^{11}C – 20.4 min, and ^{18}F – 109.8 min), there is a need for fast asymmetric synthesis methods of amino acids that are used for early diagnosis of brain cancer.

In this regard, the development of simple, convenient, and fast methods for the synthesis of nonprotein amino acids, including isotopically labeled analogs in enantiomerically pure form, is currently a very relevant and timely problem.

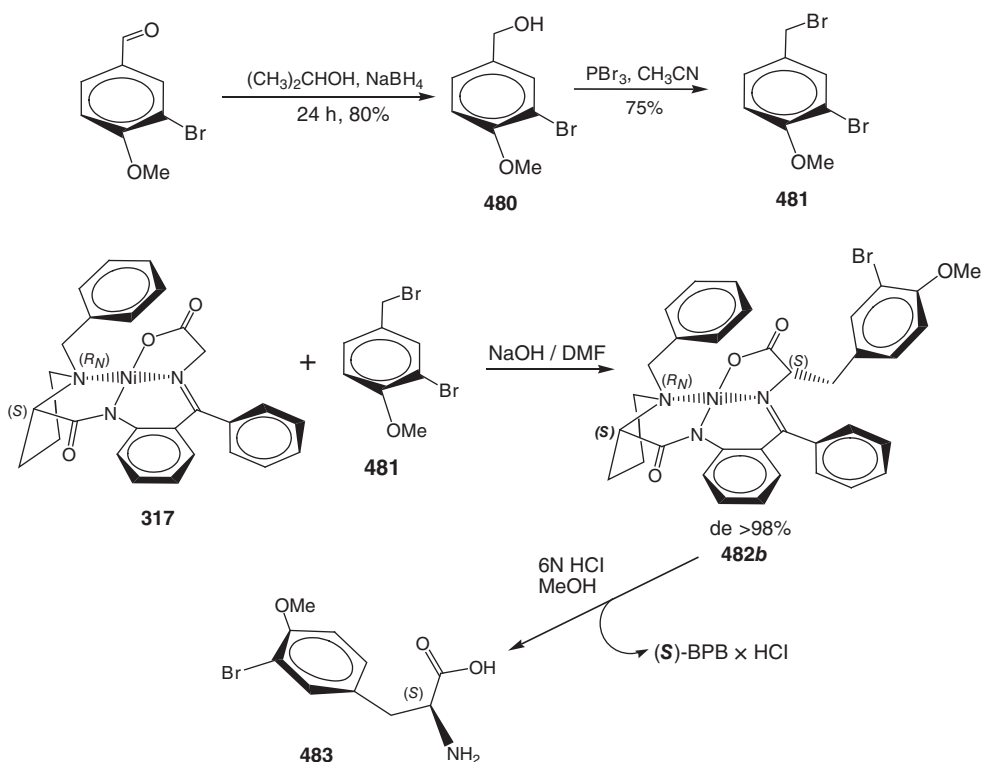
9.3.1

Preparation of Active Tyrosine Derivatives

9.3.1.1 Catalytic Methods of Substitution

For the synthesis of precursors that meet PET requirements, the ^{18}F isotope must be introduced at a very late stage of synthesis. To introduce ^{18}F into the aromatic ring of a protected amino acid via nucleophilic substitution of the halogen atom (Br, I) using Pd- and Cu-based catalysts, seemed to be the easiest way. For this, the asymmetric synthesis of amino acid precursor followed by testing of this precursor in a model reaction of introducing “cold” ^{19}F was envisaged.

At first, the asymmetric synthesis of Ni^{II} ion complex of Schiff base of (*S*)-*O*-methyl-3-bromotyrosine with chiral auxiliary (*S*)-BPB was performed by C-alkylation of glycine complex Ni^{II} -(*S*)-BPB-Gly (**317**) by 4-methoxy-3-bromobenzyl bromide (**481**) [209, 210] (see Scheme 9.75).



Scheme 9.75

Alkylating agent **481** was prepared from commercially available 4-methoxy-3-bromo-benzaldehyde by the initial reduction with sodium borohydride in isopropyl alcohol to the 4-methoxy-3-bromobenzyl alcohol (**480**) followed by

bromination with phosphorus tribromide. The progress of the reaction can be monitored by TLC [SiO_2 , eluent CHCl_3] following the disappearance of traces of starting complex **317** and establishment of a thermodynamic equilibrium between the diastereoisomers of alkylation product.

Complex **482** is obtained as a mixture of two diastereoisomers with (R_N, R, S) (**482a**) and (R_N, S, S) (**482b**) configuration, with (R_N, S, S)-diastereomer (ee 98%) being predominant [209, 210]. The individual (S, S)-diastereomer (**482a**) was isolated by column chromatography [SiO_2 , 20×2 cm, eluent CHCl_3]. It was found that (R_N, S) configuration of the proline fragment of glycine original complex **317** did not change in the course of C-alkylation, as it was previously shown in the example of alkylation of other amino acid complexes. The absolute configuration of α -carbon atom of the amino acid moiety of alkylated complexes **482a** and **482b** was determined using the polarimetric method by the sign of the optical rotation at 589 nm. Figure 9.30 shows the structure of main diastereomeric complex **482b**, established by XRD analysis.

α -Amino acid – (S)- O -methyl-3-bromotyrosine (**483**) – was isolated from diastereomerically pure complex **482b** by standard method after acid decomposition and ion exchange demineralization. The optical purity of the isolated amino acid and diastereoselectivity of synthesis (de) were determined by chiral GLC and ^1H NMR analysis, as well as by polarimetric measurements (de >98%).

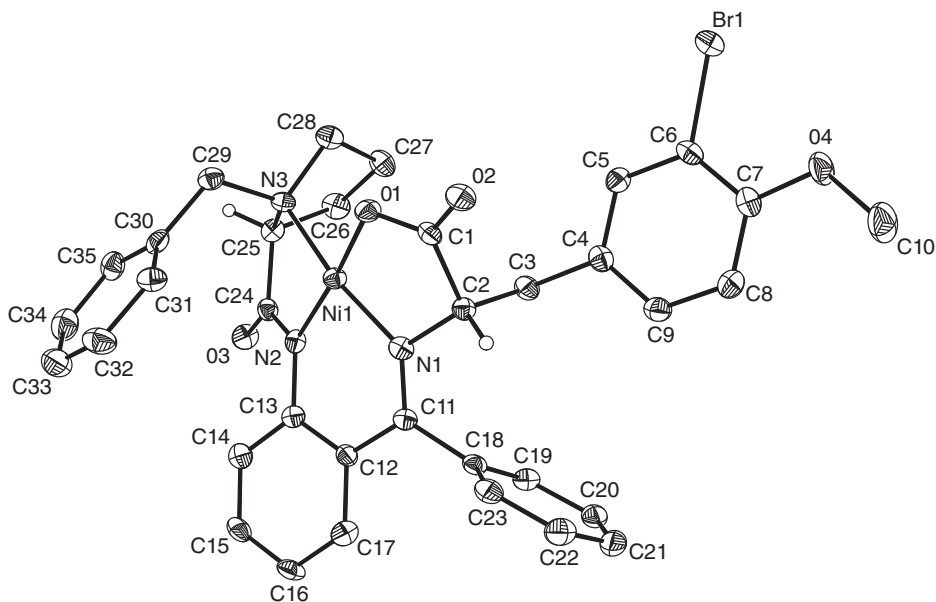
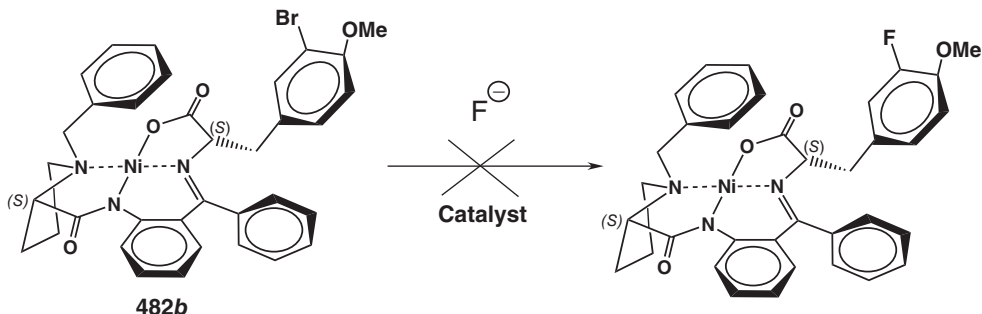


Figure 9.30 Structure of Ni^{II} complex of Schiff base of (S)-BPB and (S)- O -methyl-3-bromotyrosine (**482b**) with 50% probability of ellipsoids of anisotropic displacements.

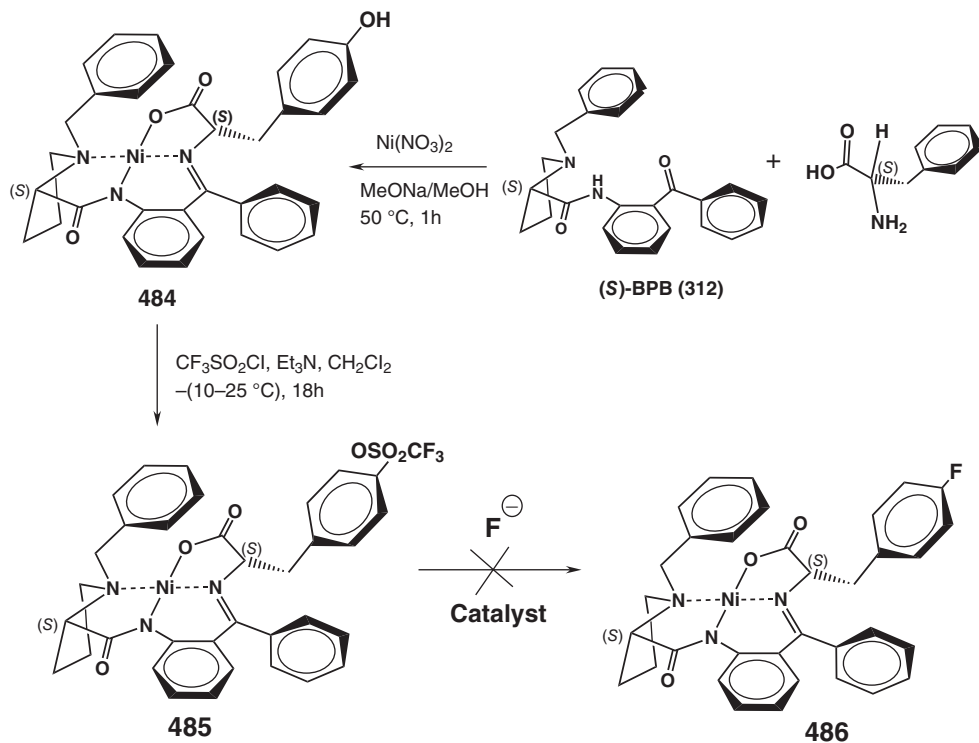
Chiral complex **482b** was used as an amino acid precursor for substitution of the bromine atom by a fluorine atom. Unfortunately, all attempts to carry out nucleophilic substitution of bromine by ^{19}F using metal complex (Pd and Cu) catalysis were unsuccessful (see Scheme 9.76).



Scheme 9.76

Catalysts	
Based on Pd complexes	Based on Cu complexes
CsF, Pd(dba) ₃ *CHCl ₃ , C ₇ H ₈	CuI ₂ , KF(CsF), C ₇ H ₈
CsF, Pd(dba) ₃ *CHCl ₃ , C ₇ H ₈ , Ph ₃ P	(CuI, 2,2-bipyridine, MeOH, 50 °C) and then (KF, CH ₃ CN, 50 °C)
CsF, Pd(dba) ₃ *CHCl ₃ , C ₇ H ₈ , Ph ₂ PCH ₂ CH ₂ PPh ₂	(CuI, NH ₂ CH ₂ CH ₂ NH ₂ , MeOH, 50 °C) and then (KF, CH ₃ CN, 50 °C)
KF, Pd(OAc) ₂ , DMF, Ph ₃ P, 140 °C	(Cu(CF ₃ SO ₃) ₂ , 2,2-bipyridine, MeOH, 50 °C) and then (KF, DMF, 120 °C)
CsF, Pd(dba) ₂ , Ph ₃ P, C ₇ H ₈	[Cu(CF ₃ SO ₃) ₂ , NH ₂ CH ₂ CH ₂ NH ₂ , DMF, 120 °C] and then (KF, DMF, 120 °C)
—	[Cu(CF ₃ SO ₃) ₂ , DMEDA, KI, Na ₂ CO ₃ , DMF, 140 °C] and then KF
—	[Cu(CF ₃ SO ₃) ₂ , NH ₂ CH ₂ CH ₂ NH ₂ , MeOH, 50 °C] and then (KF, DMF, 120 °C)

Another synthesized precursor for the introduction of a fluorine atom into the aromatic moiety of an amino acid is Ni^{II} complex of Schiff base with (S)-BPB and OTf-tyrosine (**485**) (see Scheme 9.77). This complex was synthesized from tyrosine and (S)-BPB followed by transformation of the resulting Ni^{II}-(S)-BPB-(S)-Tyr (**484**) by the reaction with TfCl to the OTf-derivative (**485**). To replace the substituent of OTf-complex **485** by the fluorine, various catalysts based on Pd complexes were investigated. Unfortunately, none of the substitution reactions



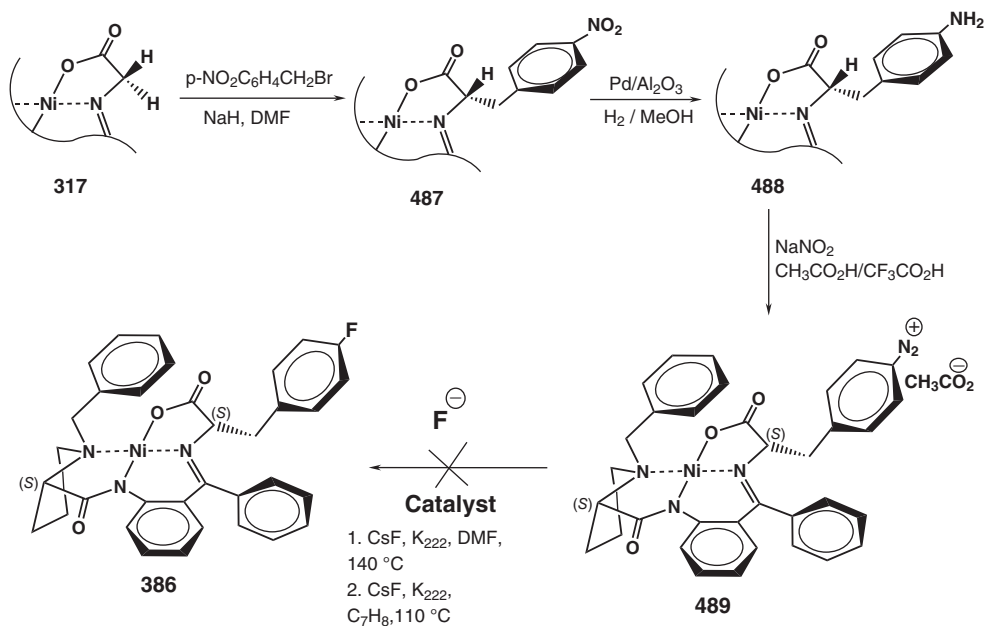
Catalysts based on Pd complexes

1. CsF , C_7H_8 , $\text{Pd}(\text{dba})_3$, PPh_3 , $110\text{ }^\circ\text{C}$
2. CsF , C_7H_8 , $\text{Pd}(\text{dba})_3$, $\text{PPh}_2\text{CH}_2\text{CH}_2\text{PPh}_2$, $110\text{ }^\circ\text{C}$
3. K_{222} , KF , C_7H_8 , $\text{Pd}(\text{PPh}_2)_2\text{Cl}_2$, $110\text{ }^\circ\text{C}$
4. CsF , C_7H_8 , $\text{Pd}(\text{PPh}_2)_4$, $110\text{ }^\circ\text{C}$
5. K_{222} , KF , C_7H_8 , $\text{Pd}(\text{PPh}_2)_2\text{Cl}_2$, $\text{PPh}_2\text{CH}_2\text{CH}_2\text{PPh}_2$, $110\text{ }^\circ\text{C}$

Scheme 9.77

presented above in Scheme 9.76 led to a detectable amount of a fluorinated Ni^{II} complex comprising fluorophenylalanine (**486**).

A classic example of fluorine atom introduction into the aromatic moiety through an amino derivative is the Balz–Schiemann reaction [211]. By alkylation of glycine complex **317** (see Scheme 9.78) with *para*-nitrobenzyl bromide, predominantly (*S,S*)-diastereomer (de >98%) of the Ni^{II} ion complex of Schiff base (*S*)-BPB with *para*-nitrophenylalanine (**487**) was obtained. The latter was reduced on $\text{Pd}/\text{Al}_2\text{O}_3$ to complex of *para*-aminophenylalanine (**488**) (with a yield of 45% after purification), which was then transformed to diazoderivative of phenylalanine (**489**).



Scheme 9.78

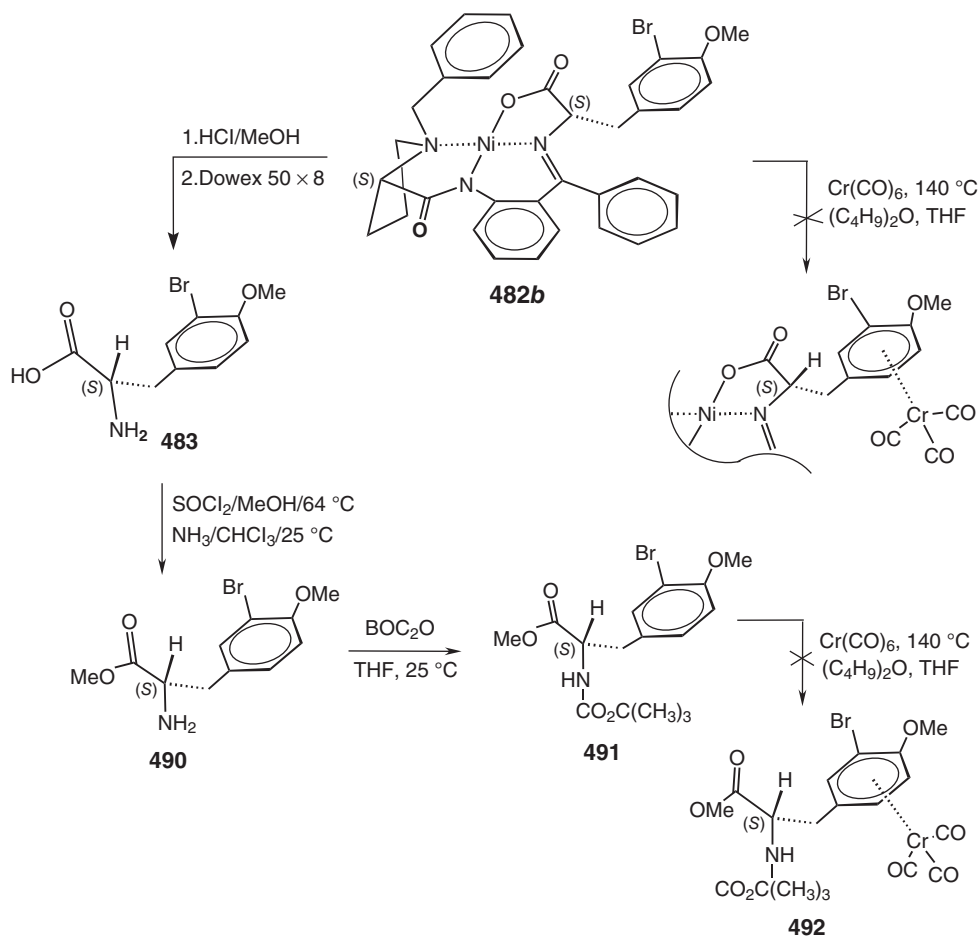
The attempt to introduce a fluorine atom into the aromatic moiety by interaction of complex **488** with NaNO_2 , $\text{CN}_3\text{SO}_2\text{H}$ in MeOH by addition of KF^{19} also proved to be unsuccessful as evidenced by ^{19}F NMR spectral analysis of the resulting product.

9.3.1.2 Nucleophilic Substitution in Activated Arenechromiumtricarbonyl Complexes

For introduction of the fluorine atom into the aromatic moiety, a nucleophilic substitution reaction in aromatic ring activated by forming a π -complex with $\text{Cr}(\text{CO})_3$ was also studied. However, an attempt to transform the square-planar complex of Ni^{II} ion of Schiff base of (*S*)-BPB and (*S*)-*O*-methyl-3-bromotyrosine (**482b**) to arenechromiumtricarbonyl π -complex by thermolysis [$\text{Cr}(\text{CO})_6$, $T = 140^\circ\text{C}$] failed because of decomposition of the starting complex (**482b**) (see Scheme 9.79) [209, 210].

After (*S*)-*O*-methyl-3-bromotyrosine separation from complex **482b**, followed by subsequent protection of the carboxyl (**490**) and amine groups into (*S*)-methyl ester-*N*-Boc-*O*-methyl-3-bromo tyrosine (**491**), an attempt was made to obtain arenechromiumtricarbonyl complex of protected amino acid (**492**) by the reaction of thermolysis, which did not lead to the desired results either.

For preparation of precursors containing fluorine atom in the activated aromatic ring, protected amino acids -(*S*)-methyl ester of *N*-Boc-*O*-methyl-3-fluorotyrosine (**495**) and (*S*)-methyl ester of *N*-Boc-3-fluorotyrosine (**496**) were synthesized by the standard procedure from the corresponding free amino acids (**493**, **494**, respectively). Initially, protection of carboxyl groups was carried

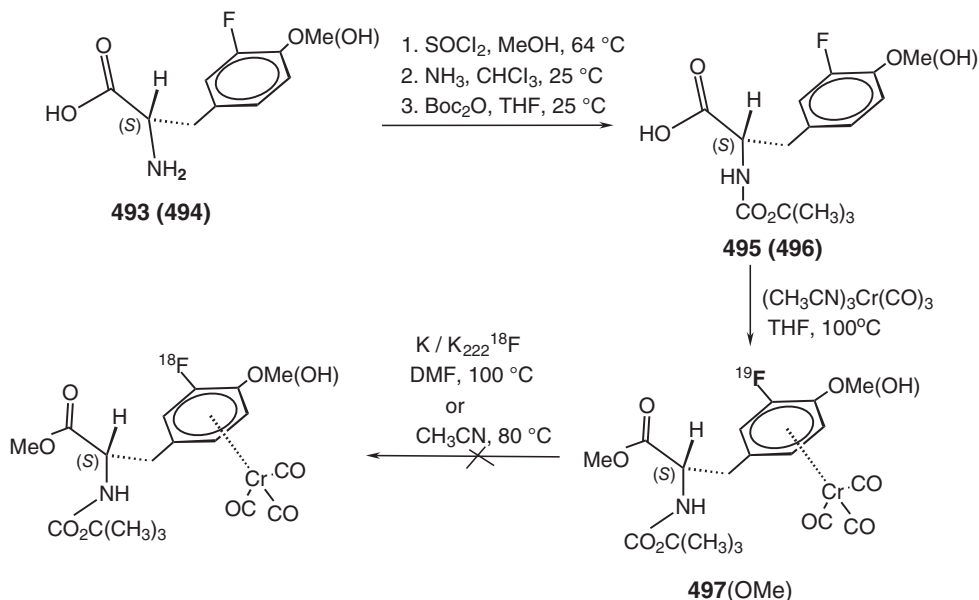


Scheme 9.79

out to obtain (S) -methyl ester of O -methyl-3-fluorotyrosine and (S) -methyl ester of 3-fluorotyrosine, then the amino group, resulting in formation of (S) -methyl ester of N -Boc- O -methyl-3-bromotyrosine (**495**) and (S) -methyl ester of N -Boc-3-fluorotyrosine (**496**) [210] (see Scheme 9.80).

Subsequent reactions of **495** with $(\text{NH}_3)_3\text{Cr}(\text{CO})_3$ or $(\text{CH}_3\text{CN})_3\text{Cr}(\text{CO})_3$ in 1,4-dioxane at 100°C , according to ^1H NMR and TLC, gave the corresponding complex with $\text{Cr}(\text{CO})_3$ (**497**). Studies have shown that by reacting complex **497** (without isolation) with thiophenol in THF, product of fluorine substitution by thiophenol group, is formed (based on elemental analysis).

Complex **497** was treated with $\text{K}[^{18}\text{F}]$ as a complex with kryptofix (K_{222}) in DMF and CH_3CN for 10 min (the experiments were performed in St. Petersburg at IHB RAS). Unfortunately, products of isotopic exchange $^{19}\text{F}/^{18}\text{F}$ were not revealed (TLC control using radiofrequency scanner). Decomposition of complex **497** by



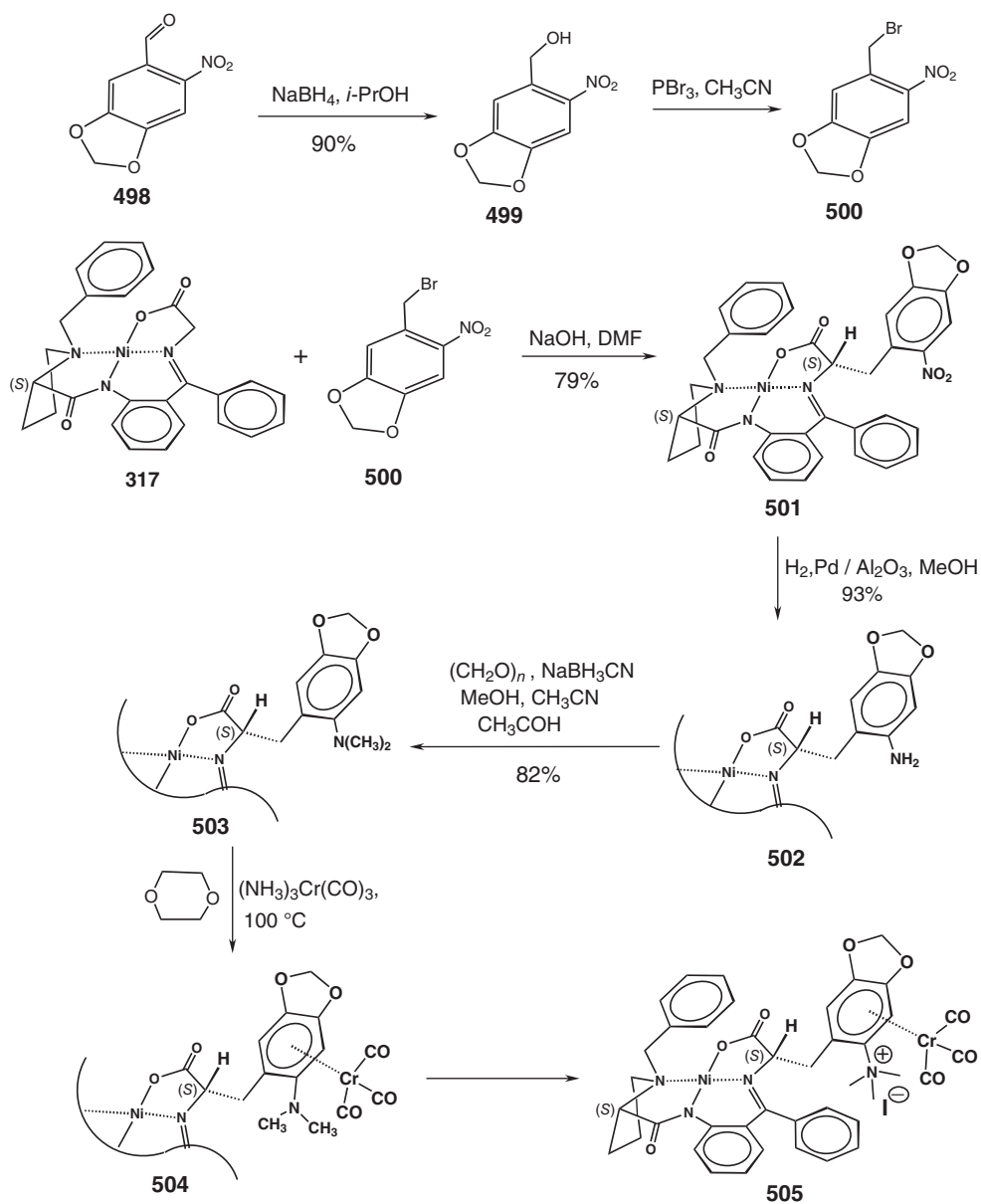
Scheme 9.80

action of iodine solution in THF and deprotection by hydroiodic acid led to initial amino acid **493** (control performed by chiral HPLC). One of the possible causes of isotopic exchange failure could be the incomplete removal of oxygen that led to decomposition of the initial arenechromiumtricarbonyl complex.

For introduction of a fluorine atom in the late stage of the synthesis, the precursor should contain ammonium leaving group $[\text{N}^+(\text{CH}_3)_3]$ in stoichiometric activated complex of transition metal. Analysis of published data shows that the ammonium group $[\text{N}^+(\text{CH}_3)_3]$ is an easily leaving one and facilitates further purification of derived precursors because of significant differences in the properties of the original and derived compounds [212].

It should be assumed that Ni^{II} complex of Schiff base of (*S*)-BPB and (*S*)-2-amino-3-(3,4-methylenedioxy-6-dimethylaminophenyl)propionic acid (**503**) can form stable π -complexes, and selectively in the desired aromatic ring, since it contains two donor groups $-\text{N}(\text{CH}_3)_2$ and $-\text{OCH}_2\text{O}-$ (see Scheme 9.81). This complex would allow to easily pass to the desired $\text{N}^+(\text{CH}_3)_3$ group, and therefore pass to the promising precursor **505** for the introduction of a fluorine atom. Furthermore, the amino acid obtained by decomposition of complex **503** can be also used as a precursor containing $\text{N}^+(\text{CH}_3)_3$ group.

To synthesize precursor **505**, 3,4-methylenedioxy-6-nitrobenzyl bromide (**500**) was obtained from commercially available 3,4-methylenedioxy-6-nitrobenzaldehyde (**498**) by reduction to 3,4-methylenedioxy-6-nitrobenzyl alcohol (**499**) and subsequent substitution of the hydroxyl group by bromine atom. Complex **501** was obtained by alkylation of glycine complex (**317**) with 3,4-methylenedioxy-6-nitrobenzyl bromide (**500**) (see Scheme 9.81). Further



Scheme 9.81

reduction of complex **501** to complex **502** was conducted in $\text{Al}_2\text{O}_3/\text{MeOH}/\text{Pd}$ system. Complex **503** was obtained by methylation of complex **502**. Studies on obtaining appropriate complex **503** with the stoichiometrically activated aromatic moiety are currently ongoing.

9.3.1.3 A New Method for Synthesis of Precursors for Known Radiotracer

(*S*)-*O*-2-([^{18}F]Fluoroethyl) Tyrosine

Obviously, the simplest method for production of labeled radiotracers based on aromatic moiety containing amino acids is labeling the lateral aliphatic substituent of the aromatic moiety. An extremely popular precursor built for this is the derivative of (*S*)-*O*-2-(tosylethyl)tyrosine [213]. Meanwhile, this precursor has a number of disadvantages, for example, the partial amino acid racemization during fluorination. It was expected that chiral Ni^{II} complexes would prove convenient protecting groups for (*S*)-*O*-2-(tosylethyl)tyrosine, since instead of amino acid racemization in the complex epimerization of the amino acid moiety would be observed, leading to an excess of its (*S*)-form.

As a starting precursor, chiral complex $\text{Ni}^{\text{II}}\text{-(S)-BPB-(S)-Tyr}$ (**484**), synthesized according to Scheme 9.77 [214, 215], was used. Tyrosine complex **484** was alkylated by ethylenechlorohydrin in the presence of various bases and in various solvents (see Scheme 9.82). When the reaction is carried out in CH_2Cl_2 along with the desired product **508** condensation, by-product **506** is also formed (see Figure 9.31).

The optimal condition turned out O-alkylation of complex **484** by ethylenechlorohydrin in a mixture of benzene/DMF 2/5 in the presence of potassium hydroxide and a phase transfer catalyst at ambient temperature. The yield of intermediate alcohol **507** (Scheme 9.82) was 70.5%.

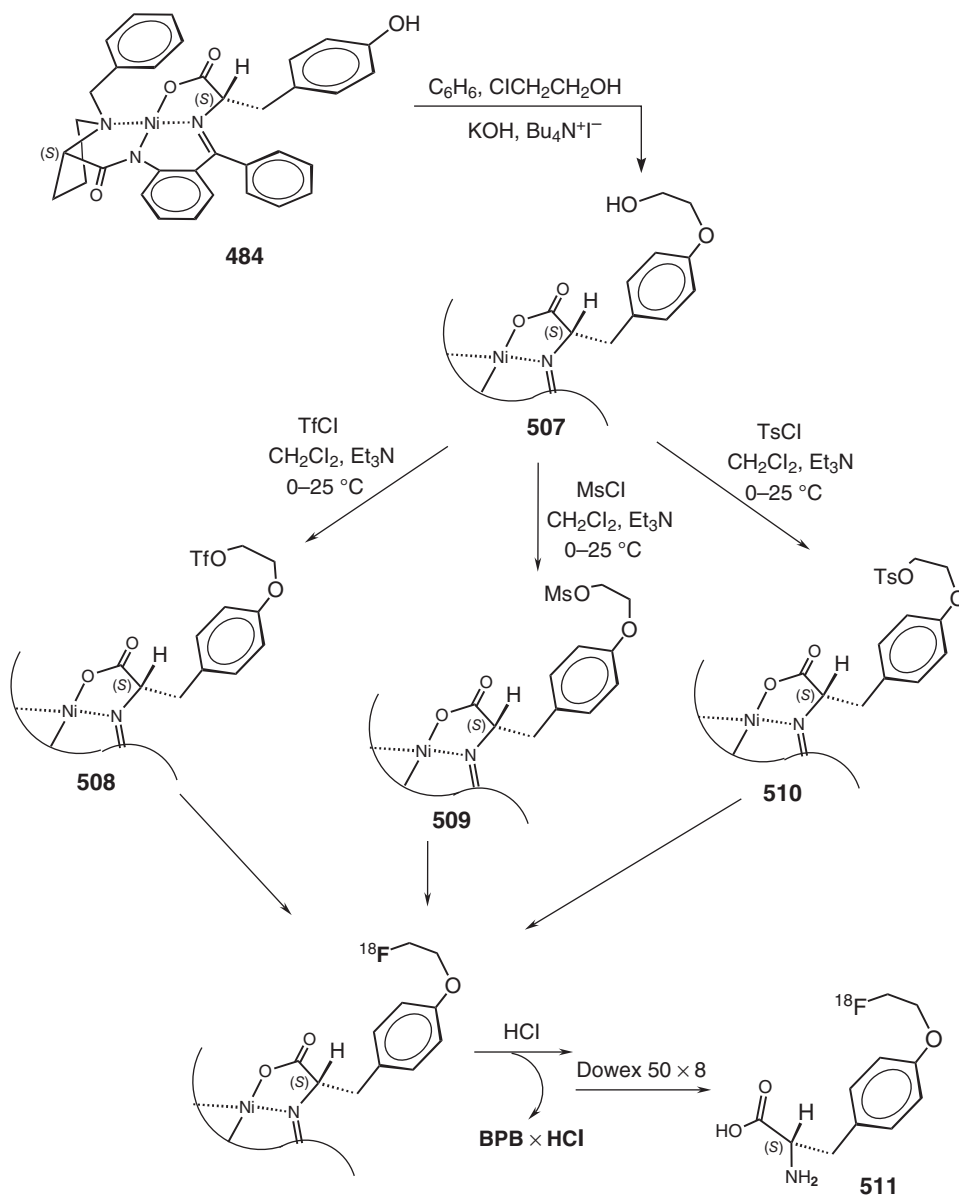
By reaction of the obtained alcohol **507** with TfCl , MsCl , and TsCl in methylene chloride, the corresponding derivatives **508–510** were produced in chemical yields 68%, 60%, and 67%. The synthesis of the radiotracer by ^{18}F labeling was done at IHB RAS.

The best results are observed in the case of precursor **510** containing OTs-group. Decomposition, isolation, and final purification of [^{18}F]FET **511** do not present special difficulties. The preliminary data showed 96% enantiomeric and 99% radiochemical purity of the product with a 25% radiochemical yield within 60 min. The developed technique is extremely simple and cheap, which makes possible the introduction of [^{18}F]FET **511** into clinical practice of PET. Thus, a new method for the asymmetric synthesis of known radiotracer for PET – (*S*)-[^{18}F]fluoroethyl-tyrosine and its precursors was developed.

9.3.2

Synthesis of Precursors for Producing a New Radiotracer (*S*)-4-[^{18}F]Fluoroglutamic Acid

The substituted (*S*)-[^{18}F]fluoroglutamic acid [(*S*)-4-[^{18}F]Glu] can be a new interesting radiotracer. It is known that the natural (*S*)-glutamic acid is used by the organism as a source of amino group for the synthesis of nonessential amino acids



Scheme 9.82

in vivo. It can be expected that rapidly growing cancerous cells will consume glutamic acid faster than the other amino acids of the organism tissue. Thus, (S)-4-[^{18}F]Fglu would be accumulated selectively in tumor cells and thus be a good PET radiotracer. Based on this assumption, it becomes advisable to develop methods for its asymmetric synthesis.

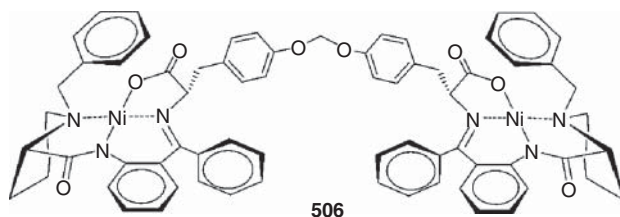
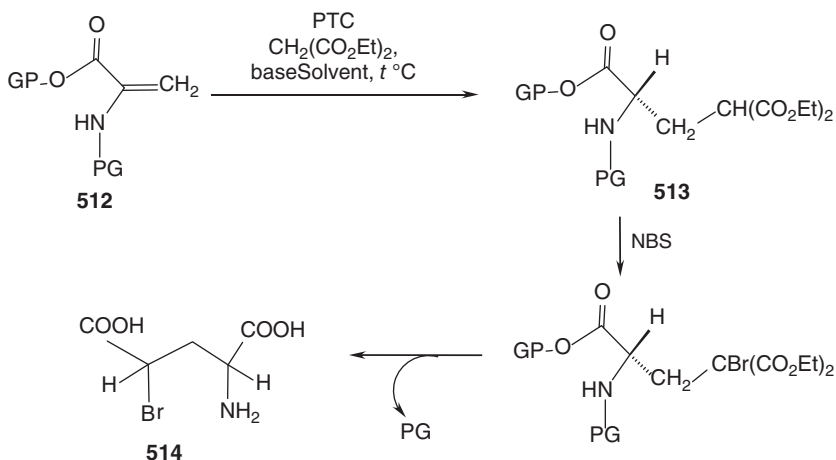


Figure 9.31 Condensation by-product **506**.

Methods described in the literature for the stereoselective synthesis of (*S*)-4-FGlu are multistep and very slow. One of the possible approaches to the synthesis of (*S*)-4-FGlu is a nucleophilic substitution of the bromine by a fluorine atom in a protected bromoglutamic acid – (*S*)-4-BrGlu. However, the synthesis of the (*S*)-4-BrGlu, even in its protected form, is a serious problem due to its extremely low stability.

9.3.2.1 Catalytic Synthesis Method

Theoretically, it could be assumed that the catalytic asymmetric addition of malonic ester to the prochiral derivative of dehydroalanine (**512**), followed by bromination of the resulting derivative of (*S*)-4-carbomethoxy glutamic acid (**513**), is the easiest way to obtain a protected (*S*)-4-BrGlu (**514**) (see Scheme 9.83).

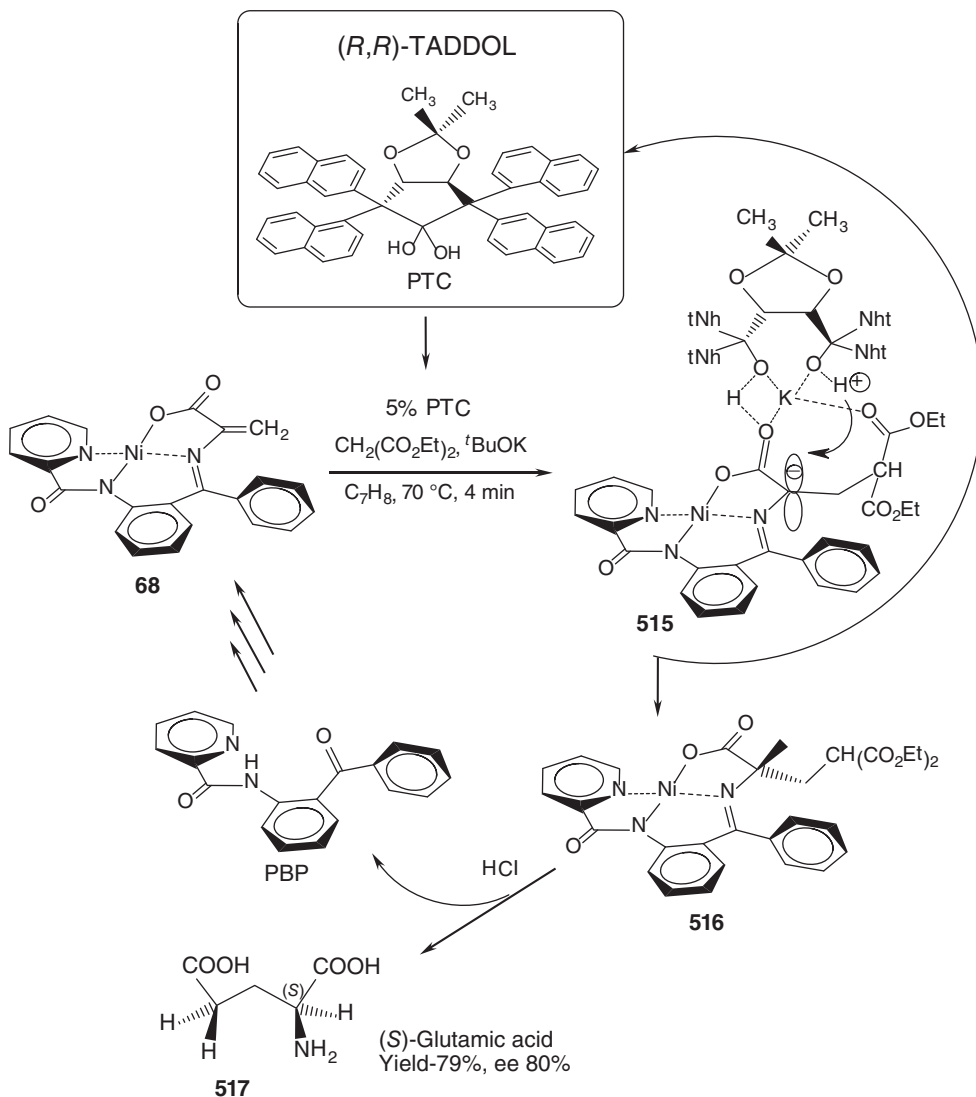


Scheme 9.83

For this purpose, in INEOS RAS (Moscow) the Michael acceptor was synthesized, which is a Ni^{II} complex of Schiff base of (2-benzoylphenyl)amidopyridyl-2-carboxylic acid (PBP) and *o*-aminobenzophenone (**65a**) [216] (see Section 8.1). Condensation of complex **65a** with formaldehyde yields the serine complex, subsequent dehydration of which, through an intermediate O-acetylation and deacetoxylation of the acetylserine complex, leads to achiral dehydroalanine complex **68** (see Section 8.1).

The next task was to implement the catalytic asymmetric Michael reaction using achiral substrate **68**. The use of chiral bases as catalysts allowed conducting the reaction asymmetrically. As such chiral bases, alcoholate (4*R*,5*R*)-2,2-dimethyl-*a,a,a',a'*-tetraphenyl-1,3-dioxolane-4,5-dimethanol [(*R,R*)-TADDOL] was used, obtained directly from the reaction mixture of (*R,R*)-TADDOL (**33a**) and a solid base (see Chapter 8).

An interesting feature of this asymmetric transformation is the fact that the stereo-differentiating stage of the process is asymmetric protonation of intermediate carbanion (**515**), which is obtained at the first step of addition of anion of the malonic ester to substrate **68** (see Scheme 9.84). Probably the TADDOL molecule



Scheme 9.84

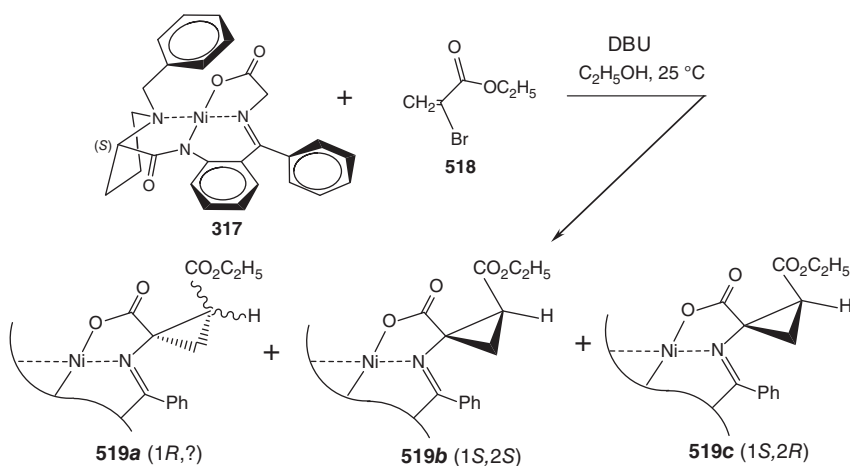
is located near the carbanion, chelating potassium cation and creating a chiral carbanion environment. Preferred transition of one of the TADDOL's protons on one side of an intermediate carbanion completes the reaction returning potassium TADDOL catalyst into the reaction mixture. After acid hydrolysis of the resulting complex of glutamic ester (**516**), target amino acid **517** was isolated with 80% enantiomeric purity.

Thus, the extremely rare catalytic process with stereodifferentiating step of asymmetric protonation was realized [217].

Unfortunately, the purity of the amino acid for PET purposes should be no less than 95%. In connection with this, the research of bromination of intermediate complex **516**, the enantiomeric purity of which was only 80%, was inappropriate, and therefore it was necessary to find an alternative method for the synthesis of protected (*S*)-4-BrGlu (**514**). It was logical to use the stoichiometric approach to this synthesis using a chiral glycine complex **317**, which has been successfully used in the asymmetric synthesis of (*S*)-*O*-methyl-3-bromotyrosine (**483**) (see Section 9.3.1.1).

9.3.2.2 Stoichiometric Approach to the Synthesis of 4-Fluoroglutamic Acid Precursors

Reaction of chiral glycine complex **317** with α -bromoacrylic ester (**518**) in ethanol promoted by diazobicycloundecene (DBU) leads to the formation of three products [218] (see Scheme 9.85).



Scheme 9.85

By silica gel chromatography three fractions were isolated, which, according to elemental analysis and ^1H NMR spectra, represent (in accordance with the decrease of their mobility on SiO_2) individual diastereomers of Ni^{II} ion complex of Schiff base of chiral auxiliary (*S*)-BPB with monoesters of stereoisomers of 1-aminocyclopropane-1,2-dicarboxylic acid [219] (**519a–c**). It was impossible to identify the absolute configuration of complex **519a** because of its small quantity (7%).

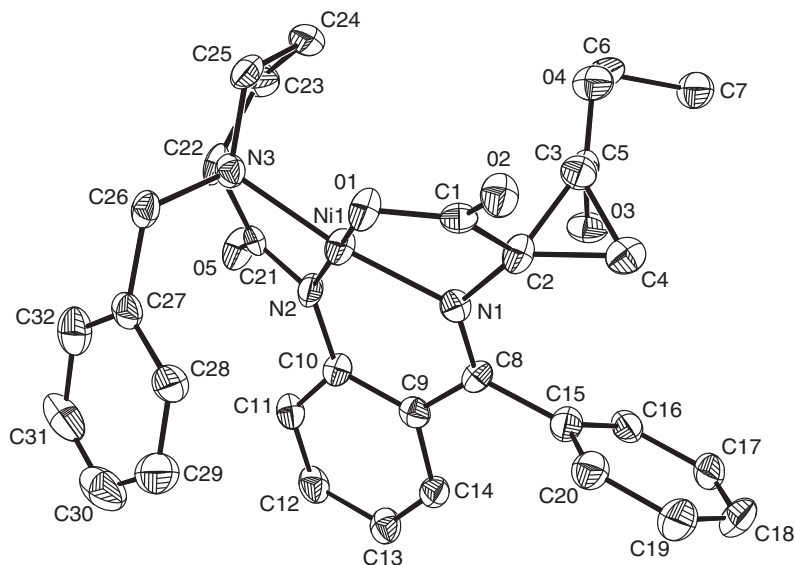


Figure 9.32 Molecular structure of complex **519c** with 50% probability of ellipsoids of anisotropic displacements defined by XRD.

According to XRD analysis, diastereomeric complex **519c** contains a fragment of (1*S*,2*R*)-1-aminocyclopropane-1,2-dicarboxylic acid (see Figure 9.32), and complex **519b** – (1*S*,2*S*)-1-aminocyclopropane-1,2-dicarboxylic acid (see Figure 9.33). The ratio of **519b** and **519c** determined by ^1H NMR spectroscopy is 1/1.

Obviously, the formation of cyclic complexes **519a–c** instead of the expected linear Michael adduct – Schiff base of monoether of 4-BrGlu – is a consequence of the secondary reaction of this derivative. We can assume that the complex of Ni^{II} ion of Schiff base of (*S*)-BPB, formed at the first step, is cyclized with monoethyl ether of 4-BrGlu (**520**) under the reaction conditions by the influence of bases by E_2 or $\text{E}_{1\text{cB}}$ mechanism (see Scheme 9.86).

By decomposition of the obtained Ni^{II} ion complexes of Schiff base with (*S*)-BPB and 1-aminocyclopropane-1,2-dicarboxylic acids (**519a–c**), the individual isomers of 1-aminocyclopropane-1,2-dicarboxylic acid can be obtained, which is not an easy synthetic task. In contrast to the racemic form of this amino acid [220], there is no information in the literature about synthesis of optically active forms of these compounds, although they are interesting analogs of glutamic acid [221].

For preparation of Michael adduct **520**, the cyclization step should be excluded, which is possible when sterically hindered amines are used as a base instead of the DBU. However, in case of using 2,6-diethylpyridine, the addition reaction of **317** to **518** does not occur even under heating in ethanol. When the reaction is conducted in the presence of a stronger sterically hindered base (*i*-Pr) $_2\text{NH}$, a mixture

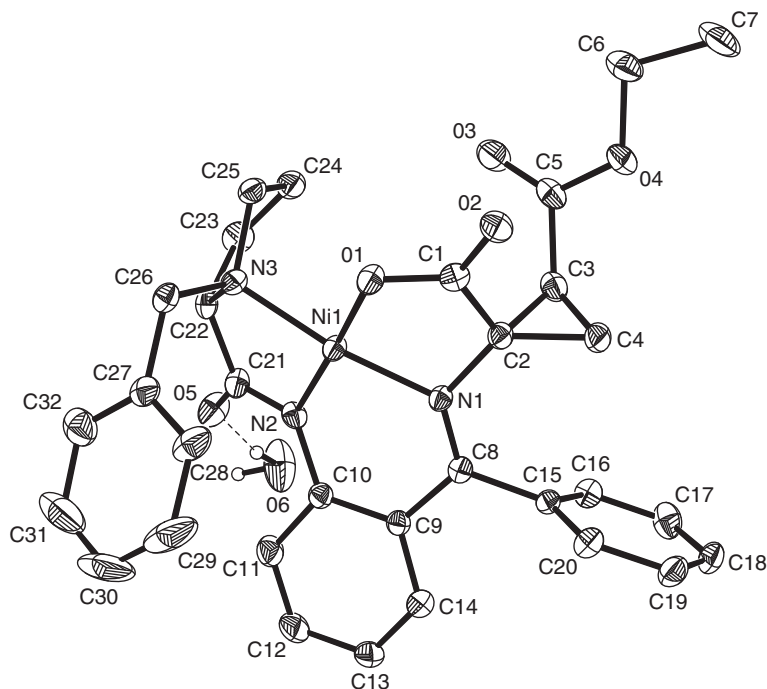
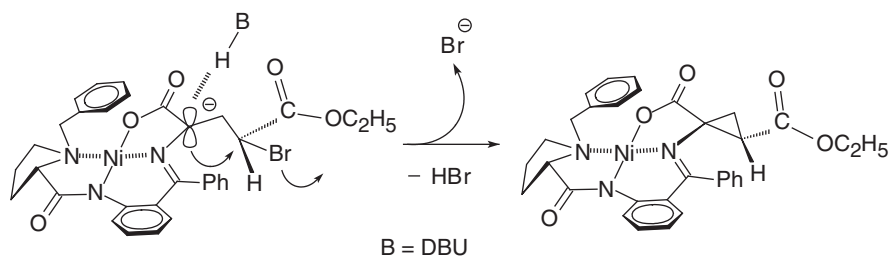


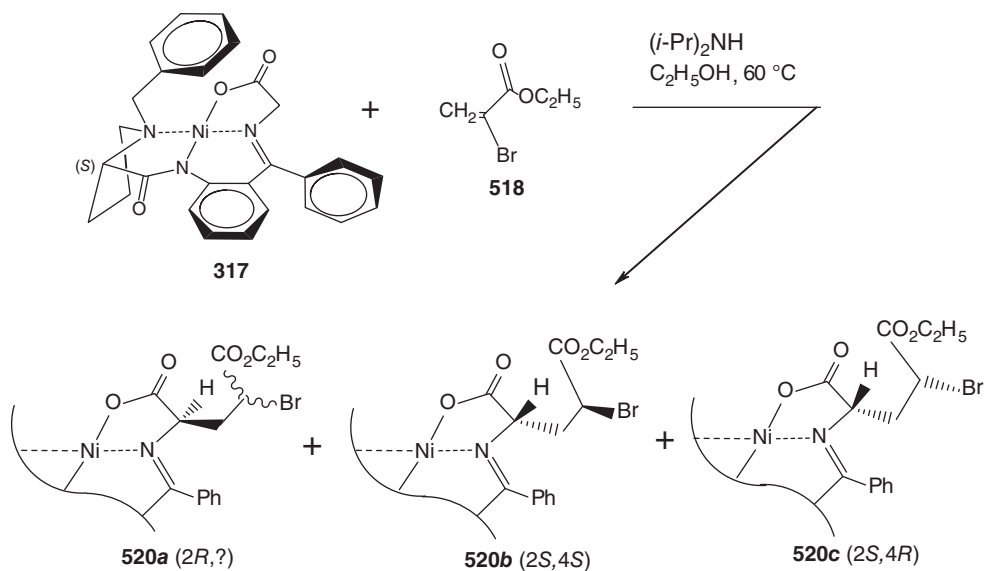
Figure 9.33 Molecular structure of complex **519b** with 50% probability of ellipsoids of anisotropic displacements defined by XRD.



Scheme 9.86

of diastereomeric complexes **520a–c** containing a fragment of monoethyl ether of 4-BrGlu is formed [222] (see Scheme 9.87).

During separation of products by preparative TLC, it was possible to isolate diastereomer **520c** as an individual compound. According to elemental, ^1H , ^{13}C NMR, and XRD analyses (see Figure 9.34), this diastereomer is a Ni^{II} complex of Schiff base of (*S*)-BPB with monoether of (2*S*,4*R*)-4-bromoglutamic acid. Two other diastereomeric complexes **520a** and **520b** were isolated as a mixture in a ratio of 1/11.



Scheme 9.87

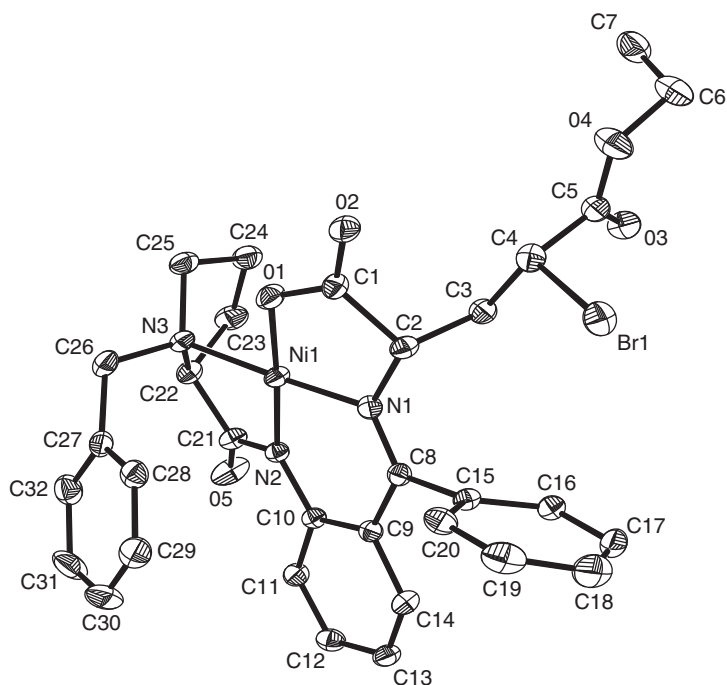


Figure 9.34 Molecular structure of complex **520b** with 50% probability of ellipsoids of anisotropic displacements defined by XRD.

Total yield of diastereomers **520a–c** is 80%. According to ^1H NMR spectrum, the diastereomeric ratio of **520a/520b/520c** is 1/11/22. Predominant diastereomer **520c** was isolated in a total yield of 52%. As by-products, **519b** and **519c** complexes in minor amounts (total <5%) were identified in the reaction mixture.

Treating **520c** with DBU in ethanol results in its selective transformation to **519c**, without formation of **519a** and **519b**. Cyclization proceeds probably either by the E_2 mechanism, including the separation of α -proton of the amino acid fragment under the influence of DBU with simultaneous intramolecular substitution of bromine ion and closure of a three-membered ring, or by E_1cB type with sequential separation of α -H to form the carbanion followed by cyclization with the release of Br^- ion (see Scheme 9.86).

Stereochemistry of transformation may be correctly described using both E_2 and E_1cB mechanisms. We can assume that formation of **519b** under experimental conditions of addition of **518** to **317** catalyzed by DBU is due to the intramolecular cyclization of initially formed **520b** (second by the amount of diastereoisomers). Based on this, the absolute configuration of amino acid fragment of **520b** can be identified as (2*S*,4*S*). Decomposition of complex **520c** by the standard method followed by purification of the amino acid by ion exchange chromatography resulted in isolation of 4-hydroxyglutamic acid (presumably based on ^1H NMR and GLC).

Analysis of published data devoted to nucleophilic substitution in aliphatic compounds indicates that the nucleophilic substitution of the bromine atom by a fluorine atom is inevitably accompanied by formation of intermediate products. Therefore, selection of experimental conditions for selective substitution of the bromine atom by fluorine is required. To monitor reaction by HPLC, it is necessary to synthesize the complex of Ni^{II} ion with Schiff base of (*S*)-BPB and monomethyl ether of 4-FGlu, decomposition of which would allow obtaining of 4-FGlu.

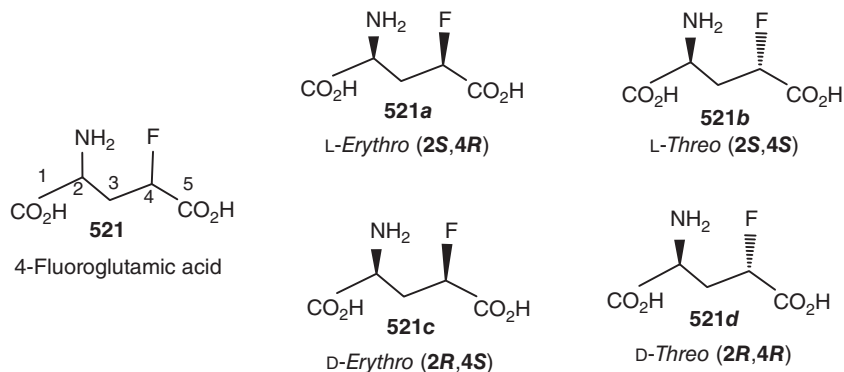
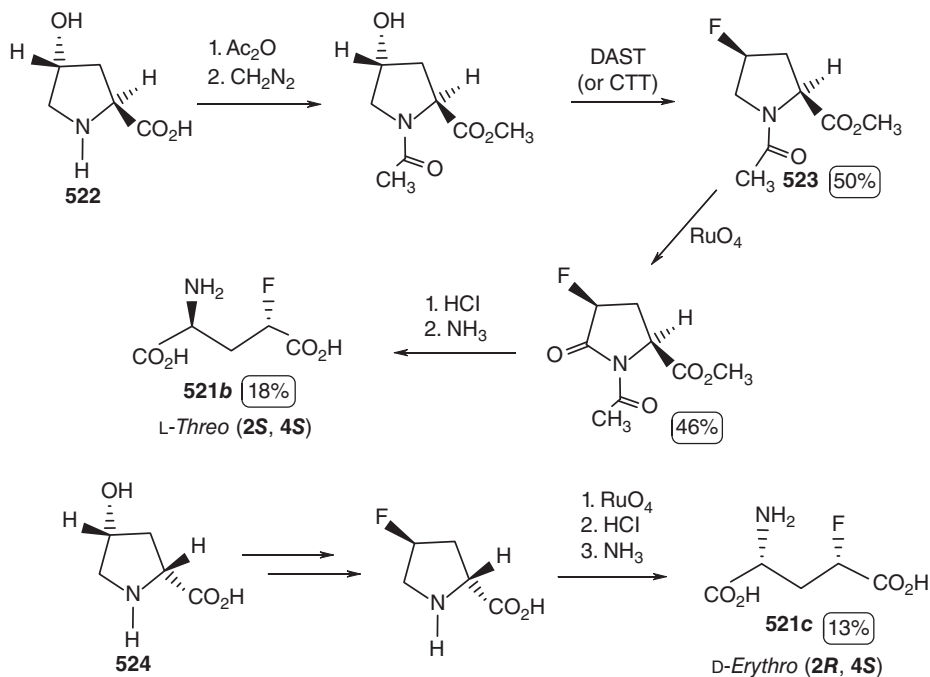
9.3.3

Asymmetric Synthesis of 4-Fluoroglutamic Acid

In the structure of 4-fluoroglutamic acid (**521**) there are two stereocentres, so it is in the form of four isomers – *L*-*erythro* (2*S*,4*R*), *L*-*threo* (2*S*,4*S*), *D*-*erythro* (2*R*,4*S*), and *D*-*threo* (2*R*,4*R*) (see Figure 9.35).

Hudlicky and Merola in 1991 [223] developed the synthesis of all four stereoisomers of 4-fluoroglutamic acid (**521**) using commercially available *trans*-4-hydroxy-*L*-proline (**522**). The authors, for the first time, prepared the *L*-*threo* (**521b**) and *D*-*erythro* (**521c**) isomers from the *trans*- and *cis*-hydroxyprolines, respectively (Scheme 9.88).

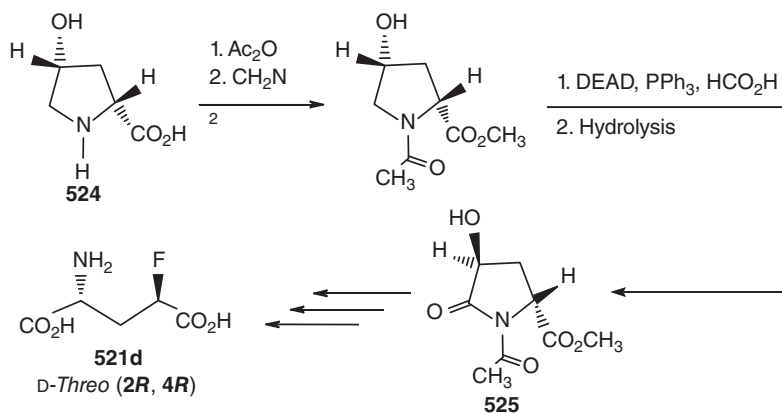
Fluorination was carried out using diethylaminosulfotrifluoride (DAST) or 2-chloro-1,1,2-trifluoroethylethylamine (CTT). Product **523** was obtained with a reversed configuration and in 50% yield. Subsequent oxidation with ruthenium oxide (yield 46%) and hydrolysis allow obtaining amino acid **521b** in 18% yield based on the starting hydroxyproline (**522**). The *D*-*erythro* isomer (**521c**) was

Figure 9.35 Stereoisomeric forms of 4-FGLu (**521**).

Scheme 9.88

obtained by the same scheme using *cis*-4-hydroxy-*D*-proline (**524**) with an overall yield of 13% [223] (see Scheme 9.88).

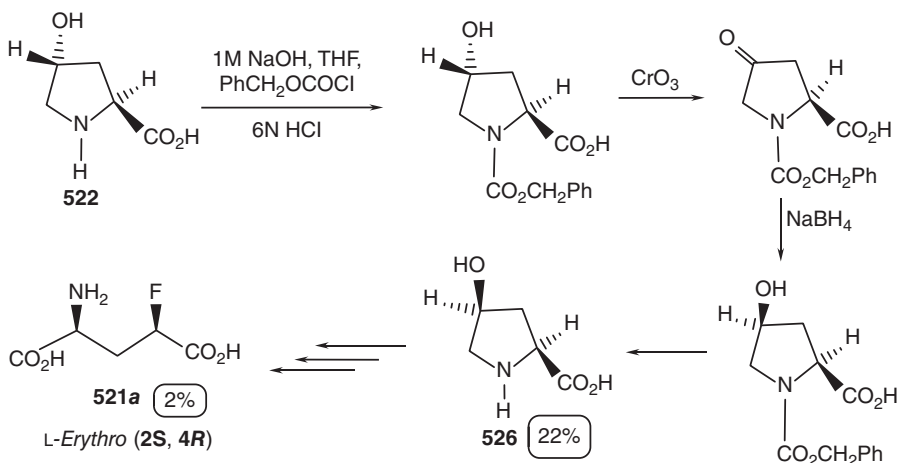
Later, Hudlicky extended this method for preparation of *D*-threo (**521d**) and *L*-erythro (**521a**) isomers from commercially available *trans*-4-hydroxy-*L*-proline (**522**) and *cis*-4-hydroxy-*D*-proline (**524**). Methyl ether of *N*-acetyl-*trans*-4-hydroxy-*D*-proline (**525**) was obtained from *cis*-4-hydroxy-*D*-proline (**524**) in a yield of 21–37% by Scheme 9.89 [224].



Scheme 9.89

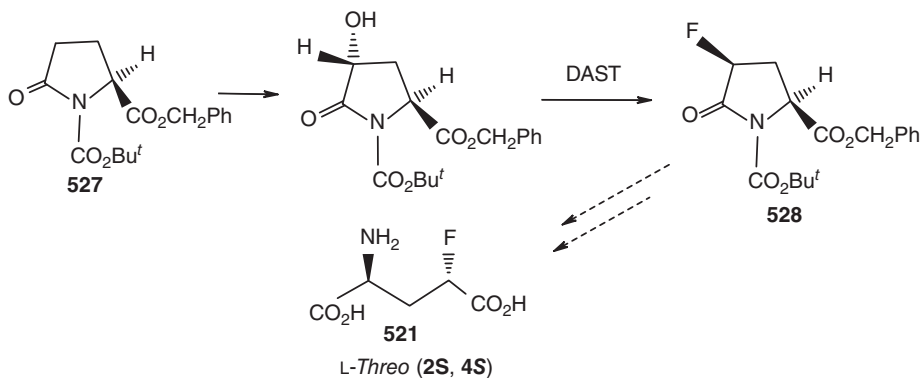
The main reaction is the configuration inversion of the hydroxy group in the ring in Mitsunobu reaction (DEAD, Ph_3P , HCO_2H). D-threo isomer 4-FGlu (**521d**) was prepared from compound (**525**) as a result of chemical transformations by Scheme 9.89.

Synthesis of L-erythro isomer (**521a**) based on *trans*-4-hydroxy-L-proline (**522**) which was converted to *cis*-4-hydroxy-L-proline, using the redox reaction sequence, is outlined in Scheme 9.90. *Cis*-4-hydroxy-L-proline (**526**) was obtained in 22% yield relative to compound (**522**). L-erythro isomer 4-FGlu (**521a**) was isolated in the manner described above (see Scheme 9.90). Yield of **521a** amino acid was only 2% [224].



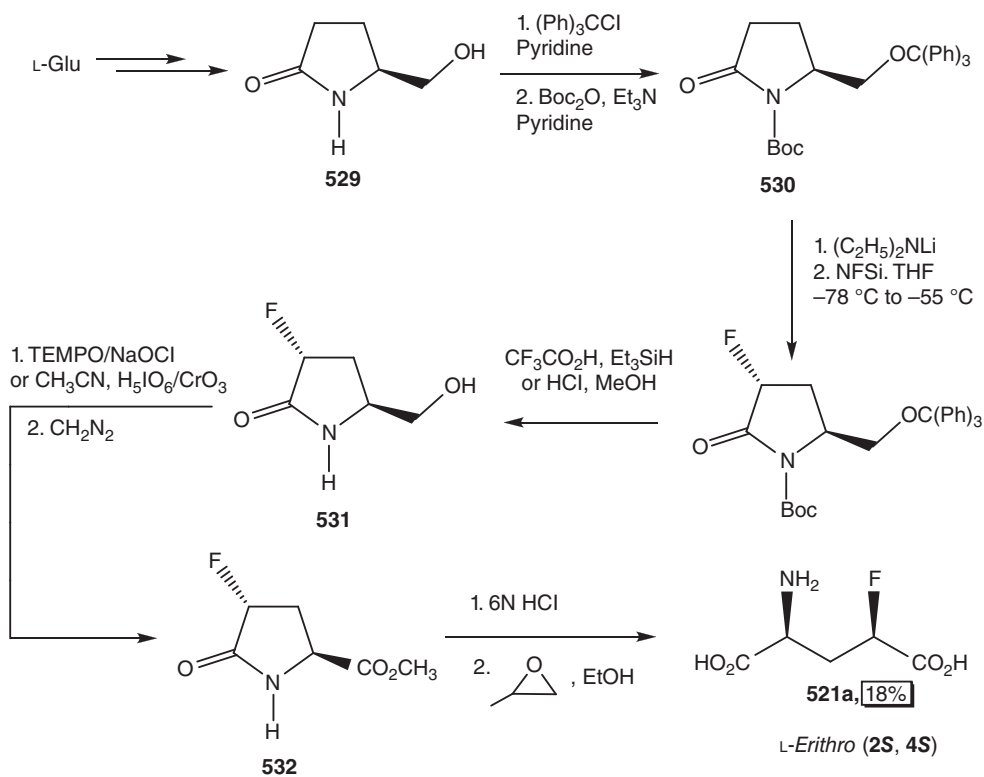
Scheme 9.90

The synthesis of compound **528** from benzyl ester of *N*-tert-butoxycarbonyl-L-pyrogutamic acid (**527**) [223] with insignificant yield (only 12%) was also described (see Scheme 9.91).



Scheme 9.91

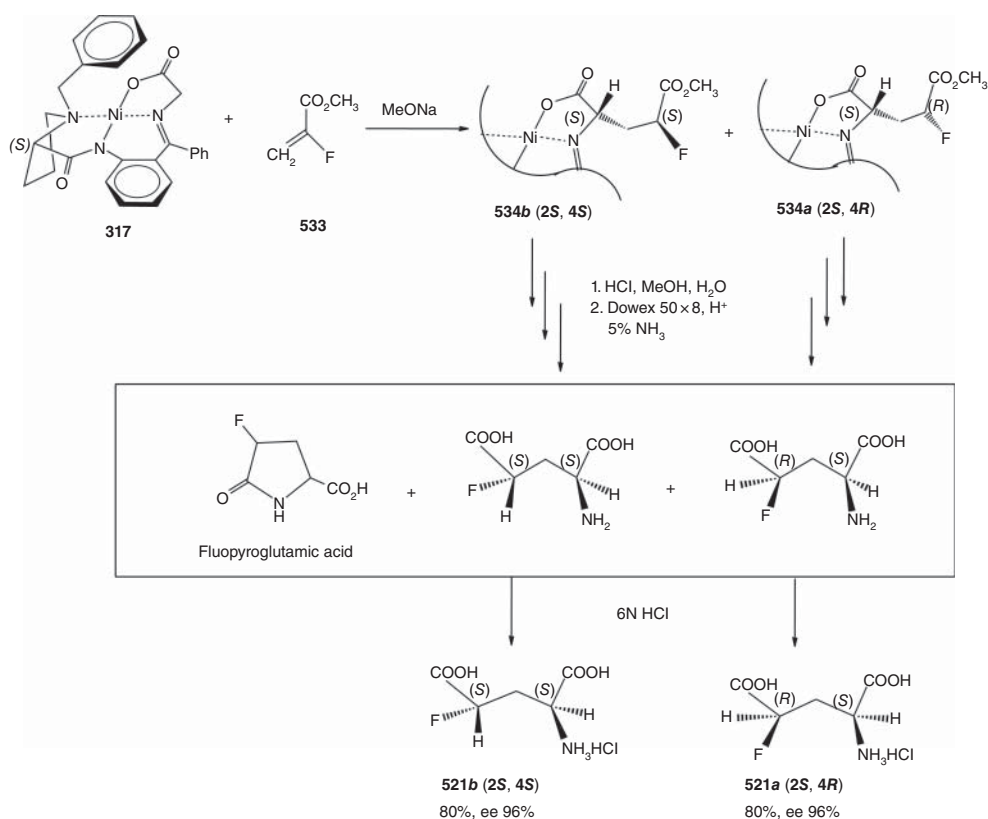
Coward and Konas [225] obtained *L*-erythro-4-fluoroglutamic acid (**521a**) from *L*-pyroglutaminol (**529**), which is commercially available and easily synthesized from *L*-glutamic acid by the Pickering's method [226] (see Scheme 9.92).



Scheme 9.92

A key step in the synthesis is the electrophilic fluorination of pyroglutaminol derivative (**530**) by *N*-fluorobenzenesulfonimide (NFSi). This method allows getting a single isomer of 3-fluoro-substituted pyroglutaminol (**531**). Further oxidation and etherification led to compound **532**, which is hydrolyzed to form *L-erythro*-4-fluoroglutamic acid (**521a**) with an overall yield of 18%. As can be seen from the above, obtaining enantiomerically and diastereomerically pure 4-fluoroglutamic acids is a serious problem, which implies the need for more simple methods for their synthesis.

Synthesis of diastereomerically and enantiomerically pure isomers 4-FGlu (**521**) was done by Michael condensation of chiral glycine complex (**317**) with methyl ether of α -fluoroacrylic acid (**533**) in methanol in the presence of sodium methylate (see Scheme 9.93).



Scheme 9.93

The reaction is conveniently monitored by TLC [SiO₂, eluent AcOEt-CHCl₃ (2/3)] following the disappearance of traces of the starting glycine complex and establishment of thermodynamic equilibrium between the

diastereoisomeric complexes of adducts. Thus, as expected, mainly Ni^{II} ion complexes of Schiff base of (*S*)-BPB and monomethyl ether of 4-FGlu (**534**) were formed.

The resultant stereoselectivity at the α -carbon atom of the amino acid fragment is subject to thermodynamic control, and after the establishment of equilibrium in a basic medium, the ratio of isomers (*2S*)/(*2R*) is $>97:1$. Diastereoselectivity at γ -carbon atom is kinetically controlled and determined by the rate of protonation of the secondary carbanion from *si*- or *re*-side of the Schiff base plane.

Complex **534** as a mixture of (*2S,4R*)- and (*2S,4S*)-stereoisomers was isolated by column chromatography in 70% overall yield. The ratio of **534a**/**534b** was determined by ^1H NMR and equaled 1/1.5. Separation of diastereomeric complexes **534a** and **534b** was performed by column chromatography on *Toyopearl HW-55F* resin, [eluent C_6H_6 -THF (7/2)]. Structures of isolated complexes were established by ^1H , ^{19}F , and ^{13}C NMR spectra, elemental analysis, and specific rotation angles. The assignment of the absolute configuration of the γ -carbon atom of amino acid fragment of complex **534a** with higher mobility on resin (R_f) was carried out by X-ray analysis. It was found that diastereomeric complex **534a** had (*2S,4R*)-configuration of the amino acid fragment (Figure 9.36) and the amino acid moiety of complex **534b** was assigned (*2S,4S*)-absolute configuration, respectively.

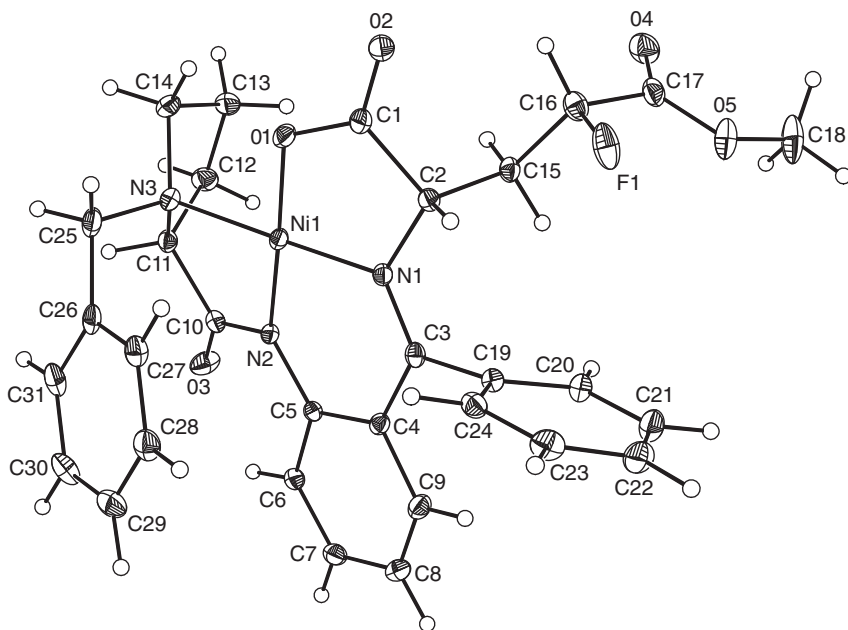


Figure 9.36 Molecular structure of complex **534a** with 50% probability of ellipsoids of anisotropic displacements defined by XRD.

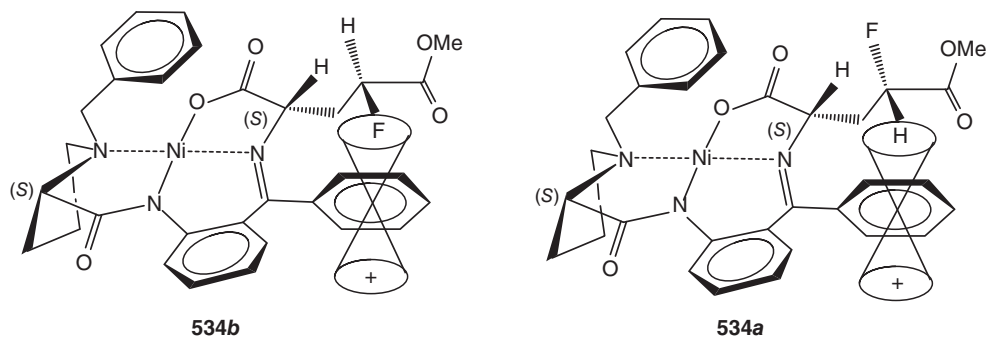


Figure 9.37 Magnetic shielding of nuclei of complexes **534a,b**.

This was additionally confirmed by the data of ^1H and ^{19}F NMR spectra of the complexes. Chemical shifts of the F atom signals in ^{19}F NMR spectra of diastereomeric complexes vary by more than 5 ppm, whereas in complex **534a** these signals are in stronger fields due to ingress of the F atom into the cone of anisotropy of benzene ring, as illustrated in Figure 9.37.

For this reason, in ^1H NMR spectrum of **534b** complex the chemical shifts of γ -hydrogen atom signal of 4-FGlu fragment are displaced by 0.12 ppm to stronger fields in comparison with complex **534a**.

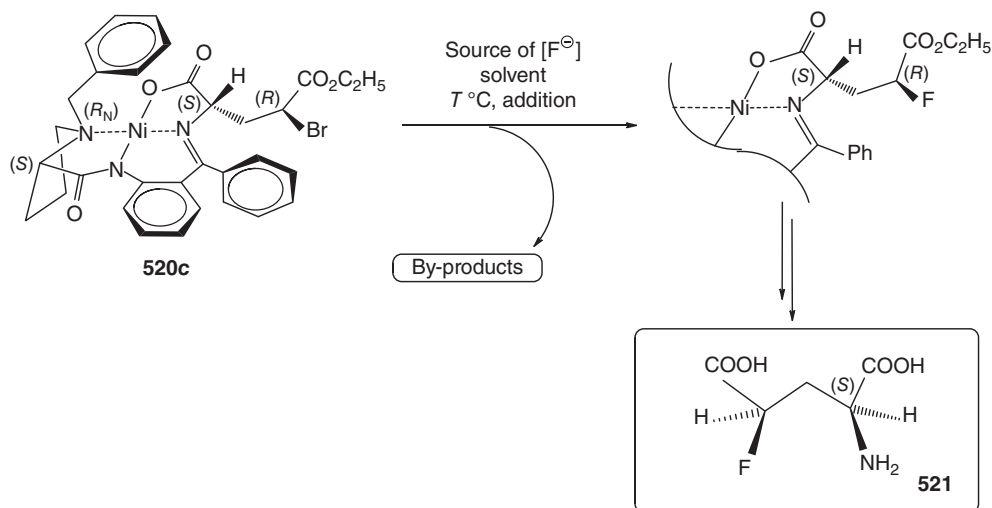
Decomposition of individual complexes **534a** and **534b** with simultaneous hydrolysis of the ester group and ion-exchange isolation of amino acids (see Scheme 9.93) followed by hydrolysis of pyroglutamic acids in 6 N HCl yielded individual stereoisomers of 4-fluoroglutaric acid – (2*S*,4*R*)-4FGlu (**521a**) and (2*S*,4*S*)-4FGlu (**521b**) in the form of hydrochlorides.

After working out methods for the synthesis of Ni^{II} ion complex of Schiff base with (*S*)-BPB and monoether of 4-FGlu (**534**), and 4-FGlu itself (**521**), it was possible to optimize the conditions for nucleophilic substitution of the bromine atom in the chiral complex of 4-BrGlu (**520c**) by a fluorine atom. The substitution reaction is presented in Scheme 9.94.

The reactions of complex **520c** with AgF, KF, and CsF in various solvents (C_6H_6 , CH_2Cl_2 , THF, CH_3CN , EtOH, Me_2CO , $t\text{BuOH}$) did not lead to products of bromine atom substitution by fluorine. The main byproducts are complexes comprising fragments of cyclopropane (**519**), as described above (see Scheme 9.85).

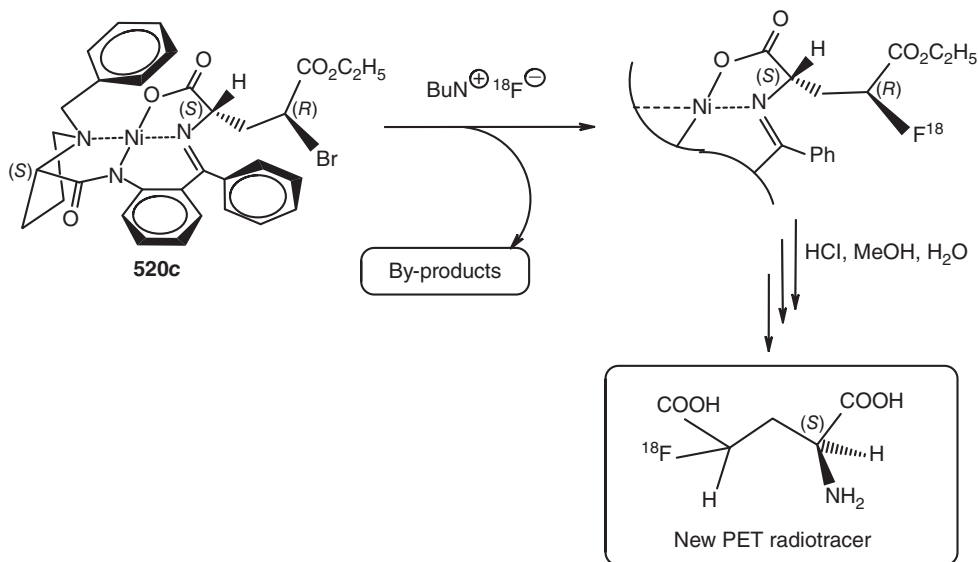
Since the bromine atom in this substrate has excellent mobility, attempts were made to obtain 4-FGlu with simultaneous decomposition of complex **520** and isolation of the amino acid in the presence of an excess of fluoride anion. Unlike the conventional systems of decomposition of the complexes $\text{MeOH}-\text{H}_2\text{O}-\text{HCl}$, substrate **520c** was decomposed in $\text{CF}_3\text{COOH}-\text{KF}$ system or 40% aqueous hydrofluoric acid. However, GLC analysis showed the presence of amino acid in the reaction medium, which was not the 4-FGlu.

Radiofluorination in the Institute of Human Brain (IHB RAS, St. Petersburg) is usually performed using $\text{Bu}_4\text{N}^+\text{F}^-$ or kryptofix K_{222} . The reaction of complex



Scheme 9.94

520c with $Bu_4N^+HCO_3^{3-}[(Bu_4N)_2CO_3]$ affords the desired product in 25.6% yield (according to ^{19}F NMR), but the reaction is accompanied by formation of considerable amounts of by-products, including complexes of cyclopropane amino acids (**519**). This should be expected because of high basicity of fluoride ion (see Scheme 9.95). However, to obtain ^{18}F labeled glutamic acid, a very small amount of ^{18}F -anion (10^{-15} M) is used and complex **520c** itself appears in huge excess.



Scheme 9.95

It was expected that under such conditions, the replacement of bromine by fluorine-18 would proceed in full and would not be accompanied by side reactions due to the low basicity of the medium. And, indeed, the developed method for nucleophilic substitution in precursor **520c** has been successfully applied in radiochemistry laboratory IHB RAS for preparation of isotopically labeled (2*S*)-4-[¹⁸F]fluoroglutamic acid.

Thus, using the above approach for the stoichiometric asymmetric synthesis of amino acids, a method for the synthesis of a new precursor for a promising PET radiotracer – (2*S*)-4-[¹⁸F]fluoro-glutamic acid and its precursors has been developed.

9.4

Modified Chiral Auxiliary Reagents for Efficient Asymmetric Synthesis of Amino Acids

Analysis of the molecular structures of square-planar Ni^{II} ion complexes with Schiff base of amino acids and chiral auxiliary reagents based on derivatives of natural amino acid (*S*)-proline shows that the presence of high enantiomeric effects in these complexes is due to the spatial arrangement of two phenyl groups of *N*-benzylproline and 2-aminobenzophenone moieties in metal coordination plane. These groups create a specific environment around the chiral amino acid moiety and provide kinetic and thermodynamic stereoselectivity of transformation reaction of amino acid moieties. Moreover, selectivity appears when the benzyl group is inserted into (*S*)-proline moiety and increases with the increase in the radical size at the aldimine carbon atom (–C=N– bond).

Thus, it is shown that increasing the volume of substituent R at aldimine carbon in a number of chiral carbonyl derivatives of *N*-benzyl-(*S*)-proline based on 2-aminobenzaldehyde (R=H, BBA), 2-aminoacetophenone (R=CH₃, BPA) and 2-aminobenzophenone (R=C₆H₅, BPB) causes additional distortion of metalocycle system, whereby the side group of amino acid moiety of complexes in the case of amino acid (*R*)-configuration takes a more pseudoaxial arrangement.

This leads to an increase in stereoselectivity of synthesis of (*S*)-α-amino acids among the complexes with chiral auxiliaries (*S*)-BBA < (*S*)-BPA < (*S*)-BPB (from 25% to 90%).

Theoretically, an even greater increase in stereoselectivity of synthesis of amino acids with the incorporation of additional substituents to the phenyl groups of *N*-benzylproline and 2-aminobenzophenone moieties could be expected. The inclusion of electronegative substituents in the phenyl ring of *N*-benzylproline moiety can increase CH acidity of amino acid moieties of complexes, consequently increasing the rate of asymmetric reactions.

This chapter focuses on the synthesis and study of new modified chiral auxiliary reagents containing various substituents (CH₃, Cl, F, Br, C₆H₅CH₂O, etc.) in the phenyl groups of *N*-benzyl-proline and aldimine (–C=N–) moieties in the reactions of amino acids asymmetric synthesis.

9.4.1

Chiral Ni^{II} Complexes of Amino Acids with Modified Aldimine Fragments

As the role of the phenyl group at the $-\text{C}=\text{N}-$ bond in Ni^{II} complexes of Schiff base of amino acids and chiral auxiliary BPB is to create additional steric hindrances around the amino acid moiety on the *re* side of the Schiff base plane (see XRD of complexes), Ryzhov and coworkers [227, 228] attempted to strengthen the nonbinding steric interactions exactly with this side of the plane by introducing additional bulky substituents to the phenyl groups of aminobenzophenone moiety of complexes (see Figure 9.38).

However, when these complexes (**535**–**541**) with modified aminobenzophenone moiety were used in the reactions of asymmetric synthesis of (*S*)- α -amino

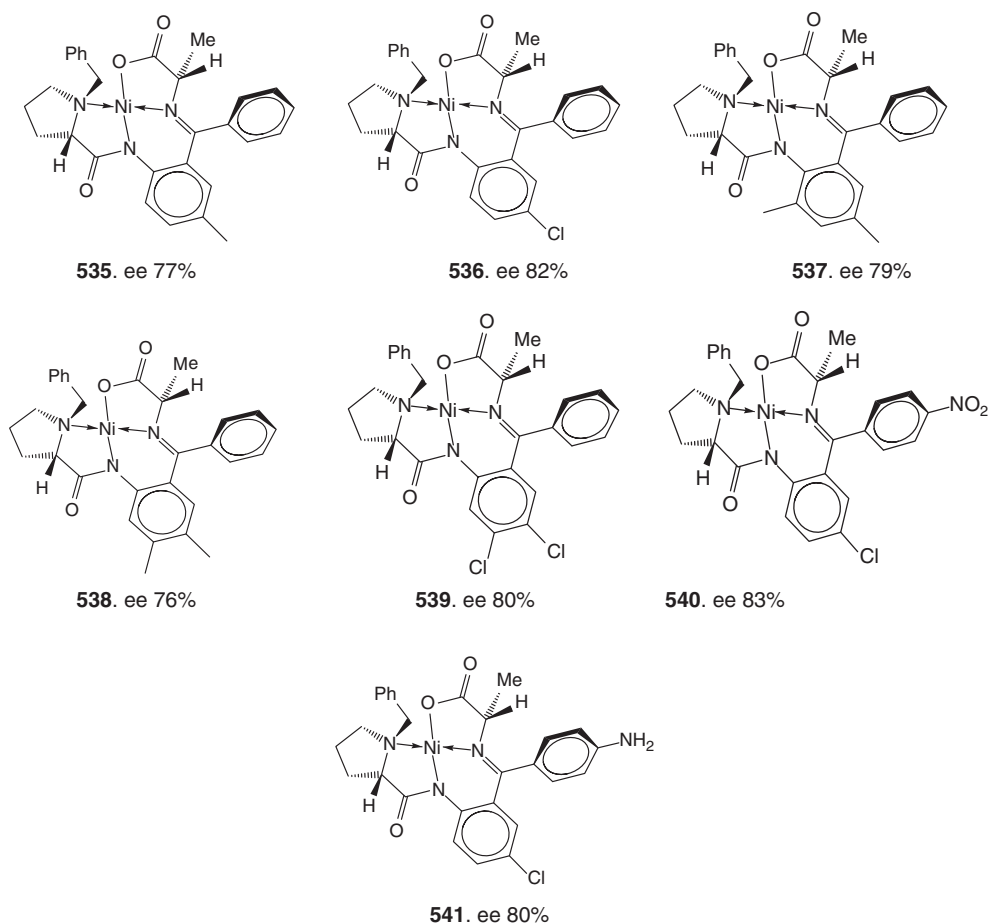
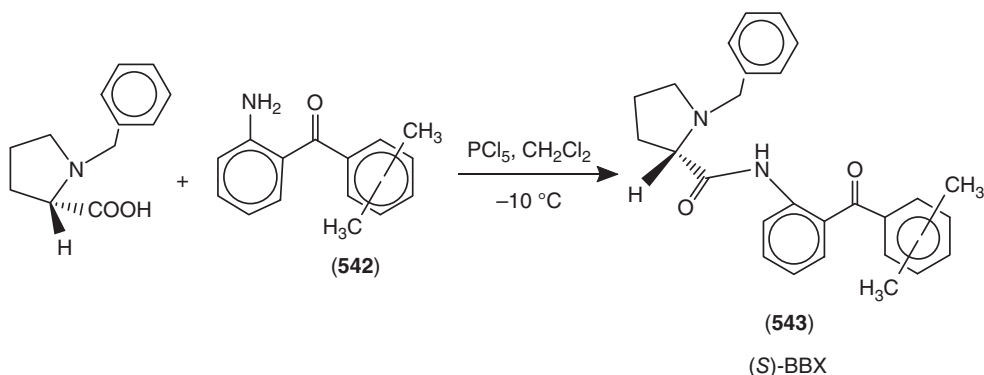


Figure 9.38 Structures of Ni^{II} complexes of Schiff bases of amino acids with modified aminobenzophenone moiety.

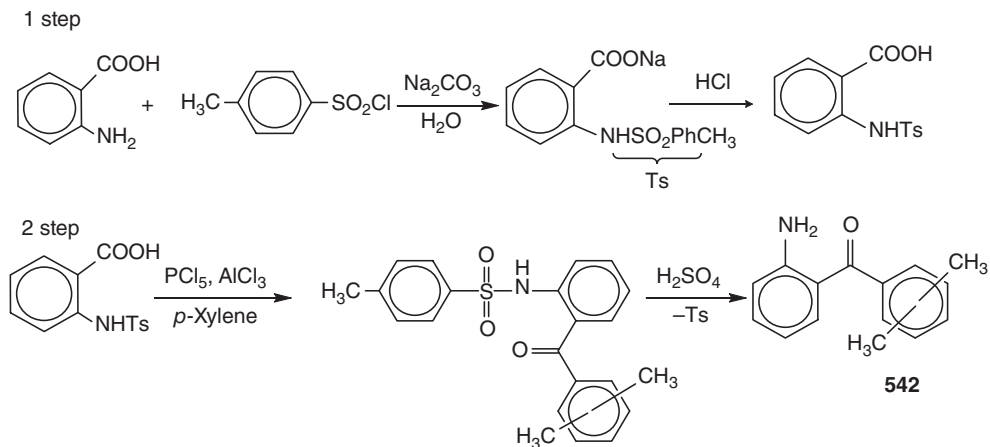
acids, no increase in the synthesis stereoselectivity, as compared with the complexes based on unsubstituted chiral auxiliary (*S*)-BPB, was observed.

Another modified analog of chiral reagent (*S*)-BPB with two methyl substituents in the aldimine phenyl group (*S*)-*N*-[2-(2,5-dimethylphenyl)benzoyl]-1-benzylpyrrolidine-2-carboxamide (BBX, **543**) was obtained by condensation of *N*-benzyl-(*S*)-proline with (2-aminophenyl)(2,5-dimethylphenyl)methanone (**542**) [229] (see Scheme 9.96).



Scheme 9.96

(2-Aminophenyl)(2,5-dimethylphenyl)methanone (**542**) can be easily obtained from anthranilic acid by converting it first to the *N*-Ts-anthranilic acid followed by condensation with *para*-xylene (see Scheme 9.97).

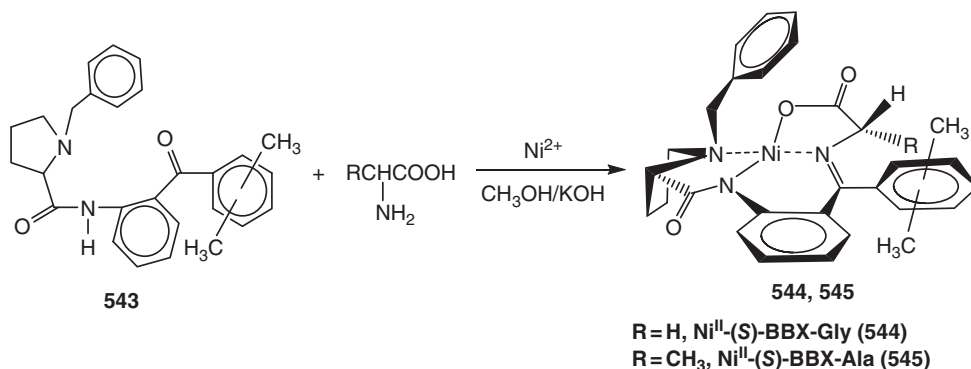


Scheme 9.97

The structure and absolute configuration of the chiral reagent BBX were determined by physicochemical methods of analysis [229]. Unlike unsubstituted BPB,

the modified chiral reagent (*S*)-BBX is more soluble in organic solvents, which considerably simplifies its separation from the reaction medium.

The complex of Ni^{II} ion of Schiff bases of amino acids (glycine and alanine) with modified reagent (*S*)-BBX was synthesized by the standard method (see Section 9.1.3) by reacting the amino acid with $\text{Ni}(\text{NO}_3)_2 \times 6\text{H}_2\text{O}$ and BBX in methanol in the presence of KOH upon heating to 55–65 °C (see Scheme 9.98) [229, 230].



Scheme 9.98

The resulting brown-colored complexes are practically insoluble in water and readily soluble in many organic solvents (acetone, chloroform, dichloromethane, etc.) and can be easily separated from the reaction mixture by precipitation from water.

Complexes have a broad absorption maximum at 500–550 nm in the field of *d-d*-transitions and they are diamagnetic. The structure and absolute configuration of synthesized complexes **544** and **545** were determined by ^1H NMR spectroscopy, chiral GLC, elemental analysis and polarimetric measurements. The ratio of (*S,S*)- and (*S,R*)-diastereomers of alanine complex (**545**) according to ^1H NMR and chiral GLC was 59/41 (%).

Studies have shown that in the case of complexation with the chiral reagent (*S*)-BBX, two complexes with the same amino acid, differing from each other by location of 2,5-substituents of the phenyl ring in the aldimine fragment in relation to the coordination plane of the complex, are formed. The formation of these isomeric complexes under the experimental conditions and their transformation into each other confirm the presence of the hindered rotation of the phenyl ring with 2,5-substituents. Consequently, such isomeric complexes are atropisomers [231]. Figure 9.39 illustrates atropisomeric glycine complexes.

It follows from the aforesaid that in addition to diastereoisomerism, these complexes have characteristic atropisomerism – the existence of regioisomers due to hindered rotation around a simple $\text{sp}^2\text{--sp}^2$ bond. Unfortunately, the attempts to chromatograph the atropisomeric alanine and glycine complexes turned out unsuccessful. The structure of atropisomers of glycine and alanine complexes was studied in their mixture by ^1H NMR.

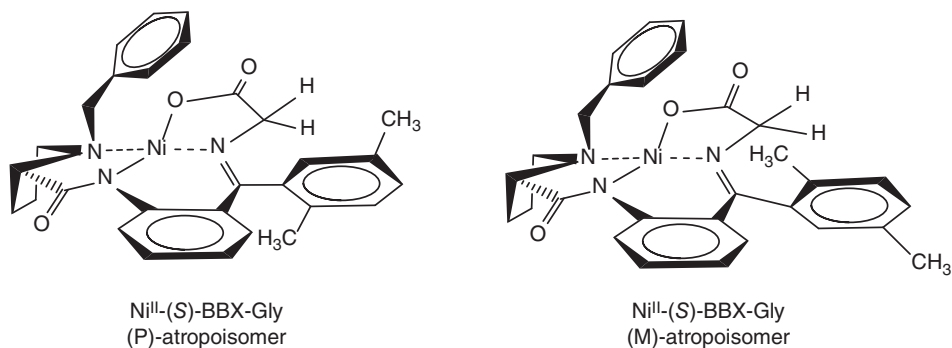
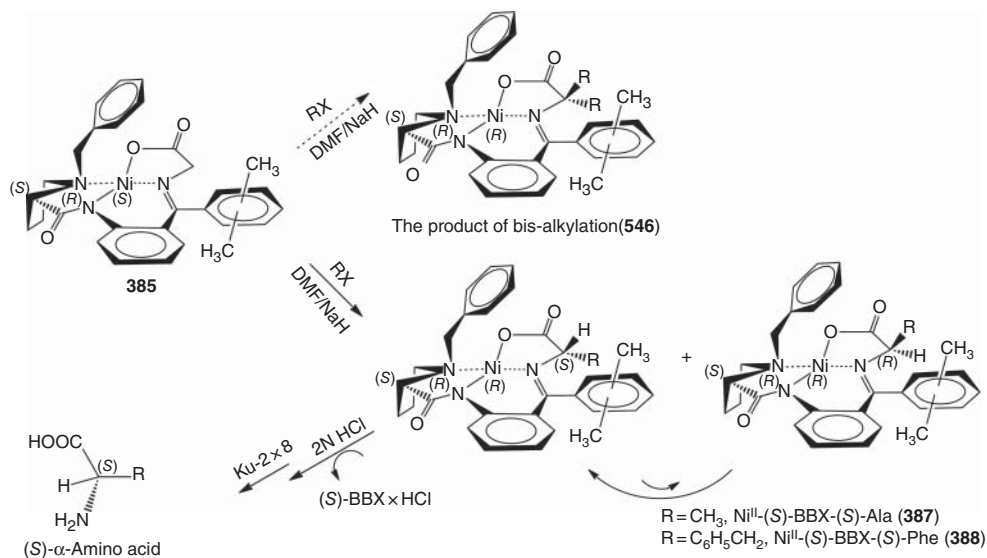


Figure 9.39 Atropisomeric Ni^{II} complexes of Schiff base of glycine with (S)-BBX chiral reagent (**544**).

Since the Ni^{II} complexes of Schiff bases with (S)-BBX and chiral amino acids exist as four isomers (two diastereomeric complexes with two atropisomers), for effective determination of the structure and properties of individual atropisomers, it is appropriate to investigate complexes of achiral amino acids. In practice, it was done using atropisomeric dehydroalanine complexes, which were separated by chromatography on SiO_2 (see Section 9.4.2).

To evaluate the effectiveness of the chiral auxiliary (S)-BBX (**543**), C-alkylation reactions of Ni^{II} complex of its Schiff base with glycine and alanine were studied [229]. Scheme 9.99 presents alkylation reaction of glycine complex **544** with alkylhalides ($\text{C}_6\text{H}_5\text{CH}_2\text{Br}$, CH_3I) in DMF, in the presence of solid NaOH or NaH.



Scheme 9.99

Table 9.17 The results of C-alkylation of Ni^{II} complexes of Schiff bases of glycine (**544**) with alkyl halides in DMF in the presence of NaH.

No.	Glycine complexes	Alkylating agent	AA	Time (min)	Yield (%) ^{a)}	ee (%) ^{b)}
1	$\text{Ni}^{\text{II}}\text{-(S)-BBX-Gly}$	BnBr	(S)-Phe	24 (h)	60	52
2	$\text{Ni}^{\text{II}}\text{-(S)-BBX-Gly}$	CH_3I	(S)-Ala	32 (h)	40	22
3	$\text{Ni}^{\text{II}}\text{-(S)-BPB-Gly}^{\text{c)}$	BnBr	(S)-Phe	60	75	86
4	$\text{Ni}^{\text{II}}\text{-(S)-BPB-Gly}^{\text{c)}$	$\text{CH}_2=\text{CHCOOCH}_3$	(S)-Glu	120	78	88

a) Chemical yield at alkylation step.

b) Averaged data based on ^1H NMR and chiral GLC analyses.

c) Results of alkylation of unmodified glycine complex with (S)-BPB (see Section 9.2.2).

In alkylation process, the formation of *mono*- and *bis*-alkylated (**546**) products is possible, as was the case during alkylation of (S)-BPB-based glycine complex. However, in case of alkylation of modified complex $\text{Ni}^{\text{II}}\text{-(S)-BBX-Gly}$ (**544**), only the monoalkylation product was detected in the reaction mixture. The progress of alkylation reaction is conveniently monitored by TLC following the disappearance of the spot of starting complex **544**.

Alkylation stereoselectivity (ee) was assessed by chiral GLC analysis determining enantiomeric purity of amino acids obtained after acid hydrolysis of a mixture of diastereomeric complexes and ion-exchange purification (prior to crystallization) as well as by ^1H NMR spectroscopy, by the ratio of signal integrals of methylene protons of the *N*-benzylproline moiety in the range of 2.55–4.40 ppm. Averaged data are presented in Table 9.17.

For comparison, the table also shows similar data for the alkylation of glycine in Ni^{II} complex of its Schiff base with unmodified chiral reagent (S)-BPB.

Attempts to perform condensation of methacrylate with a glycine moiety in complex **544** using different solvents and bases were unsuccessful, presumably because of steric hindrances introduced by the methyl substituents of aminobenzophenone fragment (this reaction occurs easily in the case of unmodified glycine complex with BPB).

It is shown that during alkylation reaction of complex $\text{Ni}^{\text{II}}\text{-(S)-BBX-Gly}$ (**544**) by $\text{C}_6\text{H}_5\text{CH}_2\text{Br}$ three phenylalanine complexes are formed: two diastereomeric complexes of (S,S)- and (S,R)-configuration, from which (S,S)-diastereoisomer is in the form of two atropisomers, and (S,R)-diastereoisomer is only in the form of a single atropisomer (Figure 9.40). Probably, the formation of (P)-atropisomer for (S,R)-diastereoisomeric complex is sterically unfavorable.

As can be seen from Table 9.17, in transition from normal glycine complex with (S)-BPB to modified glycine complex with (S)-BBX (**544**) a decrease in stereoselectivity (ee) of asymmetric C-alkylation reaction is observed [229]. In addition, a sharp slowdown of alkylation reaction is detected in the case of **544**.

Attempts to alkylate the modified alanine complex (S)-BBX (**545**) by benzyl bromide, methyl iodide, and ethyl bromide or iodide were unsuccessful. The reason

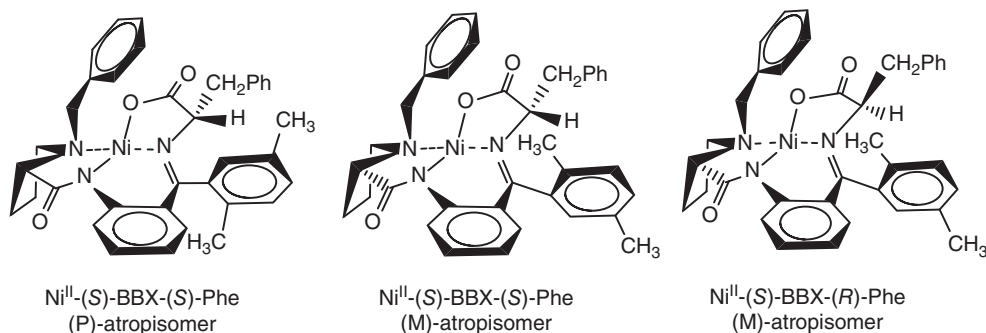


Figure 9.40 Structure of atropisomers of diastereomeric Ni^{II} complexes of Schiff base of phenylalanine with (S)-BBX.

probably lies in the sterically hindered approach of alkylating agent to the prochiral carbanion from the *re* side of the Schiff base plane caused by the phenyl group of *N*-benzylproline moiety and from the *si*-side – by methyl substituents of the phenyl group of aminobenzophenone fragment.

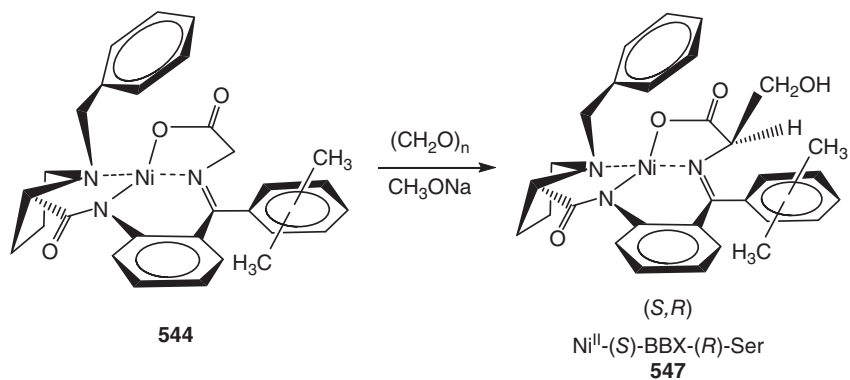
After decomposition of a mixture of diastereomeric complexes of alkylation products and isolation of the target amino acids by standard methods [122–129], the starting modified chiral reagent (S)-BBX (**543**) is regenerated with retention of the original optical activity.

By analogy to the known methodology for the synthesis of Ni^{II} complexes of Schiff bases of dehydroamino acids with unmodified chiral auxiliary (S)-BPB, glycine complex **544** was used for the synthesis of modified complexes of dehydroamino acids based on (S)-BBX. Unmodified complexes of dehydroalanine (**327**) and dehydroaminobutyric acid (**330**) were prepared from the corresponding complexes of (R)-serine and (R)-threonine by intermediate O-acetylation and α,β -elimination of acetic acid moiety from the acetylated complexes (see Section 9.1.4)[170, 174]. This approach has been used for the synthesis of modified Ni^{II} complexes of Schiff bases of (R)-serine and (R)-threonine with (S)-BBX [226, 227].

As expected, aldol condensation of modified glycine complex **544** with paraformaldehyde in the presence of a strong base preferably forms a complex of (R)-serine (see Scheme 9.100).

Diastereoselectivity of aldol condensation was determined by ^1H NMR and chiral GLC analysis of amino acids isolated from the acid hydrolysate of a diastereomeric complexes mixture.

Low diastereoselectivity of aldol condensation (ee $\sim 4\text{--}8\%$ in 6–8 h) in the case of modified glycine complex **544** apparently relates to the formation of atropisomers of (R)-serine complexes (**547**), as was observed in C-alkylation reactions of the same glycine complex by alkyl halides. Atropisomeric complexes of (R)-serine were chromatographed on SiO_2 [$\text{CHCl}_3\text{--CH}_3\text{COCH}_3$ (10 : 1)] and individually evaluated by ^1H NMR.



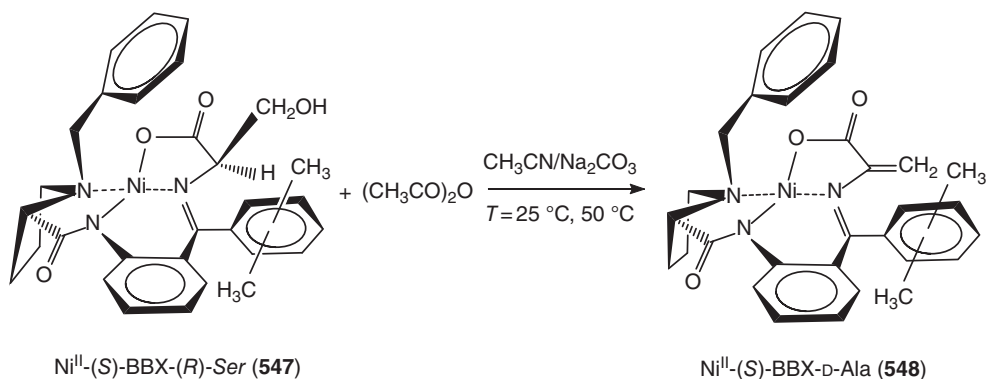
Scheme 9.100

Attempts to carry out condensation of acetaldehyde with the moiety of modified glycine complex **544** using a variety of bases and solvents turned out unsuccessful, presumably due to steric hindrances introduced by the methyl substituents of the aminobenzophenone fragment.

Complex (*R*)-serine **547** was used to obtain the appropriate complex of dehydroalanine.

9.4.1.1 Synthesis and Research of Dehydroalanine Complexes with Modified Aldimine Fragment

Based on previous experience in this area (see Section 9.1.4) in order to obtain Ni^{2+} ion complex with Schiff base of modified chiral auxiliary (*S*)-BBX and dehydroalanine, O-acetylation of serine fragment of complex **389** and deacetoxylation of the O-acetylserine intermediate complex under *in situ* conditions (without isolation of intermediate acetylated products)[229, 232] were carried out. Scheme 9.101 illustrates the formation of Ni^{II} complex of Schiff bases of dehydroalanine with (*S*)-BBX (**548**).



Scheme 9.101

The resulting dehydroalanine complex, as well as other (*S*)-BBX-based complexes, is a neutral and diamagnetic molecule highly soluble in organic solvents. Since the initial serine complex and its O-acetylation and deacetoxylation products differ from each other by R_f value on SiO_2 , it is convenient to monitor the process by TLC on SiO_2 plates in the $\text{CHCl}_3/\text{CH}_3\text{COCH}_3$ (7/1) solvent system.

As compared with the (*R*)-serine complex based on usual chiral reagent (*S*)-BPB (**319**, see Section 9.1.4), acetylation of complex **547** proceeds slowly and accelerates by the use of excess of acetic anhydride; the reaction of α,β -elimination of acetic acid from acetylated complex, on the contrary, proceeds quite easily. Formation of dehydroalanine complex **548** is observed even at room temperature in the process of O-acetylation of serine complex **547**; but for complete deacetylation, the reaction mixture should be heated up to 50°C .

By using spectral techniques such as ^1H NMR and NOESY it was found that all complexes based on the chiral reagent (*S*)-BBX were formed as two atropisomers, (*M*)-atropisomer and (*P*)-atropisomer. To study the influence of atropisomerism on formation of dehydroalanine complex (**548**), atropisomers of complex **547** were separately investigated in the reactions of O-acetylation and deacetoxylation. It was found that in case of both atropisomers of (*R*)-serine complex **547**, the dehydroalanine complex is formed as a mixture of two atropisomers. It was also found that in all cases the amount of (*M*)-atropisomer was predominant in a mixture of atropisomers.

The influence of absolute configuration of the serine fragment of complexes on the efficiency of the reactions of acetylation and deacetoxylation was also investigated. It was determined that under the influence of the pyrrolidine moiety of the macrocyclic ligand and the additional substituents in the phenyl group of aminobenzophenone moiety, α -proton of the amino acid fragment occupied a more axial position in the case of (*R*)-absolute configuration of O-acetylserine fragment than in the (*S*)-O-AcSer complex (see Figures 9.41 and 9.42).

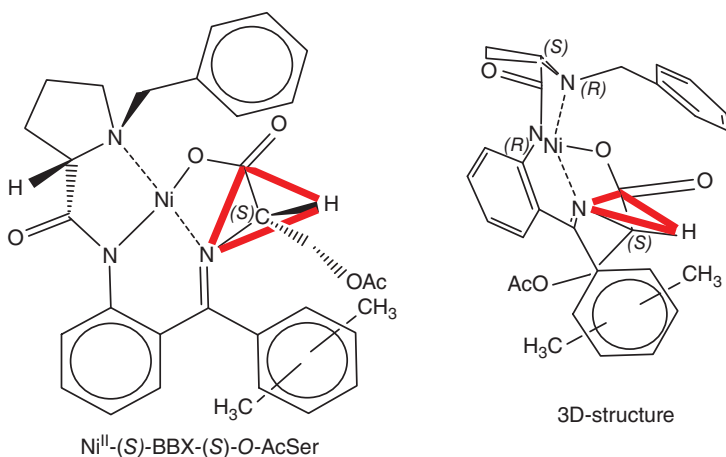


Figure 9.41 The spatial arrangement of $\alpha\text{-H}$ of the amino acid fragment in (*S*)-O-acetylserine complex.

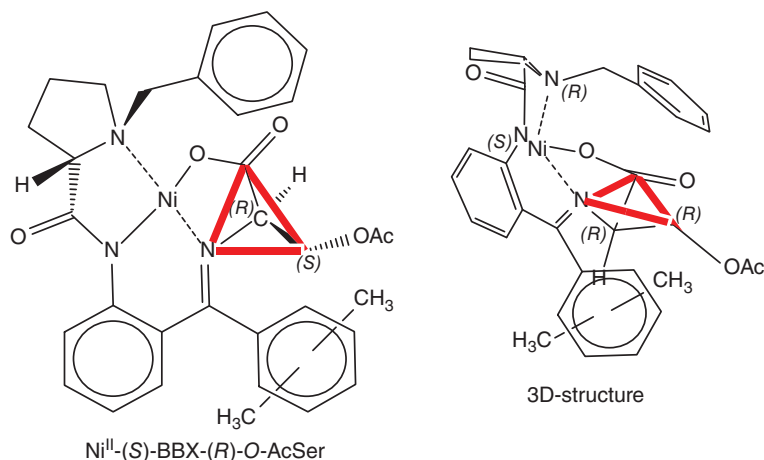


Figure 9.42 The spatial arrangement of α -H of the amino acid fragment in (*R*)-O-acetylserine complex.

This increased the detachment rate of the α -proton of the amino acid fragment, according to Dunathan's hypothesis on the stereoelectronic control of the reaction direction, thus increasing the reaction rate of β -elimination of the acetic acid moiety from acetylserine fragment in the case of its (*R*)-absolute configuration.

By preparative chromatography on SiO₂ [CHCl₃:CH₃COCH₃ (10:1)] ($R_{f(P)}=0.58$, $R_{f(M)}=0.5$), it was possible to separate atropisomeric complexes Ni^{II}-BBX- Δ -Ala (**548**) and fully characterize their structures. The individual atropisomers were further purified by gel-filtration chromatography on Sephadex LH-20 [C₆H₆/C₂H₅OH (5/1)]. Structure of atropisomers was determined by ¹H NMR and NOESY spectroscopic methods (Figure 9.43).

Orientation of xylene ring and spatial location of methyl groups in atropisomeric complexes (P)-**548** and (M)-**548** were determined by ¹H NMR using Overhauser's effect (see Figure 9.44).

Arrows indicate Overhauser's effects. Studies have shown that in (M)-atropisomer of complex **548** C=C bond of the dehydroalanine moiety is shielded by the methyl group of the xylene moiety from the *re* side of the Schiff base plane. Exactly from this side it is difficult for nucleophiles to approach the double C=C bond due to the steric nonbinding interaction of the phenyl substituent of *N*-benzylproline moiety. In (P)-atropisomer of complex **548**, the methyl group of the xylene moiety shields the C=C bond of dehydroalanine fragment from the *si* side of the Schiff base plane, and the approach of nucleophiles to the C=C bond from the *re* side of the Schiff base plane is hindered by the phenyl group of *N*-benzylproline moiety.

Therefore, it can be expected that the reactions of nucleophilic addition to the double bond of dehydroalanine in Ni^{II}-(S)-BBX- Δ -Ala complex (**548**) can proceed more easily and in higher chemical and asymmetric yields in the case of

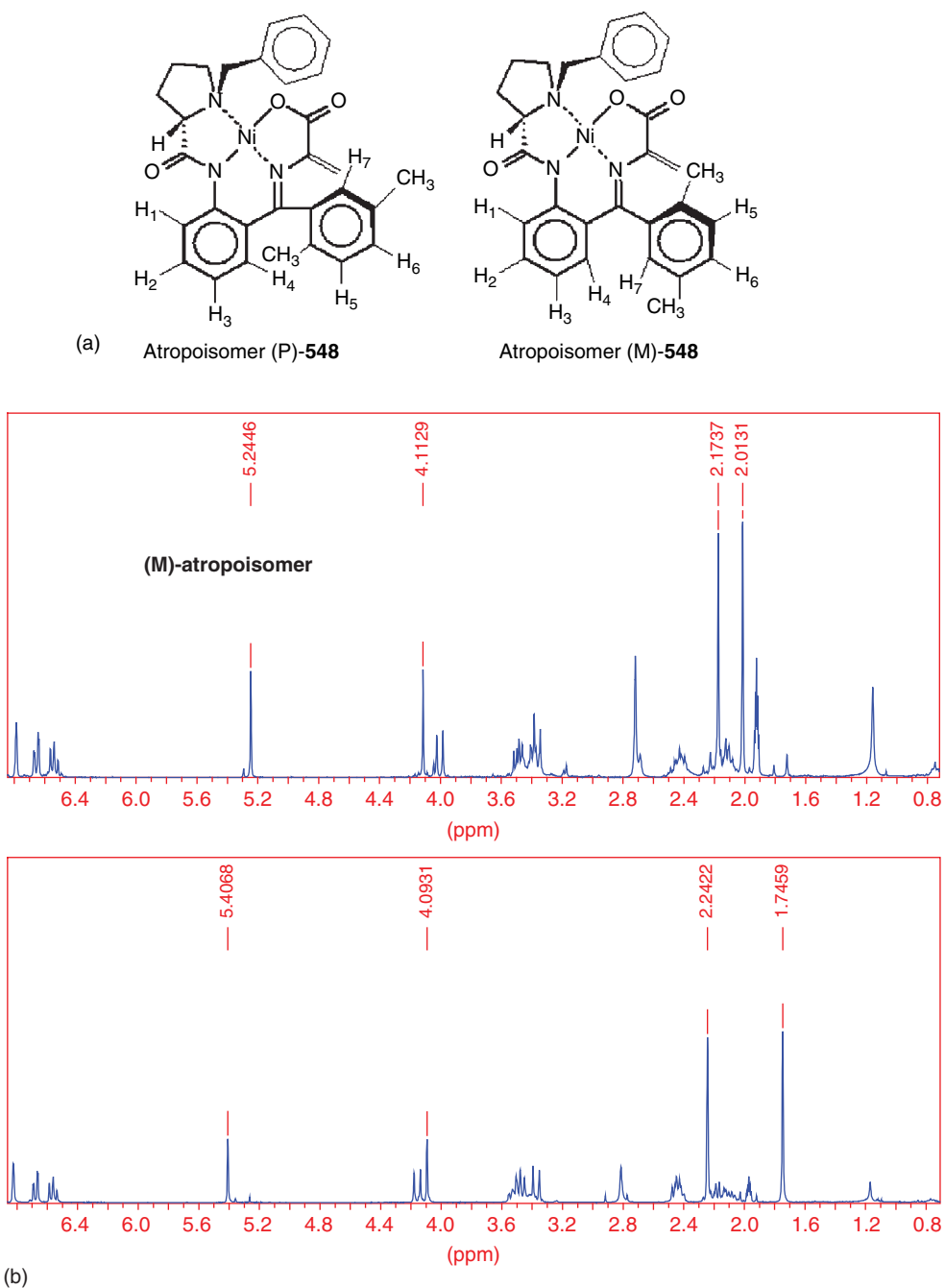


Figure 9.43 Structures and ^1H NMR spectra of atropoisomers of $\text{Ni}^{\text{II}}\text{-(S)-BBX-}\Delta\text{-Ala}$ (**548**) complex.

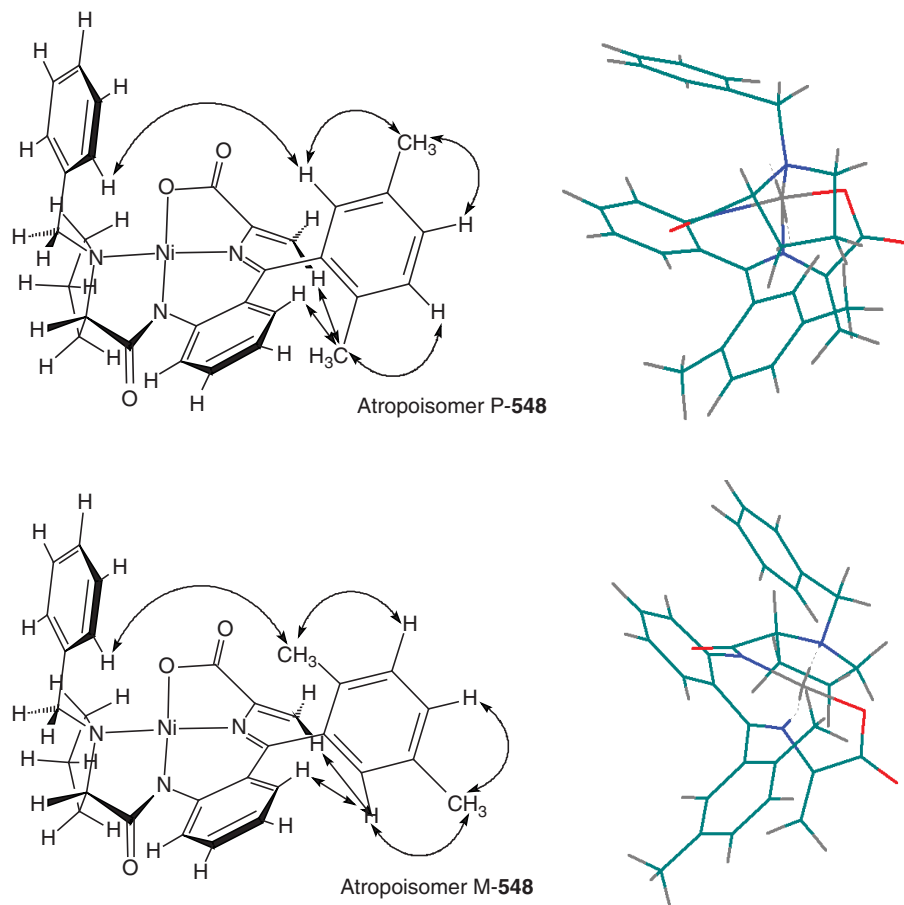


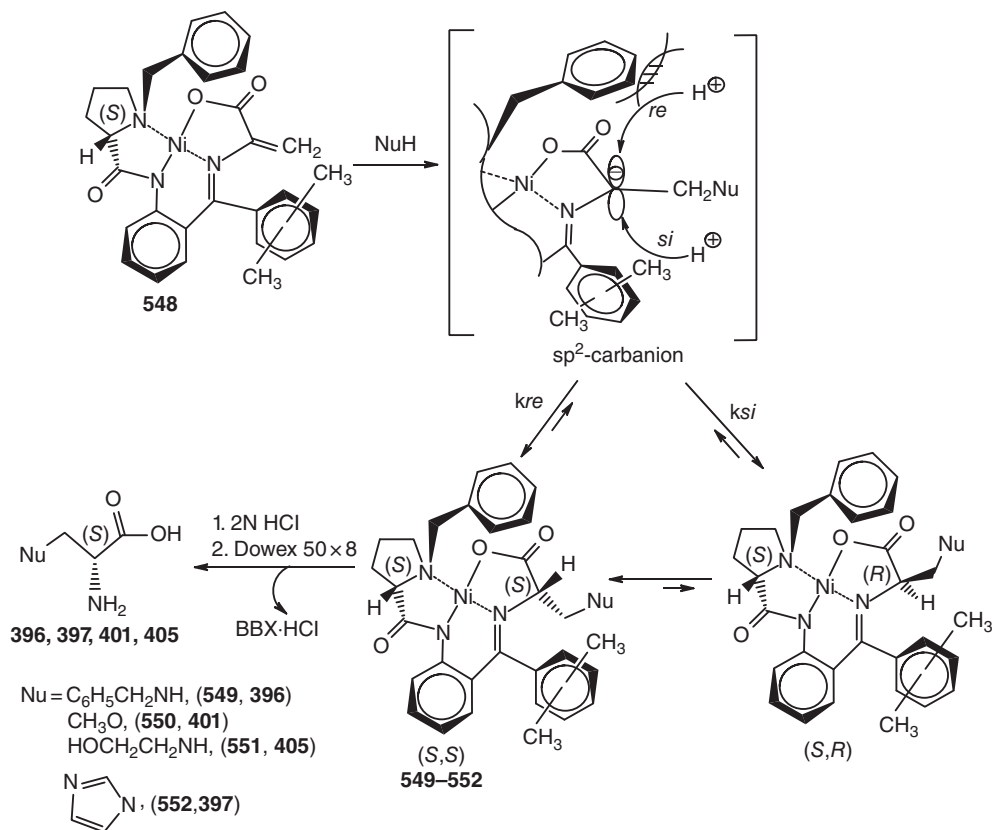
Figure 9.44 Overhauser effects in atropisomeric complexes (M)-548 and (P)-548 and their spatial structure, designed by MM2 program.

(M)-atropisomer than in the case of (P)-atropisomer. It could be assumed that atropisomeric dehydroalanine complexes might exhibit different activity in similar reactions of nucleophilic addition due to both steric and electronic influence of methyl substituents.

9.4.1.2 Asymmetric Addition of Nucleophiles to Dehydroalanine Complex Modified by Aldimine Fragment

Nucleophilic addition reactions to modified dehydroalanine complex **548** are conducted in an argon atmosphere to avoid undesirable oxidation processes [229, 232]. Benzylamine, monoethanolamine, imidazole, and methylate ions were used as nucleophiles (see Scheme 9.102).

Asymmetric addition reaction progress is conveniently monitored by TLC [$\text{SiO}_2, \text{CHCl}_3/\text{CH}_3\text{COCH}_3$ (7/1)], as well as by ^1H NMR spectroscopy following

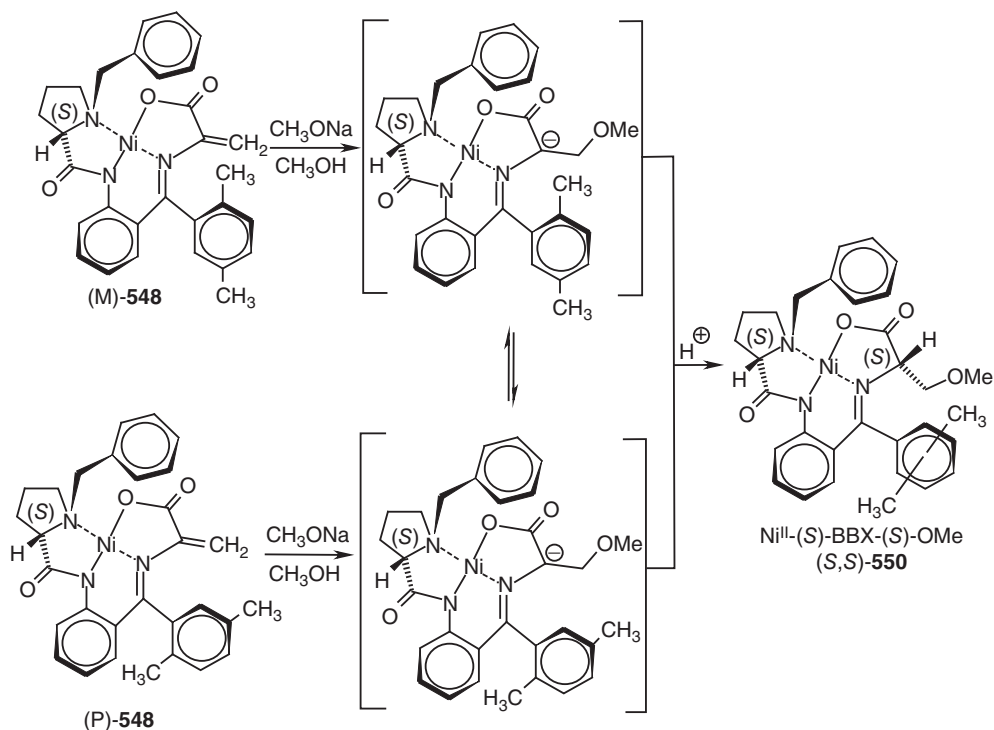


Scheme 9.102

the disappearance of the signals of vinyl hydrogens of dehydroalanine fragment at 4.09 and 5.40 ppm in case of (P)-atropisomer and 4.11 and 5.24 ppm in case of (M)-atropisomer of starting complex **548**.

In contrast to unmodified Ni^{II} dehydroamino acid complexes (see Section 9.2.4), the control over the process of nucleophiles addition to modified complex **548** becomes complicated since this dehydroalanine complex and adducts are in the form of two atropisomers. To determine the effectiveness of different atropisomeric dehydroalanine complexes in nucleophilic addition reactions, primarily the asymmetric Michael addition reaction of methoxy ion (CH₃O[−]) to the individual atropisomers of dehydroalanine complexes – (M)-**548** and (P)-**548** was studied (see Scheme 9.103). It appeared that for both atropisomers of dehydroalanine complex (**548**), the obtained adduct was in the form of an identical atropisomeric mixture.

The proposed mechanism involves the joint transformation of atropisomers in the form of planar carbanion of the addition product. After addition of the nucleophile in the presence of a base, the rigid π -system of the original complex



Scheme 9.103

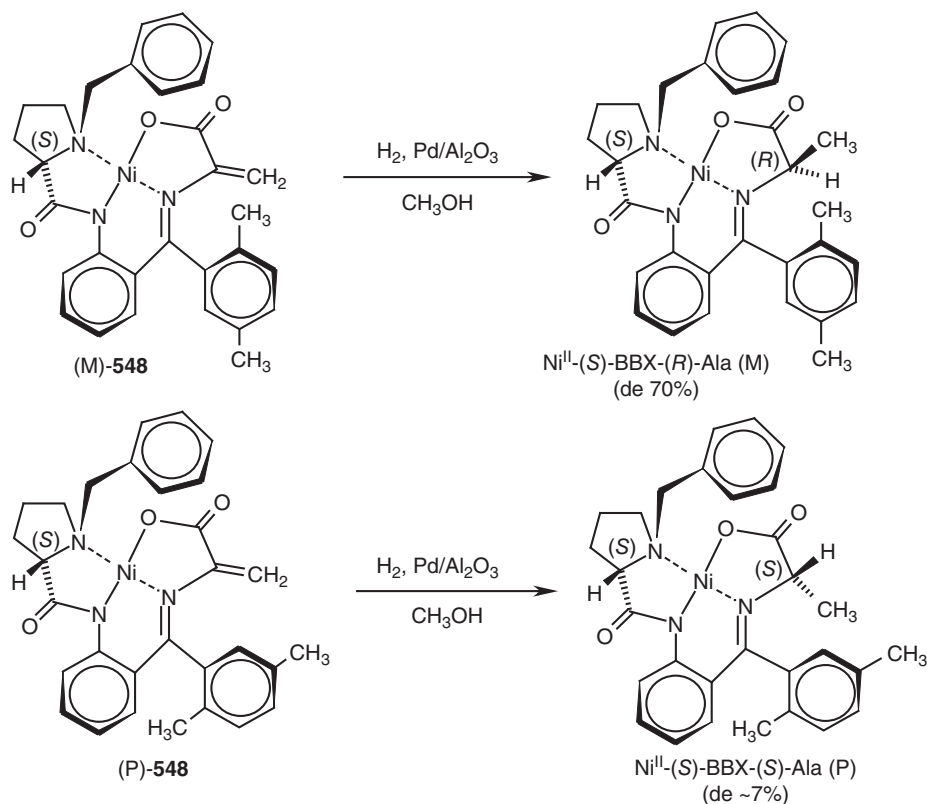
turns to a labile structure in the form of a carbanion adduct and rotation around the $\text{sp}^2\text{--sp}^2$ bond becomes free. As a result of this process, a mixture of (P)- and (M)-atropisomers of adduct **550** is formed with the establishment of the thermodynamic equilibrium between them.

To confirm the proposed mechanism, which explains the joint transformation of atropisomers after formation of the intermediate planar carbanion adducts, special experiments were conducted on catalytic hydrogenation of dehydroalanine fragment in individual atropisomeric complexes **548**, where the formation of intermediate plane carbanion is excluded (see Scheme 9.103).

It was found that the hydrogenation of two separate atropisomeric dehydroalanine complexes (M)-**548** and (P)-**548** afforded alanine complex in the form of one atropisomer: (M)-atropisomeric complex of (*R*)-alanine is obtained from atropisomeric complex (M)-**548** and (P)-atropisomeric complex of (*S*)-alanine – from atropisomeric complex (P)-**548** (see Scheme 9.104).

Undoubtedly, the obtained results on catalytic hydrogenation, amply justify the proposed mechanism of the interconversion of atropisomers via intermediate planar carbanions.

To determine the effectiveness and perform comparative analysis, unmodified complex of dehydroalanine $\text{Ni}^{\text{II}}\text{-(S)-BPB-}\Delta\text{-Ala}$ (**327**) was also subjected to catalytic hydrogenation using $\text{Pd}/\text{Al}_2\text{O}_3$. It turned out that by hydrogenation of



Scheme 9.104

$\text{Ni}^{\text{II}}-(S)\text{-BBX-}(M)\text{-}\Delta\text{-Ala}$, the $\text{Ni}^{\text{II}}-(S)\text{-BBX-}(R)\text{-Ala}$ with a diastereomeric purity (de) of 70% was obtained, while the hydrogenation of $\text{Ni}^{\text{II}}-(S)\text{-BBX-}(P)\text{-}\Delta\text{-Ala}$ led to $\text{Ni}^{\text{II}}-(S)\text{-BBX-}(S)\text{-Ala}$ with de $\sim 7\%$.

It was also shown that hydrogenation of unmodified complex $\text{Ni}^{\text{II}}-(S)\text{-BPB-}\Delta\text{-Ala}$ resulted in $\text{Ni}^{\text{II}}-(S)\text{-BPB-}(R)\text{-Ala}$ with de $\sim 40\%$.

These results can be interpreted as follows: the structure of atropisomeric complex $\text{Ni}^{\text{II}}-(S)\text{-BBX-}(M)\text{-}\Delta\text{-Ala}$ [(M)-548] (see Figure 9.44) shows that the *re* side of the double $\text{C}=\text{C}$ bond plane is shielded by the phenyl group of the benzylproline fragment and additionally by the methyl group of the aminobenzophenone moiety.

This means that the attack of hydrogen comes preferably from the *si* side of the Schiff base plane, forming a large excess of alanine with (*R*)-configuration. When $\text{Ni}^{\text{II}}-(S)\text{-BBX-}(P)\text{-}\Delta\text{-Ala}$ complex is used, conversely, a methyl group of aminobenzophenone moiety shields the double $\text{C}=\text{C}$ bond from the *si* side of the Schiff base plane (see Figure 9.44) and phenyl substituent of the *N*-benzylproline fragment complicates the approach of the hydrogen from the *re* side. At the same time, the hydrogen attack from the *re* side is relatively preferred, as evidenced by the

Table 9.18 Results of nucleophile addition to dehydroalanine complex **548**.

Atropisomer of starting dehydroalanine complex	Nucleophiles	Medium	Time (h)	Yield (%)	de (%) ^{a)}
(P)- 548	0.2 N CH ₃ ONa	CH ₃ OH	0.5	90	88
(M)- 548	0.2 N CH ₃ ONa	CH ₃ OH	2	82	86
(P)- 548 + (M)- 548		CH ₃ CN	7	92	74
(P)- 548		CH ₃ CN	5	90	50
(M)- 548		CH ₃ CN	7	94	82
(P)- 548 + (M)- 548	NH ₂ CH ₂ CH ₂ OH	CH ₃ CN	1	53	18 ^{b)}
(P)- 548 + (M)- 548	C ₆ H ₅ CH ₂ NH ₂	CH ₃ CN	3	80	79

a) Ratio of adducts of diastereomeric complexes determined by ¹H NMR analysis.

b) Enantiomeric purity of chiral amino acids determined by GLC analysis after decomposition of a mixture of diastereomeric complexes adducts and ion-exchange separation of amino acid mixtures.

formation of a product with a slight predominance of (*S*)-absolute configuration (de ~7%).

Taking into account the fact that the addition of nucleophiles to the individual atropisomers of dehydroalanine complex resulted in the same mixture of atropisomeric complexes of addition products, thereafter when adding other nucleophiles we used a mixture of atropisomeric complexes (M)-**548** and (P)-**548**.

The results of asymmetric nucleophilic addition to the C=C bond of dehydroalanine in chiral Ni^{II}-(*S*)-BBX- Δ -Ala complex are presented in Table 9.18.

In Figure 9.45, Overhauser's effects are shown by arrows, which proves the (*R*)-absolute configuration of the α -carbon atom of amino acid moiety for fraction I (with higher *R_f* value) [(*S,R*)-diastereomer] and (*S*)-configuration – for fraction II (with smaller *R_f* value) [(*S,S*)-diastereomer].

In addition, ¹H NMR analysis shows that in these reactions in the state of intermediate planar carbanion, no rotation around the sp²–sp² bond is observed; hence, there is no conversion between the atropisomers of adducts.

The results indicate that this reaction is controlled by both kinetic and thermodynamic factors. Analyzing the results, it can be assumed that in the intermediate planar carbanion, resulting from addition of imidazole to atropisomeric complexes (P)-**548** and (M)-**548**, due to the bulky imidazole substituent of the amino acid moiety the rotation around the sp²–sp² bond is sterically hindered. Consequently, the joint conversion between atropisomers of adducts is retarded and thermodynamic equilibrium is established only between diastereomers of

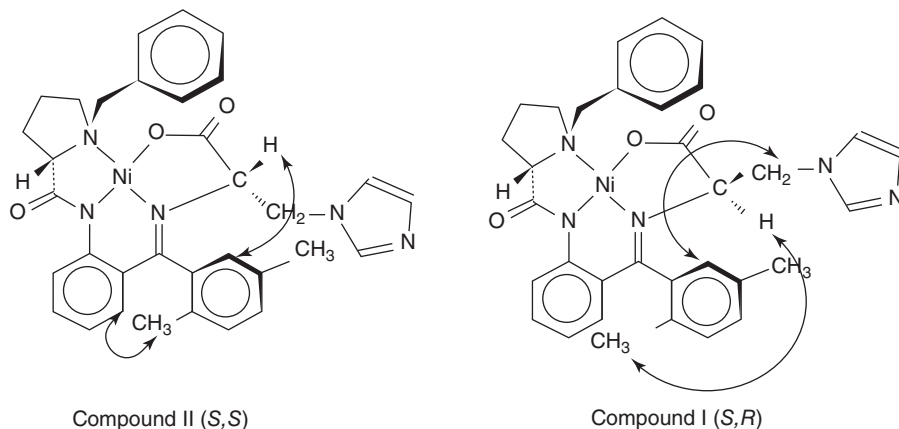
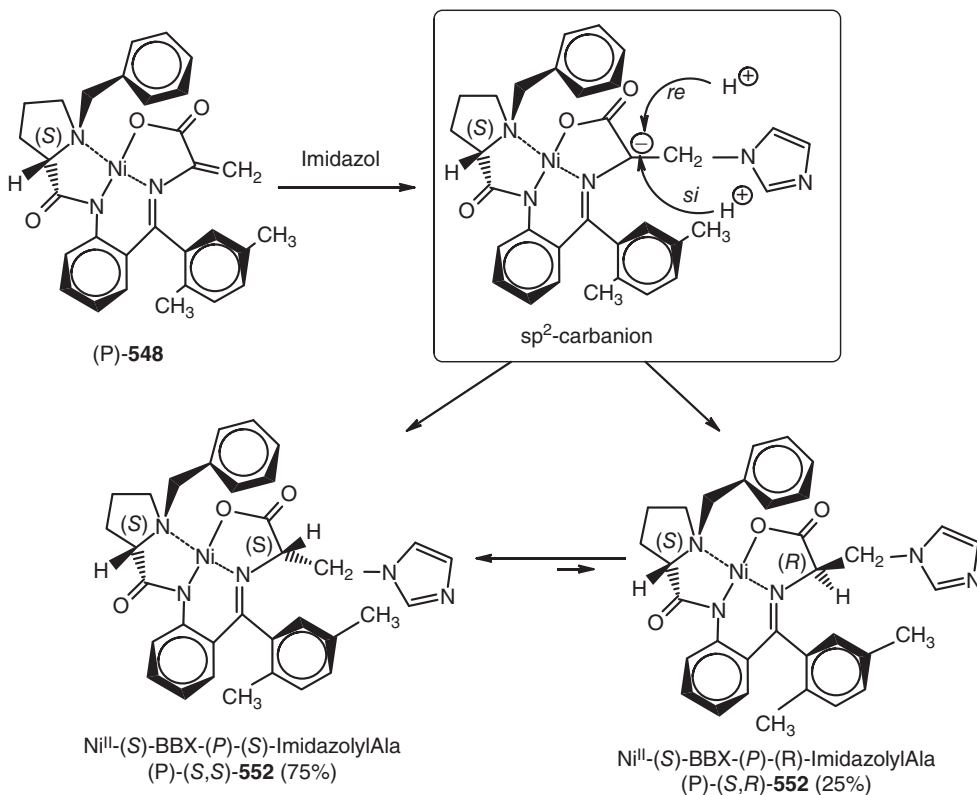
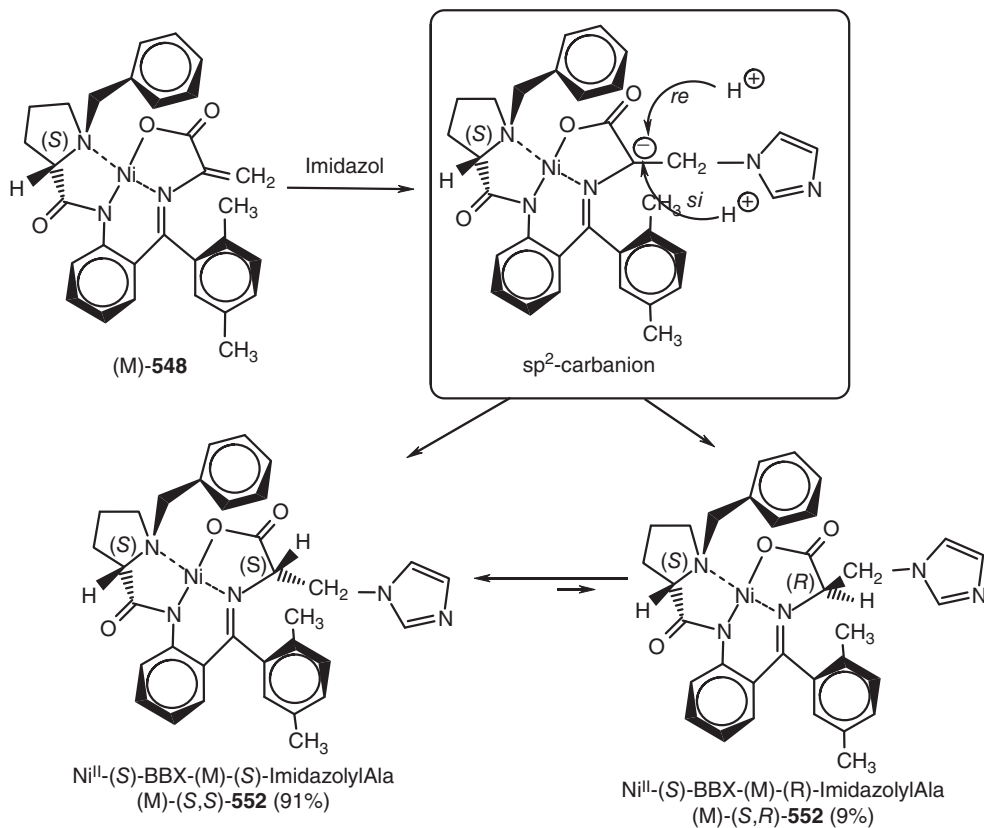


Figure 9.45 Overhauser's effects in (*S,S*)- and (*S,R*)-diastereomers of complex **552**.

adducts. Further, the process of protonation of carbanions occurs, where the arrangement of methyl groups of aminobenzophenone moiety plays an important role (see Schemes 9.105 and 9.106).



Scheme 9.105



Scheme 9.106

As can be seen from Scheme 9.106 and Figure 9.44, during attachment of the imidazole to the (M)-atropisomer of initial dehydroalanine complex 548, one of the methyl groups of xylene moiety additionally shields the *re*-side of the planar carbanion, which is simultaneously shielded by the phenyl group of *N*-benzylproline moiety. Consequently, carbanion protonation from the *si*-side of the Schiff base plane is thermodynamically more favorable, which leads to formation of (*R*)-absolute configuration of the α -carbon atom of amino acid moiety in the initial stage of the reaction.

Upon addition of imidazole to the (P)-atropisomer of dehydroalanine complex 548, the additional shielding of the *re*-side of the Schiff base plane by one of the methyl groups of xylene moiety is relatively weak. Consequently, protonation of carbanion occurs from both the *si*- and *re*-sides of the Schiff base plane, whereby in the initial stage of the reaction simultaneously two complexes are formed.

However, as can be seen from the structures of diastereoisomeric complexes of imidazole adducts to (M)-548 and (P)-548 built on the basis of the

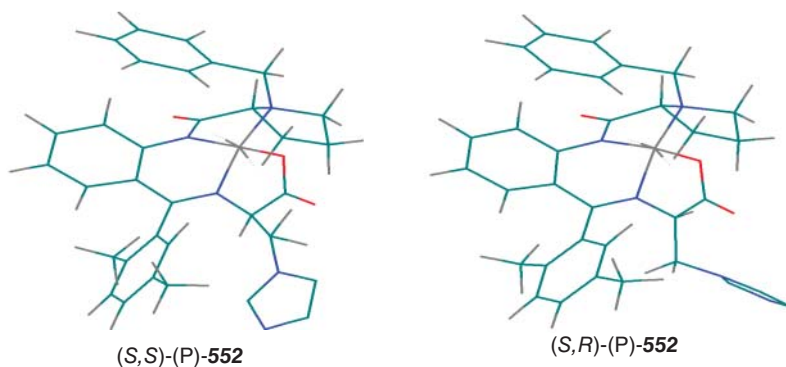


Figure 9.46 Structures of (*S,S*)- and (*S,R*)-diastereomers of (*P*)-atropisomeric β -imidazolylalanine complex (**552**) based on molecular-mechanical calculations.

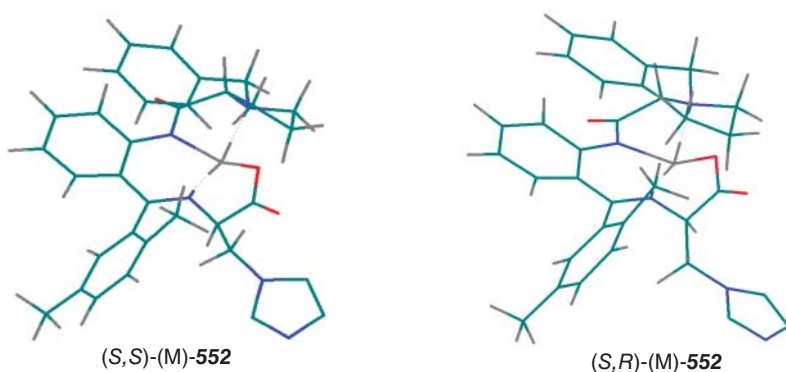


Figure 9.47 Structures of (*S,S*)- and (*S,R*)-diastereomers of (*M*)-atropisomeric β -imidazolylalanine complex (**552**) based on molecular-mechanical calculations.

molecular-mechanical calculations (see Figures 9.46 and 9.47), in the case of both atropisomers thermodynamically more advantageous is the arrangement of bulky imidazolylmethyl radical of the amino acid moiety on the *si*-side of the Schiff base plane, which corresponds to (*S*)-absolute configuration of the α -carbon atom of amino acid moiety. This is due to the spatial shielding of the *re*-side of the Schiff base plane by the phenyl group of *N*-benzyl-proline moiety and one of the methyl groups of xylene moiety, which is more pronounced in the case of (*M*)-atropisomer [(*S,S*)/(*S,R*)=10/1] than in the case of (*P*)-atropisomer [(*S,S*)/(*S,R*)=3/1]. This is also evidenced by the internal energy of the obtained diastereoisomeric adducts calculated using the MM2 program.

Calculations showed that the internal energy of (*S,S*)-diastereomer of atropisomeric complex (*M*)-**552** is 77.21 kJ, while the energy of other diastereoisomer of the same atropisomeric complex [(*S,R*)-(*M*)-**552**] is equal to 159.19 kJ. The internal energy of (*P*)-**552** atropisomeric complex is 78.84 and 87.28 kJ for (*S,S*)- and (*S,R*)-diastereoisomers, respectively.

Diastereomeric excess of the addition products of other nucleophiles to modified chiral dehydroalanine complex **548** was determined by chiral GLC analysis of amino acids, isolated from the mixture of diastereomeric complexes. After the disappearance of the characteristic red color of complexes during treatment of complexes with aqueous solution of 2 N HCl in CH₃OH at $T = 45-50^\circ\text{C}$, the starting modified chiral auxiliary (*S*)-BBX was isolated from the hydrolysate in quantitative chemical yield (>95%) and complete retention of optical purity.

Based on these results, it can be assumed that the chiral Ni^{II} complexes of Schiff bases of amino acids (or dehydroamino acids) modified by the aldimine phenolic substituent are ineffective in the reactions of asymmetric synthesis of amino acids due to the appearance of atropisomerism in diastereomers of C-alkylation products (or nucleophilic addition).

9.4.2

Chiral Ni^{II} Complexes of Schiff Bases of Amino Acids Modified by *N*-Benzylproline Moiety

This section focuses on preparation and study of new analogs of chiral auxiliary BPB and their Ni^{II} complexes of Schiff bases with amino acids substituted in the phenyl group of *N*-benzyl-proline moiety.

It should be noted that the square-planar complexes of Ni^{II} ion with Schiff base of amino acids and chiral reagents based on the (*S*)-proline in modified version were used by different research teams. Thus, Blake and coworkers investigated the stereodifferentiating abilities of ligands of analogous structure, differing only in substituents at the nitrogen atom of the proline moiety [233] (see Figure 9.48). The authors used substituents that provide additional coordination with the central metal ion in the complexes. However, despite expectations, the central atom of the metal ion in complexes of Schiff bases of (*S*)-2-[*N*-(2-picolyl)prolyl]amino]benzophenone (**553**) and (*S*)-2-[*N*-(3-picolyl)prolyl]amino]benzophenone (**554**) still had the square-planar geometry, in spite of the possibility of further coordination. However, this resulted in distortion of chelate rings and more effective shielding of one of the sides of α -amino acid fragment.

Popkov proposed that Ni^{II} ion complexes based on another modified chiral reagent (*S*)-2-[*N*-(2,4,6-trimethylbenzyl)prolylamino]benzophenone [234] be used. Ni^{II} ion complex of Schiff base with glycine (**555**) synthesized on its basis was used in alkylation reaction with alkyl iodide. In thermodynamic control conditions, an alkylated product of (*S*)-configuration with diastereomeric purity of 97% was obtained. Complex **555** was also used for stereospecific synthesis of ¹¹C-labeled alanine that is used in PET diagnostics [235].

Simultaneously, according to Belokon's group, new square-planar Ni^{II} ion complexes with Schiff base of α -amino acids with chiral auxiliary reagents (*S*)-*N*-(2-benzoylphenyl)-1-[3,5-di(trifluoromethyl)benzyl]-pyrrolidyl-2-carboxamide

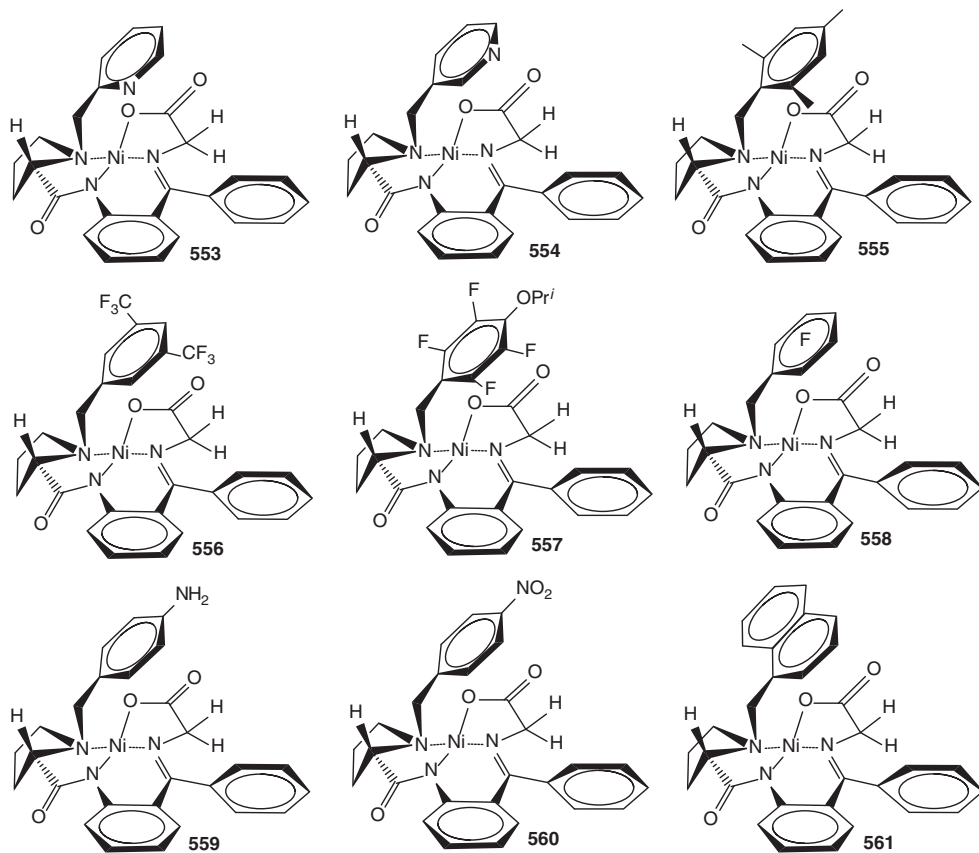


Figure 9.48 Ni^{II} ion complexes with Schiff base of α -amino acids and chiral auxiliary reagents modified in benzylproline moiety.

(CF_3BPB) (**556**), (*S*)-*N*-(2-benzoylphenyl)-1-(4-iso-propoxytetrafluorobenzyl)-pyrrolidyl-2-carboxamide (POFBPB) (**557**), (*S*)-*N*-(2-benzoylphenyl)-1-(pentafluorobenzyl)pyrrolidyl-2-carboxamide (FBPB) (**558**), (*S*)-*N*-(2-benzoylphenyl)-1-(4-aminobenzyl)pyrrolidyl-2-carboxamide (ABPB) (**559**), (*S*)-*N*-(2-benzoylphenyl)-1-(4-nitro-benzyl)pyrrolidyl-2-carboxamide (NBPB) (**560**), and (*S*)-*N*-(2-benzoylphenyl)-1-naphthylpyrrolidyl-2-carboxamide (NPB) (**561**) were synthesized. The efficacy of these complexes was studied in asymmetric C-alkylation reactions of their amino acid moieties by alkyl halides. It was found that these complexes were extremely active and gave mainly bis alkylation products with ee ~45–73% [236].

The increasing interest in recent years in isotope-labeled amino acids, successfully used in PET for diagnostics of cancer in early stages, requires the development of rapid methods for the asymmetric synthesis of amino acids suitable for producing short-lived isotope labeled analogs (^{11}C and ^{18}F , the half-life of which is equal to 20.4 and 109.8 min, respectively).

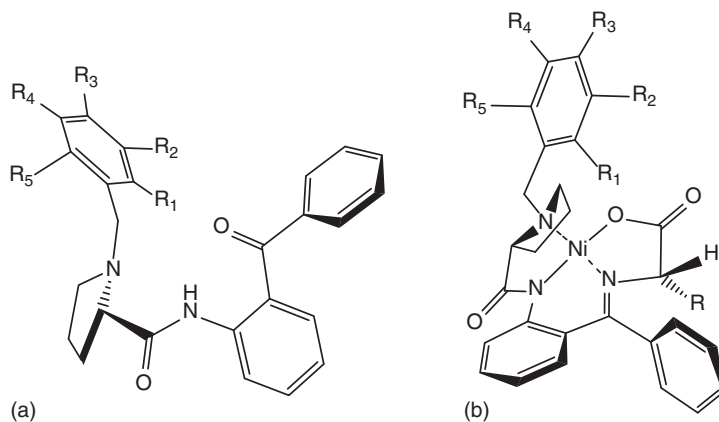


Figure 9.49 The structure of chiral auxiliaries modified by the phenyl group of *N*-benzylproline moiety (a) and of Ni^{II} -complexes of their Schiff bases with amino acids (b).

The enantiomeric purity of the amino acids used is of vital importance, since in metabolic processes only the L-enantiomer is involved and the D-enantiomer impurity significantly reduces the radiocontrast, and accordingly, the efficiency of PET diagnostics. Therefore, the creation of efficient, modified chiral auxiliary reagents enabling the rapid and highly selective asymmetric synthesis of α -amino acids remains an urgent task.

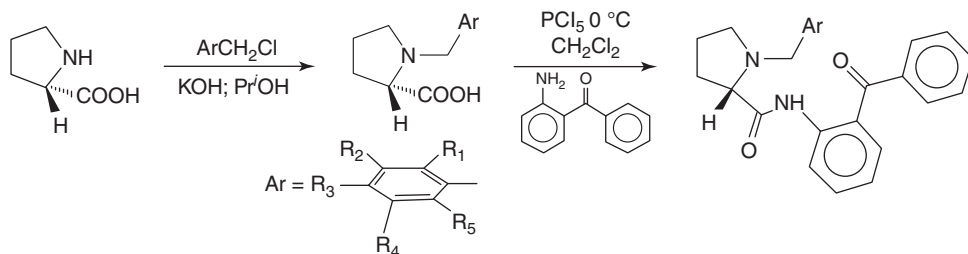
9.4.2.1 New Modified Chiral Reagents and Ni^{II} Complexes of their Schiff Base with Amino Acids

In order to develop highly selective and rapid methods for the asymmetric synthesis of amino acids, modified analogs of chiral auxiliary (*S*)-BPB and Ni^{II} -complexes of their Schiff bases with amino acids containing a variety of electron-donor or electron-acceptor substituents in the aromatic ring of *N*-benzylproline moiety [237–239] were synthesized (see Figure 9.49a,b).

Synthesis of regenerable chiral reagents based on various *N*-benzylprolines was performed by the standard procedure (see Section 9.1.3) using corresponding substituted benzyl chlorides at the step of proline *N*-alkylation. It was shown that conversion of substituted *N*-benzylprolines to acid chlorides occurred quantitatively using PCl_5 instead of SOCl_2 (see Scheme 9.107).

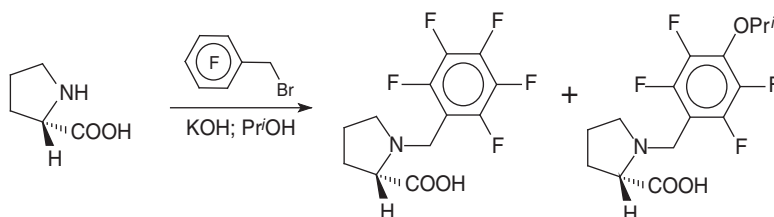
In the first phase, BPB chiral derivatives containing 3,4-dichlorophenyl, pentafluorophenyl, and 3,5-di(trifluoromethyl)phenyl substituents in *N*-benzylproline moiety were synthesized. During alkylation of (*S*)-proline by 3,4-dichlorobenzylchloride by the standard procedure, (*S*)-*N*-(3,4-dichlorobenzyl)proline was obtained in 70% yield.

However, in the synthesis of (*S*)-*N*-(pentafluorobenzyl)proline under standard conditions (Pr^tOH , KOH , 40–50 °C), it was found that one of the fluorine atoms in the pentafluorobenzyl moiety was nucleophilically substituted by *iso*-propoxy group. By ^{19}F -NMR method it was found that the fluorine atom located in the



Scheme 9.107

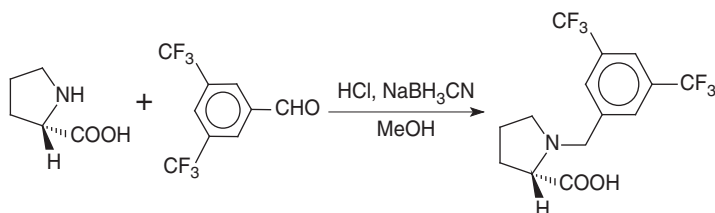
para-position of the benzyl moiety was replaced by the *iso*-propoxy group, and (*S*)-*N*-(4-*iso*-propoxytetrafluorobenzyl)proline was obtained as the main product (see Scheme 9.108).



Scheme 9.108

By reducing the amount of the used base, it was possible to obtain a mixture of (*S*)-*N*-(4-*iso*-propoxytetrafluorobenzyl)proline and (*S*)-*N*-(pentafluorobenzyl)proline in equal amounts, but only (*S*)-*N*-(4-*iso*-propoxytetrafluorobenzyl)proline was recovered by crystallization from the mixture.

For the synthesis of (*S*)-*N*-(3,5-di(trifluoromethyl)benzyl)proline as a starting reagent, more available 3,5-di(trifluoromethyl)benzaldehyde was used; the latter in the reduction by NaBH_3CN under the reaction conditions reacted with (*S*)-proline (Scheme 9.109) [240], but the chemical yield of the product in this case was low (20–25%).



Scheme 9.109

The resulting (*S*)-*N*-(3,4-dichlorobenzyl)-, (*S*)-*N*-[3,5-di(trifluoromethyl)benzyl]-, and (*S*)-*N*-(4-*iso*-propoxytetrafluorobenzyl)prolines in both a mixture with (*S*)-*N*-(pentafluorobenzyl)proline and in pure form were used for the synthesis of appropriate chiral auxiliary reagents. Studies have shown that the standard acid chloride method (see Section 9.1.3) with the use of SOCl_2 as a condensing agent in this case proved to be ineffective, since isolation of the product from the reaction mixture was attended by large losses (10%).

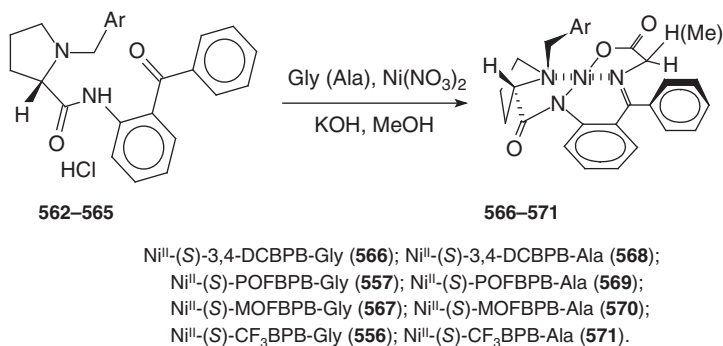
For the synthesis besides the anhydride method, the carbodiimide method was also used [241], based on activation of the carboxyl group of the proline moiety by the reaction of nucleophilic addition of dicyclohexylcarbodiimide. 2-Aminobenzophenone was further added to the intermediate acylating agent, but the effectiveness of this method also turned out to be low.

The *phosphorazo* method with preactivation of 2-aminobenzophenone through interaction with PCl_3 also proved ineffective [242]. An optimal coupling agent for such systems was the PCl_5 . Reactions were carried out in CH_2Cl_2 at 0°C with slow addition of an equimolar amount of PCl_5 (see Scheme 9.107). When the reaction mixture was processed by the previously described method (see Section 9.1.3), after neutralization with aqueous K_2CO_3 the chiral reagents were isolated as free bases in a mixture with unreacted amount of benzylproline. Isolation of the desired product from such mixtures was accompanied by high losses due to which the synthesized modified chiral reagents were isolated as hydrochlorides [238]. As a result, (*S*)-*N*-(2-benzoylphenyl)-1-(3,4-dichlorobenzyl)pyrrolidyl-2-carboxamide (3,4-DCBPB, **562**), (*S*)-*N*-(2-benzoylphenyl)-1-(3,5-di(trifluoromethyl)benzyl)pyrrolidyl-2-carboxamide (CF_3 BPB, **563**), and (*S*)-*N*-(2-benzoylphenyl)-1-(4-*iso*-propoxytetrafluorobenzyl)pyrrolidyl-2-carboxamide (POFBPB, **564**) were synthesized with a chemical yield of 76, 69%, and 62 %, respectively. Similarly chiral auxiliary reagent (*S*)-*N*-(2-benzoylphenyl)-1-(pentafluorobenzyl)pyrrolidyl-2-carboxamide (FBPB, **565**) was synthesized in the mixture, with POFBPB isolated by preparative chromatography (SiO_2 , $\text{C}_6\text{H}_{14}/(\text{C}_2\text{H}_5)_2\text{O} = 1/1$).

Modified chiral reagents **562**–**565** were converted to the corresponding Ni^{II} ion complexes of Schiff bases with glycine and alanine, according to the standard procedure (see Section 9.1.3). Formation of complexes with chiral reagents (*S*)-3,4-DCBPB and (*S*)-POFBPB occurred quite easily and in high yield (>80%) [236, 237, 239] (see Scheme 9.110).

During the attempt to obtain Ni^{II} complexes of Schiff bases of alanine and glycine with (*S*)-FBPB, due to nucleophilic substitution of one of the fluorine atoms in the aromatic ring, complexes of these amino acids with (*S*)-*N*-(2-benzoylphenyl)-1-(4-methoxytetrafluorobenzyl)pyrrolidyl-2-carboxamide (MOFBPB) were obtained, and complexes containing unsubstituted reagent – Ni -(*S*)-FBPB-Ala and Ni -(*S*)-FBPB-Gly – were isolated in small amounts (20% and 4%, respectively) and only when synthesis was performed in Pr^iOH .

During synthesis of Ni^{II} ion complexes with Schiff base of alanine, a mixture of diastereomeric complexes is obtained. Since the synthesis of the complex is carried out in a strongly basic medium, the epimerization of the amino



Scheme 9.110

Table 9.19 The ratio of diastereomers in a series of modified Ni^{II} ion complexes of Schiff base of alanine.

Alanine complex	(<i>S,S</i>)/(<i>S,R</i>) ^a
$\text{Ni}^{\text{II}}\text{-(S)-BPB-Ala}$	92/8
$\text{Ni}^{\text{II}}\text{-(S)-3,4-DCBPB-Ala (568)}$	98/2
$\text{Ni}^{\text{II}}\text{-(S)-POFBPB-Ala (569)}$	97/3
$\text{Ni}^{\text{II}}\text{-(S)-MOFBPB-Ala (570)}$	94/6
$\text{Ni}^{\text{II}}\text{-(S)-CF}_3\text{BPB-Ala (571)}$	97/3

a) Thermodynamic ratio of diastereomeric complexes determined by ^1H NMR.

acid fragment occurs rapidly wherein the ratio of diastereomeric complexes reflects the thermodynamic equilibrium between them. The ratios of diastereomeric alanine complexes were determined by ^1H NMR and are presented in Table 9.19.

Figure 9.50 shows the molecular structure of $\text{Ni}^{\text{II}}\text{-(S)-3,4-DCBPB-(S)-Ala (568)}$ based on XRD analysis⁵⁾ [233, 234]. Some significant structural features of this complex should be noted. Dichlorobenzyl group more effectively shields the coordination plane of complex – torsion angle $\text{Ni-N(15)-C(26)-C(27)}$ is -50° , angle Ni-N(15)-C(26) 108° , whereas for complexes with unsubstituted benzyl group, these values are typically -57° and 110° , respectively.

In addition, the distance between the Ni-C(27) in complex **568** is 2.992 (5) Å (which is less than the sum of van der Waals radii), whereas for the unmodified complex (S)-BPB, this value is equal to 3.2 Å. Apparently, there is a weak interaction between the Ni atom and dichlorobenzyl group, further stabilizing the “endo” conformation of the complex with the dichlorobenzyl group, fixed on the central

5) XRD analysis was performed by Khurstalev (XRD Laboratory; INEOS, RAS).

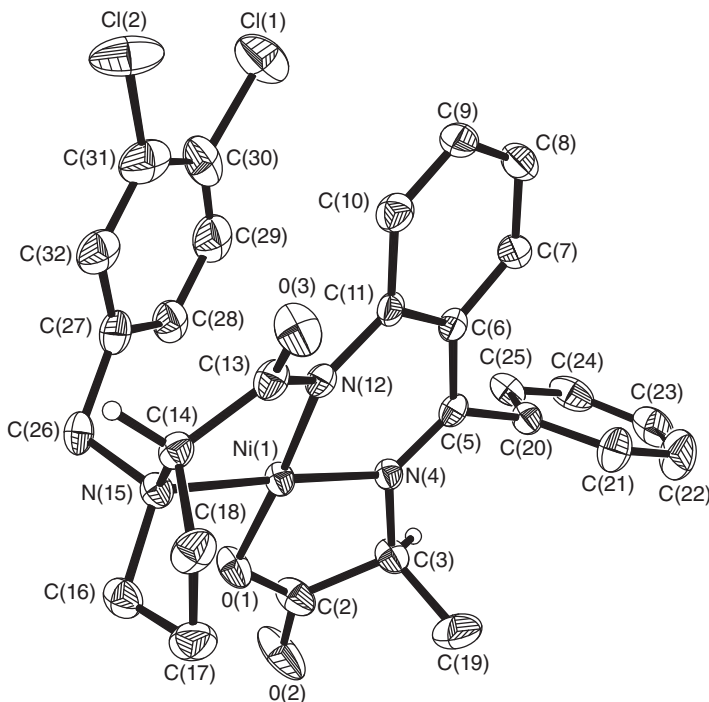


Figure 9.50 Molecular structure of $\text{Ni}^{\text{II}}\text{-(S)-3,4-DCBPB-(S)-Ala}$ (**568**) based on XRD analysis.

Ni atom and reducing the distance between the Ni-C (27) in (*S*)-3,4-DCBPB complexes.

The obtained results show that modified amino acid complexes with direct halogen (Cl or F)-substituted phenyl group of *N*-benzylproline moiety have the greatest thermodynamic diastereoselectivity. Further studies showed an increase in the rate of asymmetric transformation reactions of amino acid moieties in these complexes.

In this connection, the next step was to study the new modified analogs of chiral reagent BPB containing chlorine atoms in different positions of the phenyl substituent of the *N*-benzylproline moiety. At the same time, in order to reveal the influence of the substituent nature on the stereoselectivity and reaction rate of amino acid syntheses, electron-donating groups ($\text{CH}_3\text{-}$, $\text{C}_6\text{H}_5\text{CH}_2\text{O-}$, etc.) were introduced into the aromatic ring of *N*-benzylproline moiety.

For this purpose, the following modified chiral auxiliary reagents were synthesized by the standard methods: (*S*)-*N*-(2-benzoylphenyl)-1-(2-chlorobenzyl)pyrrolidyl-2-carboxamide (2-CBPB, **572**), (*S*)-*N*-(2-benzoylphenyl)-1-(3,4-dimethylbenzyl)pyrrolidyl-2-carboxamide (3,4-DMBPB, **573**), (*S*)-*N*-(2-benzoylphenyl)-1-(2,6-dimethylbenzyl)pyrrolidyl-2-carboxamide (2,6-DMBPB, **574**), (*S*)-*N*-(2-benzoylphenyl)-1-(2,6-dichlorobenzyl)pyrrolidyl-2-carboxamide,

the description of 574 and 575 compounds, and (*S*)-*N*-(2-benzoylphenyl)-1-(4-benzyloxybenzyl)-pyrrolidyl-2-carboxamide (4-BOBPB, 576)[243–245]. Modified chiral reagents 572, 573, and 576 easily form square-planar Ni^{II} complexes of Schiff base with glycine and alanine by standard methods of complexation (see Section 9.1.3) – Ni^{II}-(*S*)-2-CBPB-Gly (577), Ni^{II}-(*S*)-3,4-DMBPB-Gly (588), Ni^{II}-(*S*)-4-BOBPB-Gly (579), Ni^{II}-(*S*)-2-CBPB-(*S*)-Ala (580), Ni^{II}-(*S*)-3,4-DMBPB-(*S*)-Ala (581), Ni^{II}-(*S*)-4-BOBPB-(*S*)-Ala (582). Investigations showed that the chiral auxiliary reagents 574 and 575, containing substituents in positions 2 and 6 of the phenyl ring of *N*-benzylproline moiety regardless of the nature of the substituents and the reaction conditions, did not react with the Ni^{II} ion and amino acids for complexation [243, 245].

The ratios of (*S,S*)- and (*S,R*)-diastereoisomers of alanine complexes 580–582 were determined by ¹H NMR analysis of their mixture by comparing the signal integrals of the methylene protons of benzyl group of *N*-benzylproline moiety in 3.45–3.86 and 4.37–4.80 ppm range, and by chiral GLC analysis of amino acid mixture derived from the acid hydrolysate of a mixture of diastereomeric complexes by ion exchange method (prior to crystallization). The results are shown in Table 9.20.

As follows from the data in Table 9.20, the modified chiral auxiliary reagents (*S*)-2-CBPB, (*S*)-3,4-DMBPB, and (*S*)-4-BOBPB compared with their unsubstituted analog (*S*)-BPB provide the highest diastereoselectivity in complexation reactions with alanine. Extremely high indices were especially recorded with the use of chiral reagent (*S*)-2-CBPB (ee >98%).

The structures of Ni^{II}-(*S*)-2-CBPB-(*S*)-Ala (580) and Ni^{II}-(*S*)-3,4-DMBPB-(*S*)-Ala (581) complexes were also examined by X-ray analysis (see Figure 9.51) [244].

Analysis of XRD data shows that the introduction of substituents into the aromatic ring of *N*-benzylproline moiety changes the position of its benzyl group over the nickel coordination plane, which in turn causes a change in the angle of inclination of the phenyl substituent at the azomethine bond.

Table 9.20 The complexation results of modified chiral reagents in –CH₃OH in the presence of KOH, at 55–60 °C.

Starting chiral reagent	Amino acid complex	Chemical yield (%)	(<i>S,S</i>)/(<i>S,R</i>) (%) ^{a)}
(<i>S</i>)-2-CBPB (572)	Ni ^{II} -(<i>S</i>)-2-CBPB-Gly (577)	85.3	—
(<i>S</i>)-2-CBPB (572)	Ni ^{II} -(<i>S</i>)-2-CBPB-(<i>S</i>)-Ala (580)	92.1	99/1
(<i>S</i>)-3,4-DMBPB (573)	Ni ^{II} -(<i>S</i>)-3,4-DMBPB-Gly (578)	75.2	—
(<i>S</i>)-3,4-DMBPB (573)	Ni ^{II} -(<i>S</i>)-3,4-DMBPB-(<i>S</i>)-Ala (581)	80.6	98/2
(<i>S</i>)-BOBPB (576)	Ni ^{II} -(<i>S</i>)-BOBPB-Gly (579)	74.1	—
(<i>S</i>)-BOBPB (576)	Ni ^{II} -(<i>S</i>)-BOBPB-(<i>S</i>)-Ala (582)	87.2	98/2

a) The averaged ratios of diastereomers based on ¹H NMR and chiral GLC analyses.

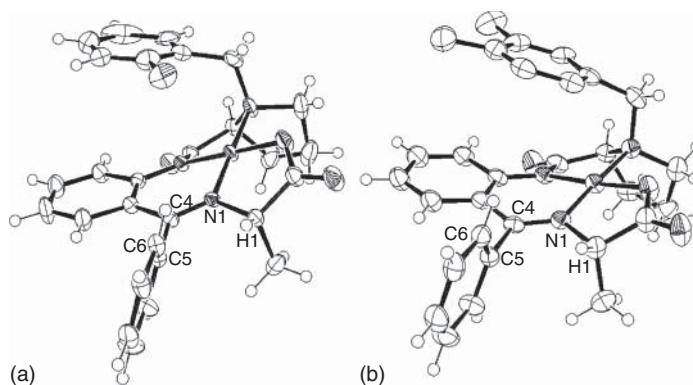


Figure 9.51 Molecular structures of complexes based on XRD data: (a) $\text{Ni}^{\text{II}}\text{-(S)-2-CBPB-(S)-Ala}$ (**580**); (b) $\text{Ni}^{\text{II}}\text{-(S)-3,4-DMBPB-(S)-Ala}$ (**581**).

As can be seen in Figure 9.52, in projections of two alanine complexes based on chiral reagents (*S*)-2-CBPB and (*S*)-3,4-DMBPB, as well as in the structure of a similar alanine complex based on (*S*)-3,4-DCBPB chiral reagent (see Figure 9.51), a change in the inclination angle of the phenyl group of the benzophenone moiety of complexes relative to the nickel coordination plane is observed (deviation of dihedral angle, marked in Figures as N1-C4-C5-C6 from 90°). This angle for $\text{Ni}^{\text{II}}\text{-(S)-3,4-DCBPB-(S)-Ala}$ (**568**), $\text{Ni}^{\text{II}}\text{-(S)-3,4-DMBPB-(S)-Ala}$ (**581**) and $\text{Ni}^{\text{II}}\text{-(S)-2-CBPB-(S)-Ala}$ (**580**) complexes is 6° , 8° , and 20° , respectively. By increasing this angle, the steric interaction between the phenyl group at azomethine bond and α -hydrogen H1 of (*S*)-amino acid fragment increases, whereby the (*S*)-alanine chelate metallocycle gets distorted and H1 hydrogen occupies the unfavorable equatorial position. In case of (*R*)-amino acid complexes, the phenyl group at azomethine bond interacts not with the α -hydrogen but with the alkyl radical, with a considerably greater strength. Thus, the discommodity of the (*R*)-enantiomer of the amino acid complex should greatly increase in a series of chiral reagents from 3,4-DCBPB $\rightarrow$ 3,4-DMBPB $\rightarrow$ 2-CBPB, while the discommodity of the (*S*)-amino acid complex increases in this series insignificantly. Therefore, the difference in the energies of diastereomeric complexes of (*S*)- and (*R*)-amino acids in this series of chiral reagents increases, which means that in the case of thermodynamic control the diastereomeric composition of equilibrium mixture of complexes will contain a smaller amount of amino acid of (*R*)-absolute configuration.

Taking the aforesaid as a basis, increase of the kinetic and thermodynamic diastereoselectivity in a series of complexes of chiral auxiliaries (*S*)-BPB, (*S*)-3,4-DCBPB, (*S*)-3,4-DMBPB, and (*S*)-2-CBPB in the asymmetric reactions of C-alkylation of amino acid moieties and nucleophilic addition of dehydroamino acid moieties of complexes could be expected.

As shown by subsequent experiments on testing modified complexes of amino acids, in C-alkylation reactions, a noticeable reduction in the duration of

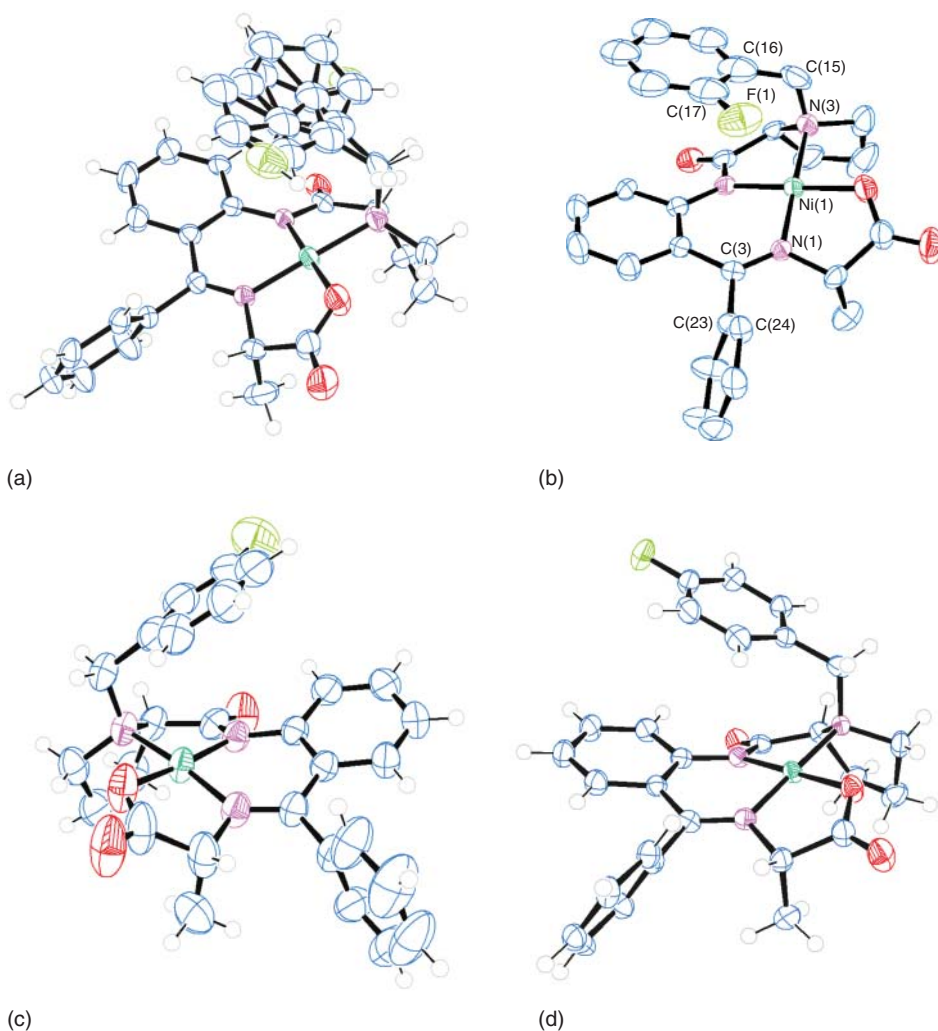


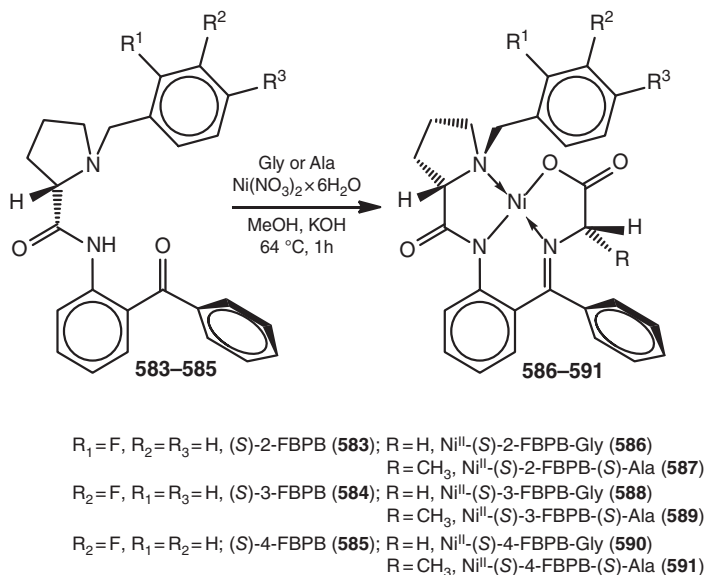
Figure 9.52 Structures of modified alanine complexes according to X-ray diffraction studies: (a) $\text{Ni}^{\text{II}}\text{-(S)-2-FBPB-(S)-Ala}$ (**587**, mixture of atropisomers *A* and *B*);

(b) $\text{Ni}^{\text{II}}\text{-(S)-2-FBPB-(S)-Ala}$ (**587**, atropisomer *A*), hydrogen atoms are not shown for simplicity; (c) $\text{Ni}^{\text{II}}\text{-(R)-3-FBPB-(R)-Ala}$ (*enant-589*); (d) $\text{Ni}^{\text{II}}\text{-(S)-4-FBPB-(S)-Ala}$ (**591**).

asymmetric reactions in the case of complexes of chiral auxiliary reagents that contain electronegative chlorine atoms in the phenyl group of *N*-benzylproline moiety is observed.

Later, in order to develop fastest (transient) methods for the asymmetric synthesis of amino acids, chiral auxiliary reagents were modified by introduction of more electronegative fluorine atoms into the phenyl group of *N*-benzylproline moiety [246]. For this purpose, based on the above

procedures, F-containing analogs of chiral auxiliary reagent BPB – (*S*)-*N*-(2-benzoylphenyl)-1-(2-fluorobenzyl)pyrrolidyl-2-carboxamide (2-FBPB) (**583**), (*S*)-*N*-(2-benzoylphenyl)-1-(3-fluorobenzyl)pyrrolidyl-2-carboxamide (3-FBPB) (**584**), (*S*)-*N*-(2-benzoylphenyl)-1-(4-fluorobenzyl)-pyrrolidyl-2-carboxamide (4-FBPB) (**585**) containing a fluorine atom in the *ortho*-, *meta*- and *para*-positions of the benzyl group at the nitrogen of proline moiety were synthesized. These reagents readily form Ni^{II} complexes of Schiff bases with glycine and alanine (see Scheme 9.111).



Scheme 9.111

During preparation of chiral amino acid alanine complexes (**587**, **589**, and **591**), a mixture of two diastereomers of (*S,R*)- and (*S,S*)-absolute configuration is formed, where the (*S,S*) is present in large excess. The complexes are isolated by precipitation from water and crystallized from acetone. Similarly constructed chiral reagents and amino acid complexes on the basis of (*R*)-proline were also synthesized for comparison.

The ratios of (*S,R*)- and (*S,S*)-diastereomeric alanine complexes were determined by ^1H NMR analysis of the mixtures of diastereomeric complexes and by chiral HPLC analysis of amino acids, isolated after decomposition of the diastereomeric complexes' mixture, separation of the starting chiral reagent, and amino acid demineralization. The results are shown in Table 9.21.

The absolute configuration of α -carbon atom of the amino acid moiety of the complexes was determined by the polarimetric method, as it was done for other similarly structured Ni^{II} complexes of Schiff bases of amino acids (see Section 9.2).

Table 9.21 Complexation results of fluorinated modified chiral reagents in the presence of KOH in CH₃OH at 55–60 °C.

Starting chiral reagent	Amino acid complex	Chemical yield (%)	(<i>S,S</i>)/(<i>S,R</i>) (%) ^{a)}
(<i>S</i>)-2-FBPB (583)	Ni ^{II} -(<i>S</i>)-2-FBPB-Gly (586)	86.2	—
(<i>S</i>)-3-FBPB (584)	Ni ^{II} -(<i>S</i>)-3-FBPB-Gly (588)	78.4	—
(<i>S</i>)-4-FBPB (585)	Ni ^{II} -(<i>S</i>)-4-FBPB-Gly (590)	74.8	—
(<i>S</i>)-2-FBPB (583)	Ni ^{II} -(<i>S</i>)-2-FBPB-(<i>S</i>)-Ala(587)	89.7	99.0/1.0
(<i>S</i>)-3-FBPB (584)	Ni ^{II} -(<i>S</i>)-3-FBPB-(<i>S</i>)-Ala(589)	81.5	97.5/2.5
(<i>S</i>)-4-FBPB (585)	Ni ^{II} -(<i>S</i>)-4-FBPB-(<i>S</i>)-Ala(591)	82.6	97.1/2.9

a) The averaged ratios of diastereomers by ¹H NMR and chiral HPLC analyses.

Positive values of the optical rotation of the main diastereomers of synthesized complexes **587**, **589**, and **591** at 589 nm proved their (*S,S*)-absolute configuration.

In addition, the (*S,S*)-absolute configuration of some synthesized diastereomeric complexes was confirmed by XRD analysis. Thus, for complexes **587**, **591**, and Ni^{II}-(*R*)-3-FBPB-(*R*)-Ala (*enant*-**589**, i.e., an optical antipode of (*S,S*)-**589**) it was possible to obtain suitable crystals, and their structure and absolute configuration were investigated by XRD analysis (Figure 9.52).

Two atropisomers (A and B) were revealed in the crystals of complex **587**, as shown in Figure 9.52a. The numbering of atoms in *enant*-**589** and **591** complexes (see Figure 9.52c,d) corresponds to their numbering in the prevailing atropisomer of complex **587** (see Figure 9.52b).

According to the XRD, due to the introduction of substituents into the aromatic ring of *N*-benzylproline moiety, its benzyl group changes its position above the Ni ion coordination plane (see Table 9.22).

Table 9.22 Some X-ray diffraction data of modified complexes of alanine.

Complex Parameters	Ni ^{II} -(<i>S</i>)-2-CBPB-(<i>S</i>)-Ala (580) ^{a)}	587 ^{b)}	<i>enant</i> - 589 ^{c)}	591
Distance Ni halogen	3.149	3.001 (4.651)	6.033/4.424	6.673
Distance Ni C(16)	3.403	3.052	3.122/3.087	3.372
Torsion angle Ni-N3-C15-C16	−69.16	−62.1 (−44.5)	51.52/48.36	−70.4
Torsionangle Ni-N3-C15-C16	87.75	79.72 (86.25)	−88.81/−89.23	86.51
Torsionangle N1-C3-C23-C24	69.97	73.35	−92.89/−84.11	68.49

a) Ni^{II} complex of Schiff base of (*S*)-alanine with chiral reagent (*S*)-2-CBPB (**580**).

b) Data given in parentheses are for atropisomer B.

c) Complex based on a chiral reagent (*R*)-BPB (all angles of opposite sign).

It was established that the fluorine atom in atropisomer A of complex **587**, unlike complexes *enant*-**589** and **591**, was positioned directly above the Ni^{II} ion and its apical coordination with the metal ion could not be excluded, which, in turn, significantly changed the distribution of electron density in the complex. Consequently, it can be expected that the increase in the alkylation reaction rate involving complex **587** is associated exactly with this interaction.

As can be seen from Table 9.22, in case of atropisomer A the distance Ni $\cdots$ F is equal to 3.001 Å, and Ni $\cdots$ C (16) 3.052 Å, while in complexes **589**, **591**, and **580** (with modified chiral reagent 2-CBPB), the similar distances have larger value.

Thus, due to the approximation of the 2-fluorobenzyl fragment to the nickel ion, further increase in stereoselectivity of the alkylation reactions of amino acid moieties when using complexes based on chiral auxiliary (*S*)-2-FBPB may be expected, based on the following three factors:

- 1) Conformational: the halogen atom (chlorine or fluorine) in position 2 of the benzyl group provides apparently only fixation of the position of this group over the amide bond, and is itself positioned exactly above the nickel. In case of halogens in positions 3 and 4, there is no fixation of the benzyl group over the amide moiety due to the weak interaction between the metal-halogen.
- 2) Electronic: fluorine and chlorine atoms are substituents having the +M effect ($\sigma = 0.337$ for fluorine and $\sigma = 0.373$ for chlorine) and $-I$ effect ($\sigma_1 = 0.52$ for fluorine and $\sigma_1 = 0.47$ for chlorine). Moreover, in the case of fluorine $-I$, the effect is much greater; therefore, the core is more electron depleted.
- 3) Due to the *staking*-interaction of aromatic ring of the benzyl group (in the case of fluorine more depleted of electrons than in any other case) with the system of an ionized carbanilide fragment conjugated with the Schiff base system, the formation of carbanion is facilitated due to more efficient delocalization of the negative charge with involvement of 2-fluoro-benzyl group.

Based on the XRD analysis data, the best results in the asymmetric synthesis reactions of (*S*)- α -amino acids by both stereoselectivity and duration of syntheses can be expected using complexes based on the chiral auxiliary reagent containing a fluorine atom in *ortho*-position of the phenyl group of *N*-benzylproline moiety (2-FBPB). In comparison with similarly built complexes based on chiral 2-CBPB reagent (*ortho*-position of the phenyl group of *N*-benzylproline moiety has a chlorine atom) in case of using complexes with 2-FBPB in C-alkylation reactions of amino acid moieties, shortening of the syntheses duration due to higher $-I$ effect of fluorine can be predicted. Based on the identified patterns, [244, 246] (see Figure 9.53), ultrahigh stereoselective synthesis of (*S*)- α -amino acids can be expected in alkylation of complexes based on chiral reagent (*S*)-2-FBPB (in case of atropisomer A), due to the maximum approximation of the benzyl group of *N*-benzylproline moiety to the central Ni^{II} ion. However, due to the presence in the mixture of atropisomer B, in the structure of which 2-F substituent of the phenyl group of *N*-benzylproline moiety is located further than the metal ion (see Figure 9.53), the enantioselective effects in this atropisomeric complex can be

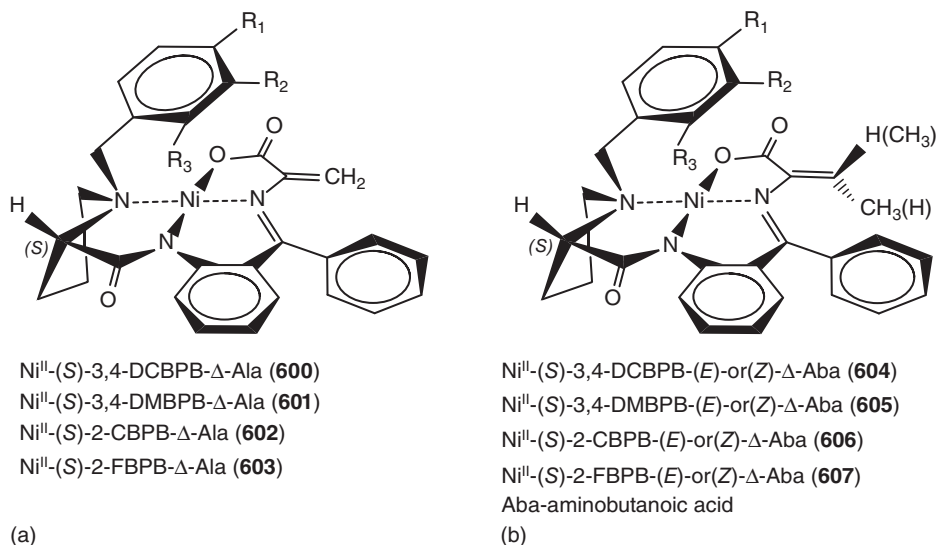


Figure 9.53 Structure of modified dehydroalanine (a) and dehydroaminobutyric acid (b) complexes.

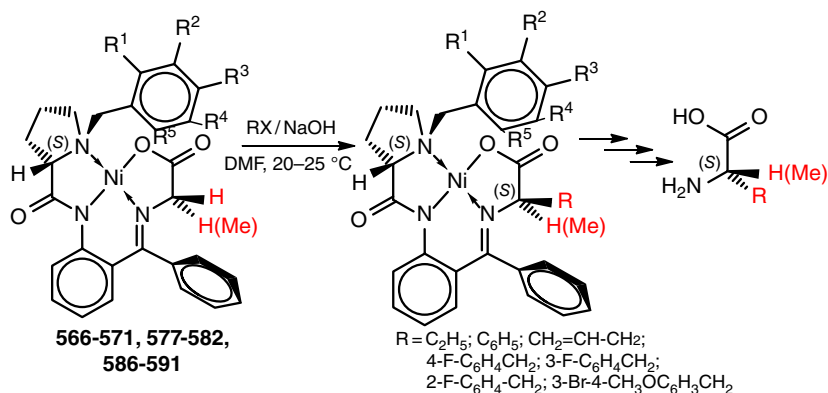
approximately at the level of complexes of other fluorine-containing chiral auxiliary reagents (*meta*- or *para*-substituted). Consequently, it is possible to expect a relatively low total stereoselectivity ($\sim 95\text{--}97\%$) during the asymmetric synthesis reactions of (*S*)- α -amino acids using complexes based on a modified chiral auxiliary 2-FBPB.

9.4.2.2 Amino Acid Complexes with Modified *N*-Benzylproline Moiety in C-Alkylation Reactions

Ni^{II} ion complexes with Schiff bases of amino acids (glycine and alanine) and complexes of chiral auxiliary reagents with modified *N*-benzylproline moiety **566–571**, **577–582**, and **586–591** were studied in C-alkylation reactions of amino acid moiety according to the procedure described above (see Section 9.2.1) [237, 244, 246] (see Scheme 9.112).

After decomposition of the resulting mixture of diastereomeric complexes and isolation of the target amino acids by ion exchange chromatography, the enantiomeric purity of amino acids was determined by chiral GLC or HPLC analyses.

It was found that for almost all modified glycine complexes, formation of bis-alkylation products took place. In particular, glycine complexes containing F-chiral auxiliary reagents that predominantly form bis-alkylation products are extremely active. Since the fluorine atom exhibits a strong electron-withdrawing effect pulling electrons from the central metal ion (not creating additional steric interactions), the resulting electron density at the reaction center of the amino acid fragment decreases greatly. All this leads to an increase in the CH-acidity of the amino acid moiety, including also a monoalkylated complex, which



Scheme 9.112

explains the high activity of these complexes as well as formation of bis-alkylated product.

At the same time, alkylation of complex $\text{Ni}^{\text{II}}\text{-(S)-3,4-DCBPB-Gly}$ (**566**) by benzyl bromide under the same conditions, results only in the monoalkylated product. The progress of the reaction is easily monitored by TLC and the reaction is complete within 5–9 min. However, the optical purity of the amino acid isolated after decomposition of complexes, in particular, α -Phe, does not exceed 86%. Diastereoselectivity of alkylation reaction of these complexes by benzyl bromide in THF is no more than 75%, and high stereoselectivity is observed only with additional epimerization of a mixture of diastereomeric complexes of alkylation products formed in the course of the reaction. For this purpose, specially upon completion of the reaction, a small amount of 4 N MeONa is added, and under the action of base in a protic medium thermodynamic equilibrium is established, and the ratio of $(S,S)/(S,R)$ ($\sim 6/1$) increases and reaches 31/1.

Glycine complexes based on modified chiral reagents containing a halogen atom in position 2 of the phenyl ring of *N*-benzylproline moiety – $\text{Ni}^{\text{II}}\text{-(S)-2-CBPB-Gly}$ (**577**) and $\text{Ni}^{\text{II}}\text{-(S)-2-FBPB-Gly}$ (**586**) are predominantly subjected to monoalkylation.

Thus, during monoalkylation of glycine complexes, two types of stereoselectivity is observed: kinetic, determined by the relative rate of attack of the alkylating agent on the *re*- or *si*- side of the intermediate carbanion, and thermodynamic, determined by the relative stability of the resulting diastereomeric complexes.

The averaged C-alkylation results of modified glycine complexes with seven alkylating agents based on ^1H NMR, chiral GLC, and chiral HPLC analyses are presented in Table 9.23.

The averaged results of kinetically controlled C-alkylation process of modified alanine complexes are presented in Table 9.24, and in all cases there is a reduction in duration and increase in stereoselectivity of the reaction at 45–50 °C.

Table 9.23 The results of alkylation of modified glycine complexes by alkyl halides.

Modified glycine complex	Chemical yield (%) ^{a)}	Time (min)	de (%) ^{b)}	Yield of bis-product (%) ^{c)}
Ni ^{II} -(S)-3,4-DCBPB-Gly (566)	74–76	8–10	95	<2
Ni ^{II} -(S)-POFBPB-Gly (557)		Predominantly bis-product		
Ni ^{II} -(S)-MOFBPB-Gly (567)		Predominantly bis-product		
Ni ^{II} -(S)-CF ₃ BPB-Gly (556)		Predominantly bis-product		
Ni ^{II} -(S)-2-CBPB-Gly (577)	78–80	8–10	>98	<2
Ni ^{II} -(S)-3,4-DMBPB-Gly (578)	73–75	10–15	95	~10
Ni ^{II} -(S)-4-BOBPB-Gly (579)	65–70	60–120	90	<15
Ni ^{II} -(S)-2-FBPB-Gly (586)	70–74	3–5	>98.0	<2
Ni ^{II} -(S)-3-FBPB-Gly (588)	45–50	12–15	92.5	~20
Ni ^{II} -(S)-4-FBPB-Gly (590)	45–50	15–20	91.5	~20

a) Chemical yield at alkylation step.

b) Diastereomeric excess based on ¹H NMR, HPLC, and chiral GLC analyses (averaged data).c) Yield of bisalkylated product based on ¹H NMR.**Table 9.24** The averaged results of alkylation of modified alanine complexes by alkyl halides.^{a)}

Modified complex of alanine	Chemical yield (%) ^{b)}	Time (min)	de (%) ^{c)}
Ni ^{II} -(S)-3,4-DCBPB-Ala (568)	85	60	>97
Ni ^{II} -(S)-POFBPB-Ala (569)	80	~120	94
Ni ^{II} -(S)-MOFBPB-Ala (570)	78	~120	93
Ni ^{II} -(S)-CF ₃ BPB-Ala (571)	54	60	92
Ni ^{II} -(S)-2-CBPB-Ala (580)	74	80	>97
Ni ^{II} -(S)-3,4-DMBPB-Ala (581)	78	80	94
Ni ^{II} -(S)-4-BOBPB-Ala (582)	58	120	88
Ni ^{II} -(S)-2-FBPB-Ala (587)	82	30	>97
Ni ^{II} -(S)-3-FBPB-Ala (589)	74	60	92
Ni ^{II} -(S)-4-FBPB-Ala (591)	76	60	90

a) Alkylating reagents in all experiments were taken in two- to three-fold excess with respect to the alanine complex.

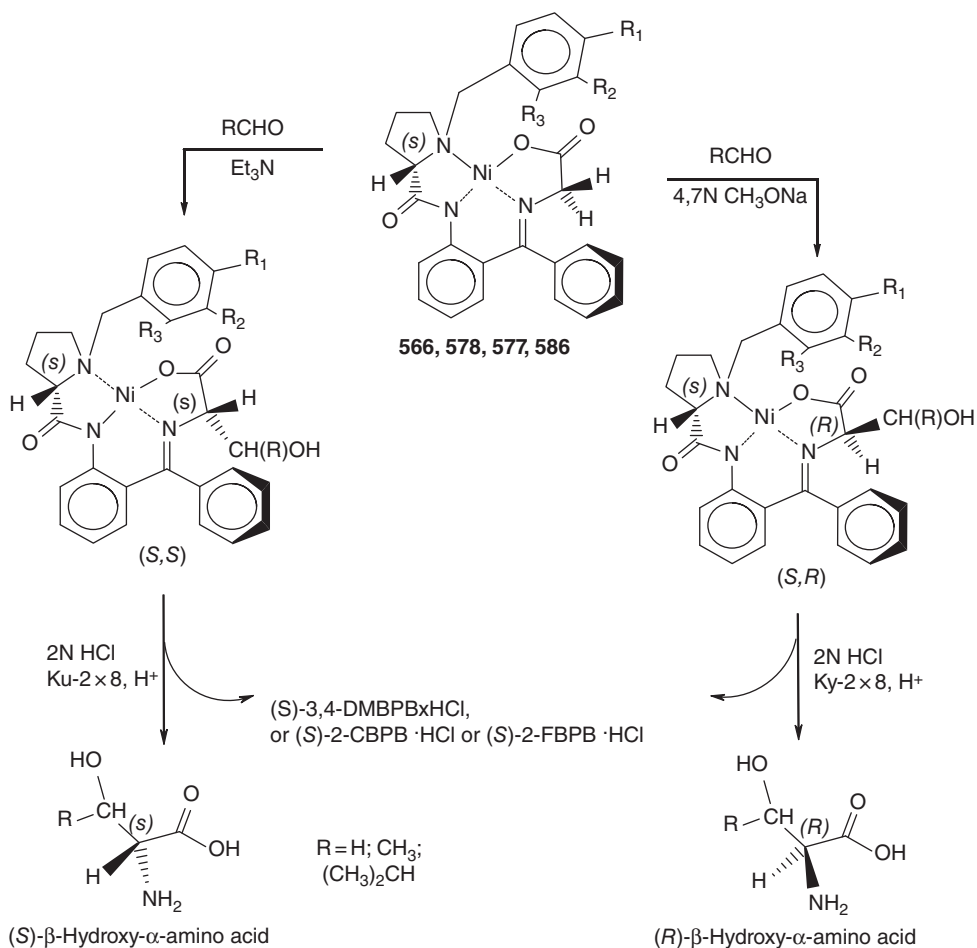
b) Chemical yield at the alkylation step based on ¹H NMR and TLC.

c) Diastereoselective excess based on chiral HPLC and GLC.

Thus, summarizing the results of C-alkylation of amino acid moieties (glycine and alanine) of modified Ni^{II} complexes of their Schiff base with chiral auxiliary reagents, it can be unequivocally stated that the introduction of substituents into the aromatic ring of *N*-benzylproline fragment of the chiral reagent increased the efficiency of reactions.

With that, the best alkylation results by both stereoselectivity of syntheses and transiency of asymmetric reactions are observed in a series of complexes of modified chiral auxiliary reagents such as 3,4-DCBPB $\rightarrow$ 3,4-DMBPB $\rightarrow$ 2-CBPB $\rightarrow$ 2-FBPB [244, 246]. Just these modified complexes of amino acids were used in further studies.

Similar to the above-mentioned asymmetric synthesis methodology of β -hydroxy- α -amino acids (see Section 9.2.3), modified glycine complexes Ni^{II} -(*S*)-3,4-DCBPB-Gly (**566**), Ni^{II} -(*S*)-3,4-DMBPB-Gly (**578**), Ni^{II} -(*S*)-2-CBPB-Gly (**577**), and Ni^{II} -(*S*)-2-FBPB-Gly (**586**) were subjected to aldol condensation in a medium of strong and weak bases [244, 247, 248] (see Scheme 9.113).



Scheme 9.113

Table 9.25 Averaged condensation data of modified glycine complexes with paraformaldehyde, acetaldehyde and isopropylaldehyde.^{a)}

Modified glycine complex	Chemical yield (%)	Time (min)		de (%) ^{b)}	
		(<i>S,R</i>)	(<i>S,S</i>)	(<i>S,R</i>)	(<i>S,S</i>)
Ni ^{II} -(<i>S</i>)-3,4-DCBPB-Gly (566)	64	240–300	60–120	97	93
Ni ^{II} -(<i>S</i>)-3,4-DMBPB-Gly (578)	62	120–220	30–90	94	69
Ni ^{II} -(<i>S</i>)-2-CBPB-Gly (577)	72	90–120	15–30	97	94
Ni ^{II} -(<i>S</i>)-2-FBPB-Gly (586)	66	60–80	10–20	97	95
Ni ^{II} -(<i>S</i>)-BPB-Gly ^{c)}	68	120–180	180–240	90	87

a) Experiments were performed at 45–50 °C.

b) Averaged data based on ¹H NMR, chiral GLC, and HPLC analyses.

c) Data for the unmodified complexes of β-hydroxy-α-amino acids (for comparison).

The efficiency of complex modification was evaluated by diastereoselectivity indices and duration of asymmetric aldol condensation reactions. Stereoselectivity of syntheses was determined by ¹H NMR, chiral GLC, and HPLC analyses of a mixture of diastereomeric complexes of β-hydroxy-α-amino acids, obtained from aldol condensation, as was done for unmodified complexes of β-hydroxy-α-amino acids (see Section 9.2.3). The results are shown in Table 9.25.

Studies have shown that regardless of the structure of the aldehyde for all modified complexes of glycine in the presence of a strong base as a result of aldol condensation preferably β-hydroxy-α-amino acid with (*R*)-absolute configuration is formed, and in the presence of a weak base – (*S*)-β-hydroxy-α amino acid.

As expected, the best results were recorded in aldol condensation of glycine complexes based on modified chiral auxiliary reagents 2-CBPB (**577**) and 2-FBPB (**586**): ee >97%, reaction time 10 to 30 min (in the case of (*S*)-β-oxy-α-amino acids). Modified complexes of (*R*)-serine, (*R*=H) Ni^{II}-(*S*)-3,4-DCBPB-(*R*)-Ser (**592**), Ni^{II}-(*S*)-3,4-DMBPB-(*R*)-Ser (**593**), Ni^{II}-(*S*)-2-CBPB-(*R*)-Ser (**594**), Ni^{II}-(*S*)-2-FBPB-(*R*)-Ser (**595**), and (*R*)-threonine (*R*=CH₃) Ni^{II}-(*S*)-3,4-DCBPB-(*R*)-Thr (**596**), Ni^{II}-(*S*)-3,4-DMBPB-(*R*)-Thr (**597**), Ni^{II}-(*S*)-2-CBPB-(*R*)-Thr (**598**), and Ni^{II}-(*S*)-2-FBPB-(*R*)-Thr (**599**) were investigated in reactions of formation of the corresponding modified complexes of dehydroamino acids (dehydroalanine and dehydroaminobutyric acid).

9.4.2.3 Dehydroamino Acid Complexes with Modified *N*-Benzylproline Moiety in Nucleophilic Addition Reactions

As already mentioned, among the modified Ni^{II} complexes of Schiff bases of amino acids, complexes based on 3,4-DCBPB-, 3,4-DMBPB-, 2-CBPB-, and 2-FBPB-modified chiral auxiliary reagents are distinguished by their stability, high efficiency, and stereodifferentiating ability, and therefore exactly these chiral reagents were used to synthesize Ni^{II} complexes of Schiff bases of dehydroamino

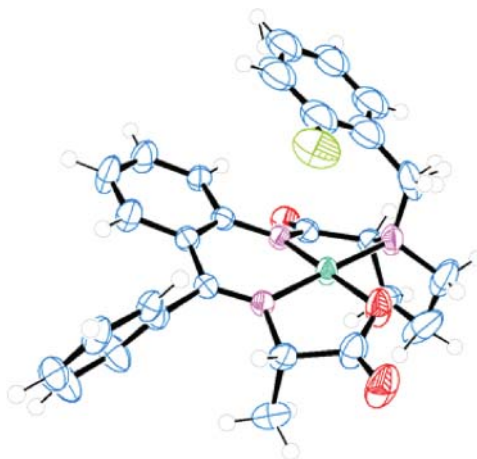


Figure 9.54 Molecular structure of modified dehydroalanine complex **602** based on XRD data.

acids. Using the methods described above for O-acetylation of β -hydroxy- α -amino acid complexes and deacetoxylation of O-acetylated complexes (see Section 9.1.4), modified dehydroalanine **600–603** [247, 248] and (*E*)- and (*Z*)-dehydroaminobutyric acid **604–607** [249–251] complexes were obtained from the corresponding (*R*)-serine (**592–595**) and (*R*)-threonine (**596–599**) complexes (see Figure 9.53).

Synthesis of modified dehydroalanine complexes **600–603** proceeds smoothly with quantitative chemical yields of final products (>80%). The structures of the modified dehydroalanine complexes were established by spectral methods of analysis.

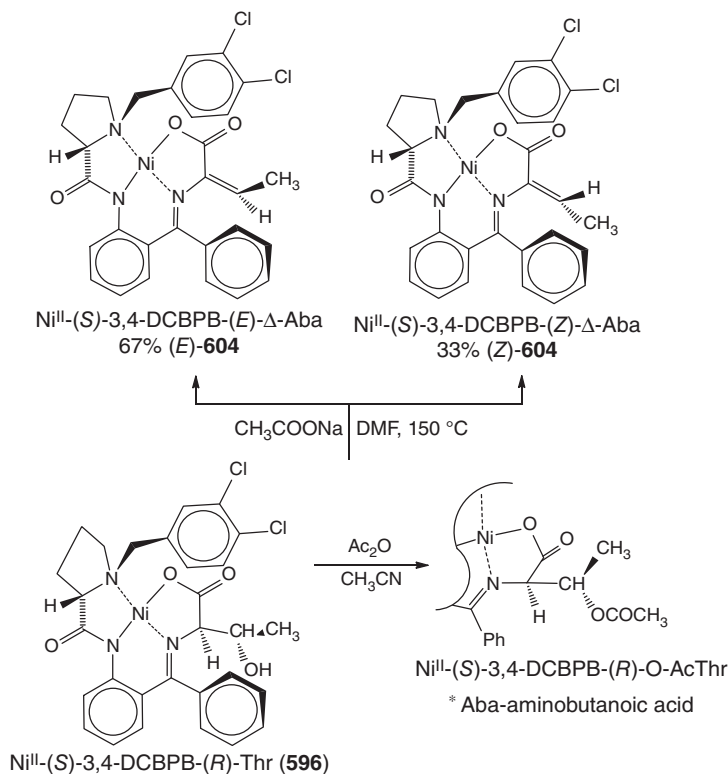
Complex $\text{Ni}^{\text{II}}\text{-(S)-2-CBPB-}\Delta\text{-Ala}$ (**602**) was crystallized to suitable crystals and its structure was examined by XRD analysis (see Figure 9.54).

It should be noted that in a number of chiral metal complexes of Schiff bases of dehydroalanine, the XRD analysis was conducted for the first time.

The synthesis of modified dehydroaminobutyric acid complexes with the formation of (*Z*)- and (*E*)-isomers in varying ratios with the total yield of ~50% proceeds relatively complicated.

The reaction of (*E*)- and (*Z*)-dehydroaminobutyric acid complexes (**604**) formation from (*R*)-threonine complex (**596**) based on modified chiral auxiliary 3,4-DCBPB[251] was studied separately (see Scheme 9.114). The ratio of (*E*)-**604**/(*Z*)-**604** was 2/1 (the ratio of (*E*)- and (*Z*)- dehydroaminobutyric acid complexes is readily determined by ^1H NMR analysis by the ratio of integrals of $\beta\text{-CH}_3$ group; see Section 9.1.4).

Studies have shown that a similar elimination reaction in the case of (*S*)-*O*-acetylthreonine with 3,4-DCBPB complex hardly takes place, and this seems to be due to the effects that arise from the axial and equatorial orientation of α -proton of the α -amino acid moiety (by analogy with serine complexes). Besides, the rate



Scheme 9.114

of planar carbanion formation during the α -H detachment plays a certain role. In case of α,β -elimination of acetic acid from $\text{Ni}^{\text{II}}\text{-(S)-3,4-DCBPB-(S)-O-AcThr}$ complex to form planar carbanion, large steric changes are required and, hence, more energy than in the case of elimination of the acetic acid moiety from $\text{Ni}^{\text{II}}\text{-(S)-3,4-DCBPB-(R)-O-AcThr}$ complex. Thus, detachment of α -H and formation of planar carbanion from the *O*-acetylthreonine complex of (*R*)-*threo* absolute configuration is thermodynamically and kinetically advantageous.

During determination of β -carbon atom configuration of the synthesized (*E*)- and (*Z*)- dehydroaminobutyric acid complexes by ^1H NMR, a significant difference in chemical shifts of methyl group signals of the dehydroaminobutyric fragment in spectra is observed (as in the case of unmodified (*E*)- and (*Z*)-dehydroaminobutyric acid complexes; see Section 9.1.4). The signal of the methyl group at the $\text{C}=\text{C}$ bond of the isomer having the highest R_f on SiO_2 [(*E*)-**604**] is observed at 1.73 ppm and that of the other isomer with a lower R_f value [(*Z*)-**604**] – at 0.83 ppm.

As in the case of complexes based on unmodified chiral reagent (*S*)-BPB, such a shift toward the strong fields indicates a significant magnetic shielding of the methyl group protons due to magnetic anisotropy of the phenyl substituent at

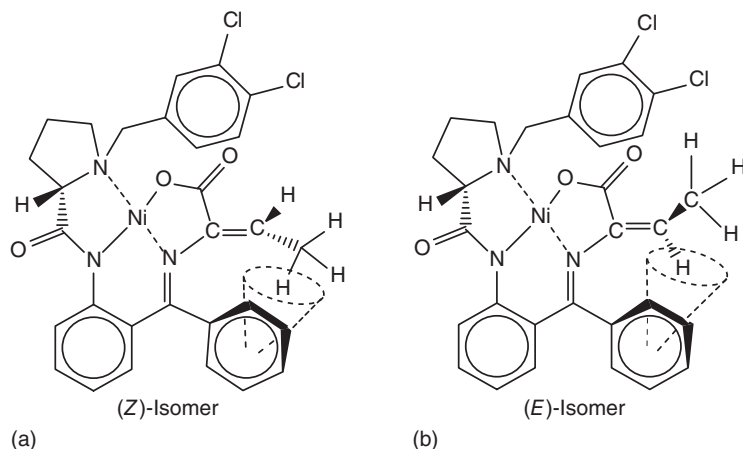


Figure 9.55 Magnetic anisotropy of the phenyl group at the C=N bond in (Z)-**604** (a) and (E)-**604** (b) complexes.

the C=N bond in the case of (Z)-configuration of the dehydroaminobutyric fragment (see Figure 9.55a).

The accuracy of such an assignment for (Z)- and (E)-configuration of dehydroaminobutyric fragment using ^1H NMR spectroscopy was previously confirmed by XRD analysis in the example of complexes with unmodified (S)-BPB.

The reason for formation of a relatively small excess of the (E)-dehydroaminobutyric acid complex [(E)-**604**] in comparison with the (Z)-dehydroaminobutyric acid complex [(Z)-**604**] in the process of elimination of (R)-O-acetylthreonine complex (in case of unmodified complexes with BPB, the ratio is 5/1) is a consequence of kinetic control, since no interconversion between the isomers under elimination conditions is observed.

This conclusion is confirmed by specially designed experiments in acetonitrile using *Dabco* (diazabicyclooctane) as a base. It was found that in contrast to the unmodified complexes with (S)-BPB, in case of complexes with (S)-3,4-DCBPB interconversion between the (Z)- and (E) isomers of dehydroaminobutyric acid complex did not occur. In the case of complexes with (S)-BPB with the initial content of (E)/(Z)=5/1 in the reaction mixture (immediately after elimination) after adding *Dabco* thermodynamic equilibrium between isomers is established, and their ratio is 1/1. In the case of modified complexes based on (S)-3,4-DCBPB (**604**), the ratio of (E)- and (Z)-isomers in the experiment remains unchanged at 2/1.

Analysis of elimination data of (R)-O-acetylthreonine complexes based on (S)-BPB and (S)-3,4-DCBPB chiral auxiliary reagents shows that evidently in both cases the elimination is a kinetically controlled process and proceeds preferably by *syn*-mechanism forming isomer of (E)-configuration.

Previously, it was shown that the reason for the *syn*-elimination preference lay in the relatively large steric hindrances of *anti*-elimination due to the occurrence of steric nonbinding interactions between the CH_3 -group of the acetylthreonine

moiety and the phenyl substituent at the C=N bond in the transition state of that process (see Section 9.1.4.2).

The relatively low preference for *syn*-elimination in the case of (*R*)-*O*-acetylthreonine complex based on (*S*)-3,4-DCBPB chiral reagent compared to the complex with unsubstituted chiral reagent (*S*)-BPB is apparently associated with the presence of additional steric nonbinding interactions between the electron-withdrawing substituents of *N*-benzylproline moiety and a leaving acetoxy group of the amino acid fragment. As it has already been shown by X-ray analysis, in complexes with chiral reagent (*S*)-3,4-DCBPB compared with similarly constructed complex based on unsubstituted chiral reagent (*S*)-BPB, the dichlorobenzyl group more effectively shields the metal coordination plane (see Figure 9.50).

This is also evidenced by the distance between the Ni-C(27): in complexes with (*S*)-3,4-DCBPB it is 2.992(5) Å (which is less than the van der Waals radii), whereas in complexes based on (*S*)-BPB, it is 3.210 Å. From this it follows that the sterically nonbinding interaction between the phenyl group of *N*-benzylproline moiety and β -CH₃-group of (*E*)-dehydroaminobutyric acid fragment is relatively more pronounced in the case of modified complex (*E*)-**604** than in the complex with the unsubstituted chiral reagent (*S*)-BPB [(*E*)-**330**].

Consequently, in the process of elimination, the relative excess of the (*E*)-isomer compared to the (*Z*)-isomer in the case of the modified complex of (*S*)-3,4-DCBPB is lower [(*E*)/(*Z*)=2/1] than in the case of (*E*)-**330** [(*E*)/(*Z*)=5/1].

Calculations of modified complexes **604** and similarly structured complexes based on unsubstituted chiral reagent (*S*)-BPB [(*E*)-**330**] (see Figure 9.57) conducted by MM2 molecular mechanics program on the basis of X-ray analysis of Ni^{II}-(*S*)-3,4-DCBPB-(*S*)-Ala (**568**) (Figure 9.51) and Ni^{II}-(*S*)-BPB-(*E*)- Δ -Aba [(*E*)-**330**] complexes (see Section 9.1.4.2, Figure 9.12) confirm the above assumption.

This is evidenced by the distance between the phenyl group of *N*-benzylproline moiety and the methyl group of dehydroaminobutyric moieties presented in Figure 9.56. This distance in (*E*)-dehydroaminobutyric acid complex based on (*S*)-3,4-DCBPB [(*E*)-**604**] is equal to 8.74 Å, and in unmodified complex [(*E*)-**330**] – 9.01 Å.

The distance between the phenyl group of *N*-benzylproline moiety and the methyl group of dehydroaminobutyric acid fragment is also relatively less in (*Z*)-isomer of complex based on (*S*)-3,4-DCBPB [(*Z*)-**604**] (8.22 Å) compared with the complex (*Z*)-**330** (8.32 Å), but this change, as compared with the (*E*)-isomer, is negligible.

In addition, if the distance between the phenyl group of aminobenzophenone and the methyl group of dehydroaminobutyric acid moieties in case of modified complex (*E*)-**604** and similarly constructed unmodified complex (*E*)-**330** is close in value (4.64 and 4.59 Å, respectively) in the case of the same complexes with (*Z*)-configuration [(*Z*)-**604** and (*Z*)-**330**], these distances differ significantly and are 3.85 and 3.62 Å, respectively.

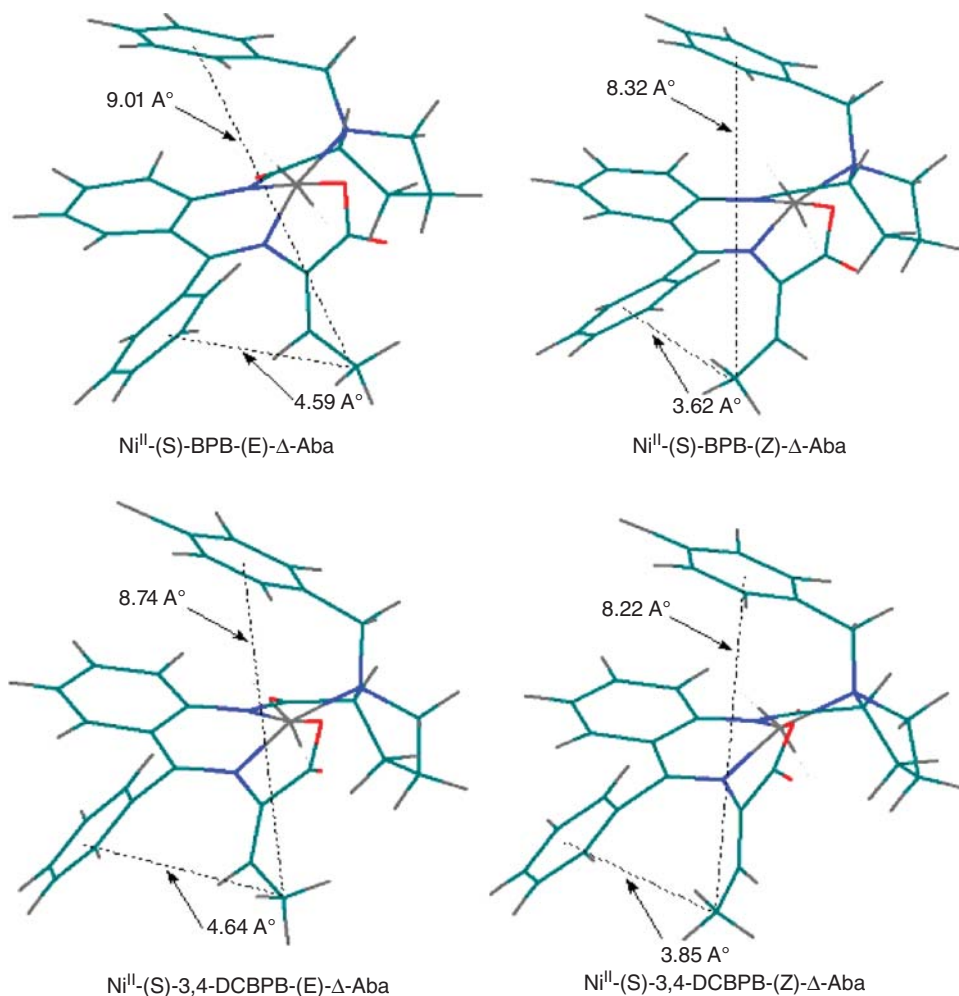


Figure 9.56 Structures of dehydroaminobutyric acid complexes based on MM2 calculations.

The ratio of (*E*)- and (*Z*)-isomers of other modified dehydroaminobutyric acid complexes **605**–**607** based on ^1H NMR data are presented in Table 9.26.

Modified complexes of dehydroamino acids **600**–**607** were investigated in nucleophilic addition reactions [250, 251] under conditions similar to those for unmodified complexes of dehydroamino acids. Scheme 9.115 illustrates the asymmetric addition of nucleophiles to the C=C bond of dehydroalanine fragment of modified complexes **600**–**603** [252].

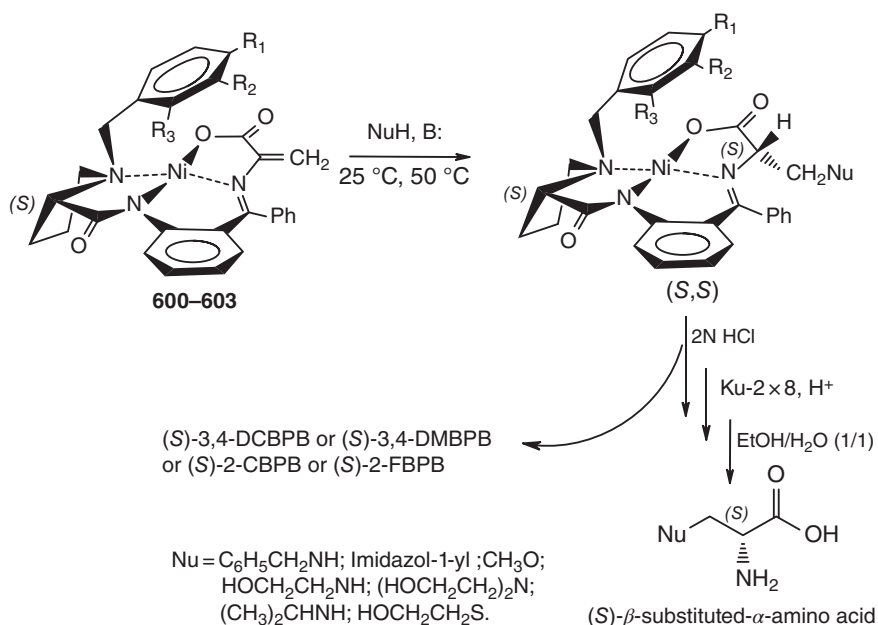
The absolute configuration of the diastereomeric complexes of nucleophilic addition products and their diastereomeric excess (de) were determined as described for the unmodified complexes of corresponding β -substituted α -amino

Table 9.26 Ratio of (*E*)- and (*Z*)-isomers, and chemical yields of modified dehydroaminobutyric acid complexes.

Complex of dehydroaminobutyric acid	(<i>E</i>)/(<i>Z</i>) ^{a)}	Chemical yield (%) ^{b)}
Ni ^{II} -(<i>S</i>)-3,4-DCBPB-Δ-Aba (604)	2/1	46
Ni ^{II} -(<i>S</i>)-3,4-DMBPB-Δ-Aba (605)	3/2	42
Ni ^{II} -(<i>S</i>)-2-CBPB-Δ-Aba (606)	2/1	50
Ni ^{II} -(<i>S</i>)-2-FBPB-Δ-Aba (607)	2/1	48
Ni ^{II} -(<i>S</i>)-BPB-Δ-Aba ^{c)} (330)	5/1	50

a) Ratio of (*E*)- and (*Z*)-isomers by ¹H NMR.b) Overall chemical yield of (*E*)- and (*Z*)-isomers.

c) For comparison, data of unmodified complexes.

**Scheme 9.115**

acids (see Section 9.2.4.1). The averaged results for diastereoselectivity of syntheses and the duration of asymmetric reactions of nucleophilic addition to the modified dehydroalanine complexes are presented in Table 9.27.

As could be expected, the best results on stereoselectivity of syntheses and duration of asymmetric nucleophilic addition reactions are observed in the case of Ni^{II} complexes of Schiff bases of dehydroalanine with modified chiral reagents (*S*)-2-CBPB and (*S*)-2-FBPB (**602**, **603**) containing a halogen atom in position 2 of the phenyl substituent of *N*-benzylproline moiety.

Table 9.27 Averaged data of addition of nucleophiles to dehydroalanine complexes.

Modified dehydroalanine complex	Chemical yield (%)	Time (min) ^{a)}	de (%) ^{b)}
Ni ^{II} -(<i>S</i>)-3,4-DCBPB- Δ -Ala (600)	80	60 (240)	95(82)
Ni ^{II} -(<i>S</i>)-3,4-DMBPB- Δ -Ala (601)	78	40 (120)	94(90)
Ni ^{II} -(<i>S</i>)-2-CBPB- Δ -Ala (602)	84	15–20 (90–180)	98(94)
Ni ^{II} -(<i>S</i>)-2-FBPB- Δ -Ala (603)	76	7–10 (50–80)	97(92)
Ni ^{II} -(<i>S</i>)-BPB- Δ -Ala (327) ^{c)}	85	180–360	~85

a) Duration of the coupling reaction of CH₃OH and HOCH₂CH₂SH. Duration of the addition of amines is given in parentheses.

b) Averaged de data (diastereomeric excess) of addition reaction of CH₃OH and HOCH₂CH₂SH (in brackets – data of amines) on the basis of chiral HPLC and GLC analyses.

c) Data of nucleophile addition to the unmodified complex of dehydroalanine (see Section 9.2.4.1).

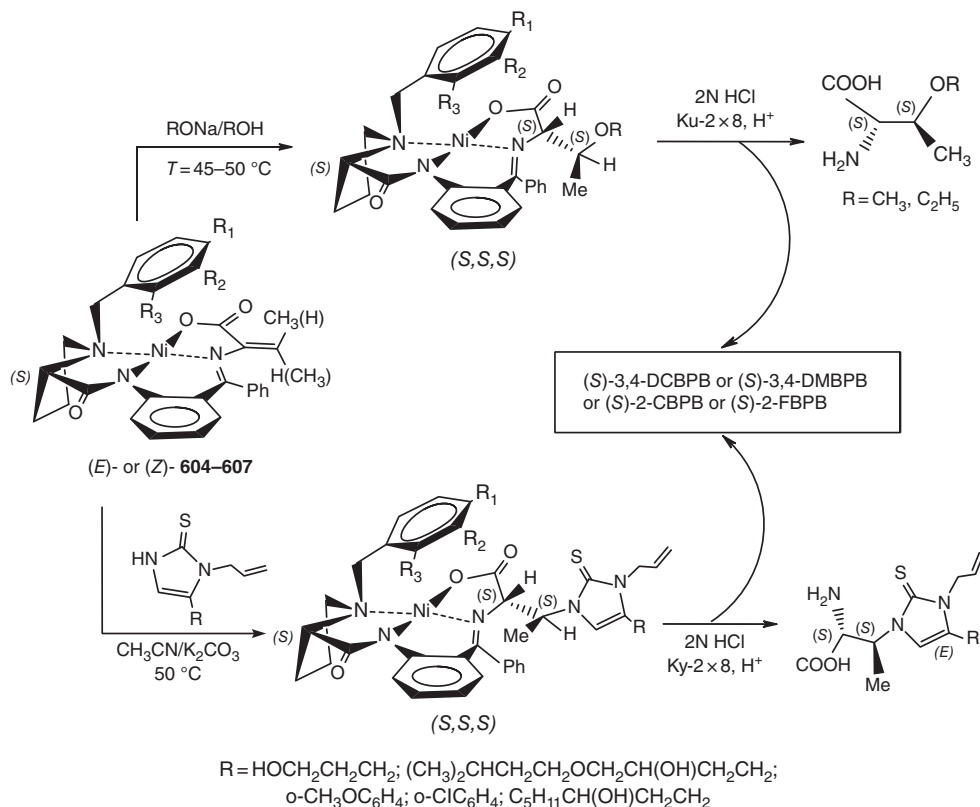
The obtained results on asymmetric addition of nucleophiles to the C=C bond of dehydro-alanine in modified complexes **600–603** clearly correlate with the data on the asymmetric C-alkylation of amino acids in the similarly constructed complexes based on the same modified chiral auxiliaries. In this case, increase in stereoselectivity and acceleration of the reaction of nucleophilic addition can be considered a consequence of conformational changes in the structure of complexes induced by the introduction of substituents into the phenyl ring of *N*-benzylproline fragment.

Modified complexes of (*E*)- and (*Z*)-dehydroaminobutyric acid **604–607** were also studied in nucleophilic addition reactions. Both simple aliphatic alcoholate ions [251] and complex heterocyclic triazoles [253] were used as nucleophiles. Addition of nucleophiles was carried out according to the previously developed technique for dehydroaminobutyric acid complexes based on unsubstituted chiral auxiliary (*S*)-BPB (see Sections 9.2.4.2 and 9.2.6.2).

Scheme 9.116 illustrates the asymmetric addition of alcoholate ions and substituted 1,2,4-triazoles to the C=C bond of the modified (*E*)- and (*Z*)-dehydroaminobutyric acid complexes. The absolute configuration of the induced new chiral centers in α - and β -positions of aminobutyric acid fragment and ratio of diastereomers of synthesized complexes of β -substituted α -aminobutyric acid were determined by ¹H NMR and chiral HPLC analyses by analogy with the developed methodology for the same amino acid complexes with unsubstituted chiral reagent (*S*)-BPB (see Sections 9.2.4.2. and 9.2.5.2).

Averaged results on diastereoselectivity, chemical yields, and the duration of asymmetric nucleophilic addition reactions are presented in Table 9.28.

Based on the data presented in Table 9.28, it is obvious that the maximum diastereoselectivity and the rate of the addition reaction in the case of both aliphatic alcoxy ions and complex heterocyclic triazoles are observed with the use of dehydroaminobutyric acid complexes with modified chiral reagents (*S*)-2-CBPB and (*S*)-2-FBPB.

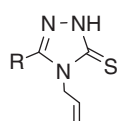
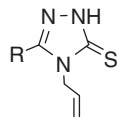
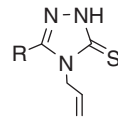
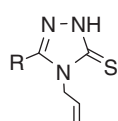


Scheme 9.116

Addition of substituted triazoles to individually pure (*E*)- and (*Z*)-dehydroaminobutyric acid complexes and their mixtures was also investigated. It was shown that regardless of the (*E*)- or (*Z*)-configuration of dehydroaminobutyric fragment of modified complexes **604–607**, the main reaction adducts were diastereoisomers containing aliphatic and heterocyclic derivatives of aminobutyric acid with (*S*)-*anti* configuration. By analogy with previous results, in this case, an increase in *de* and a sharp reduction in the nucleophilic addition reaction time at the transition from (*Z*)-dehydroaminobutyric acid complexes to (*E*)-dehydroaminobutyric acid complexes are also observed (see Table 9.28).

Analyzing the data in Table 9.28, it can be seen that practically all the used nucleophiles readily reacted (in a short time to a large extent) with (*E*)-isomers of dehydroaminobutyric acid complexes with modified chiral auxiliary reagents. It should be mentioned that in the example of complexes based on unsubstituted chiral (*S*)-BPB reagent it was shown that, irrespective of the (*Z*)- or (*E*)-configuration of the starting dehydroaminobutyric acid complex, identical results were observed

Table 9.28 The results of addition of aliphatic and heterocyclic nucleophiles to modified complexes of dehydroaminobutyric acid (averaged data).^{a)}

Modified complex of dehydroaminobutyric acid	NuH	de (%) ^{b)(S,S,S)}	Time (h)	Chemical yield (%) ^{c)}
Ni ^{II} -(S)-3,4-DCBPB-(E)-Aba, (E)- 604	RO [−]	92	1.2	88
Ni ^{II} -(S)-3,4-DCBPB-(Z)-Aba, (Z)- 604		40	35	49
Ni ^{II} -(S)-3,4-DCBPB-(E) + (Z)-Aba, (E,Z)- 604		56	35	64
Ni ^{II} -(S)-3,4-DCBPB-(E)-Aba, (E)- 604		94	6–15	84
Ni ^{II} -(S)-3,4-DCBPB-(Z)-Aba, (Z)- 604		—	—	<3
Ni ^{II} -(S)-3,4-DCBPB-(E) + (Z)-Aba, (E,Z)- 604		—	—	44
Ni ^{II} -(S)-3,4-DMBPB-(E)-Aba, (E)- 605	RO [−]	92.5	2–4	85
Ni ^{II} -(S)-3,4-DMBPB-(E)-Aba, (E)- 605		93	6–12	76
Ni ^{II} -(S)-2-CBPB-(E)-Aba, (E)- 606	RO [−]	>98	1–4	86
Ni ^{II} -(S)-2-CBPB-(E)-Aba, (E)- 606		97	6–18	92
Ni ^{II} -(S)-2-FBPB-(E)-Aba, (E)- 607	RO [−]	97	0.3–1	68
Ni ^{II} -(S)-2-FBPB-(E)-Aba, (E)- 607		97	2–5	72

a) Table shows addition of nucleophiles of (E) and (Z)-dehydroaminobutyric acid and their mixtures for complex **604**. A similar pattern was also found for other complexes **605–607**.

b) Diastereomeric excess of (S,S,S)-diastereomeric adducts according to ¹H NMR and chiral HPLC (averaged).

c) Chemical yield at the nucleophile coupling step.

with nucleophilic addition. It is obvious that such a deviation in the case of dehydroaminobutyric acid complexes with modified chiral reagents is due to the distortion of a chelate structure of complexes caused by the presence of additional substituents in the phenyl ring of *N*-benzylproline moiety.

This can be explained by analyzing the structures of these complexes. By using molecular mechanical calculations, it is shown that in dehydroaminobutyric acid complexes there are sterically nonbinding interactions between β -CH₃ group of dehydroaminobutyric fragment, phenyl substituent at the C=N bond and the hydrogen atoms of a pyrrolidine moiety that lead to significant distortion of the chelate ring of amino acid moiety (see Figure 9.57).

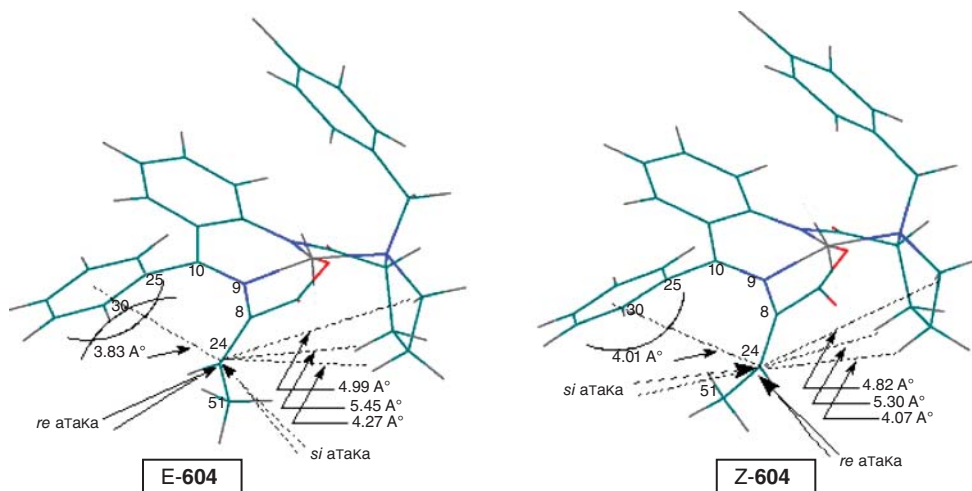


Figure 9.57 Molecular-mechanics calculations of the structures of (*E*)- and (*Z*)- dehydroaminobutyric acid complexes [(*E*)-**604** and (*Z*)-**604**] by MM2 program.

For example, torsion angles $C(30)-C(25)-C(10)=N(9)$ are 31° and 28° , $C(10)=N(9)-C(8)=C(24)$ -33° and 39° and $N(9)-C(8)=C(24)-C(51)$ 0° and 6° , respectively, for (*E*)-**604** and (*Z*)-**604** isomers. This means that the phenyl group at the $C=N$ bond is relatively more inclined toward dehydroaminobutyric fragment in the case of (*E*)-isomers than in the case of (*Z*)-isomers. Consequently, in case of (*E*)-dehydro-aminobutyric acid complexes, *si* attack of the nucleophile preferably occurs, providing (*S*)-absolute configuration of β -carbon atom with high stereoselectivity. In case of (*Z*)-isomers of dehydroaminobutyric acid complexes, *re* and *si* attacks of the nucleophile toward the dehydroamino acid moiety occur almost equally, which leads to relatively low stereoselectivity of addition reaction. This is evidenced by the molecular-mechanical calculations of the distances between the phenyl group of aminobenzophenone, β -carbon atom of dehydroamino acid, and hydrogen atoms of pyrrolidine moieties (see Figure 9.57).

The distance between the phenyl group of aminobenzophenone moiety and β -carbon atom of dehydroaminobutyric fragment in the case of (*E*)-**604** complex is equal to $3.83 \text{ \AA}$, and in case of (*Z*)-**604** complex – $4.01 \text{ \AA}$. Thus, the torsion angles, and the distance between the phenyl group at the $C=N$ bond and the β -carbon atom of dehydroaminobutyric fragment, indicate a relatively strong difficulty of *re* attack of the nucleophile in the case of (*E*)-**604**, compared with (*Z*)-**604**. Consequently, in the case of (*E*)-dehydroaminobutyric acid complexes, the most preferred is the *si* attack of the nucleophile on the dehydroaminobutyric acid moiety followed by protonation of the formed carbanion.

In both cases, protonation of intermediate prochiral carbanions of nucleophilic addition products preferably occurs from the *re* side of the Schiff base plane, providing (*S*)-absolute configuration of the α -carbon atom of amino acid moiety. This is apparently due to the presence of nonbonding steric interactions between

the phenyl groups of *N*-benzylproline and aminobenzo-phenone moieties and side-chain radical of amino acid fragment whereby a bulky lateral group of the amino acid is located on the *si*-side of the Schiff base plane, and approximation of proton occurs from the *re*-side.

Such sterically nonbonding interactions are relatively more pronounced in the case of nucleophiles addition to (*E*)-dehydroaminobutyric acid complex, rather than to (*Z*)-isomer, which causes a relatively high stereoselectivity of nucleophilic addition in case of (*E*)-**604**.

However, the rate of nucleophilic addition reaction in the case of (*E*)-dehydroaminobutyric acid complex is many times higher than the rate of the addition to complex (*Z*)-**604**. To explain this difference, molecular mechanical calculation was used and the distances between the hydrogen atoms of the pyrrolidine moiety (β , γ δ ,) and the β -carbon atom of dehydroaminobutyric acid fragment were determined (see Figure 9.57). As can be seen from Figure 9.57, hydrogen atoms of the pyrrolidine moiety stronger shield the *re* attack of nucleophiles on β -carbon atom of dehydroamino-butyric acid moiety in case of (*Z*)-configuration than the *si* attack in case of (*E*)-configuration. Presumably, this is the cause for high rate of nucleophilic addition in the case of (*E*)-dehydroamino-butyric acid complex compared to complex of (*Z*)-dehydroaminobutyric acid.

Thus, this section shows a principal possibility of highly selective and relatively transient asymmetric synthesis of important β -aliphatic and β -heterocyclic derivatives of (2*S*,3*S*)-*allo*-aminobutyric acid using Ni^{II} ion complexes of Schiff base of (*E*)-dehydroaminobutyric acid with modified chiral auxiliary reagents 2-CBPB and 2-FBPB. An increase in effectiveness of model complexes (increase in de and reduction of syntheses duration) in a series of chiral auxiliary reagents BPB $\rightarrow$ 3,4-DCBPB $\rightarrow$ 3,4-DMBPB $\rightarrow$ 2-CBPB was observed, in the example of addition of simple aliphatic and complex heterocyclic nucleophiles of 1,2,4-triazole series.

Summarizing materials of this chapter on testing the modified Ni^{II} complexes of Schiff bases of amino acids and dehydroamino acids, it can be confirmed that the chiral auxiliary reagents 2-CBPB and 2-FBPB containing a halogen atom in position 2 of the phenyl group of *N*-benzyl-proline moiety may be advised to design a highly efficient technology for preparative production of optically active nonprotein α -amino acids of different structures.

Undoubtedly, considering the high selectivity and the transience of syntheses using these modified chiral auxiliary reagents, the developed methods can be used in synthesis of ^{18}F -labeled amino acids – precursors for PET radiopharmaceuticals [254].

9.5

Stoichiometric Asymmetric Synthesis of Unsaturated α -Amino Acids

Unnatural amino acids constitute more and more attractive targets for drug design, and their asymmetric synthesis has been increasingly developed over the

past decades. It is well known that nonproteinogenic amino acids' incorporation in peptide sequences increases resistance to enzymatic proteolysis [255]. Moreover, disposing of a wide variety of unnatural amino acids allows the modulation of physical and chemical properties of the resulting peptides depending on the selected side chains [256]. In this domain, unsaturated amino acids represent very interesting building blocks. Indeed, alkenyl- or alkynyl side chains can be functionalized by many chemical functions and offer a wide range of possible transformations [257–261]. Particularly unsaturated α -amino acids give access to many synthetic applications in all fields of chemistry [262]. Among them, metal catalyzed cross-coupling reactions and cross metatheses are commonly used to generate peptide modifications [263, 264] and cyclizations [265]. They can also be substrates of biological interest for fluorination for example as PET radiotracers [266]. They are very interesting and useful tools for “click” chemistry [267, 268] in peptidomimetic drug design or covalent modification of proteins [269]. They can also be incorporated in compounds as a beta-turn inducer to promote secondary structures [270]. Finally, they can be used for the preparation of stapled peptides. Stapled peptides were first designed by Verdine as a hydrocarbon staple that ‘locked’ a flexible peptide into the shape of an alpha-helix by reaction of two α,α -disubstituted nonnatural amino acids bearing an olefin side chain [271]. In recent years, a great number of papers have appeared on stapled peptides [272–274] and it has been demonstrated that monosubstituted alkenyl amino acids are also suitable for their preparation [275, 276].

In previous chapters, the use of amino acid-Ni-BPB complexes (BPB = *N*-(benzylpropyl)aminobenzophenone) as a chiral starting material for the synthesis of amino acids was described [277, 278].

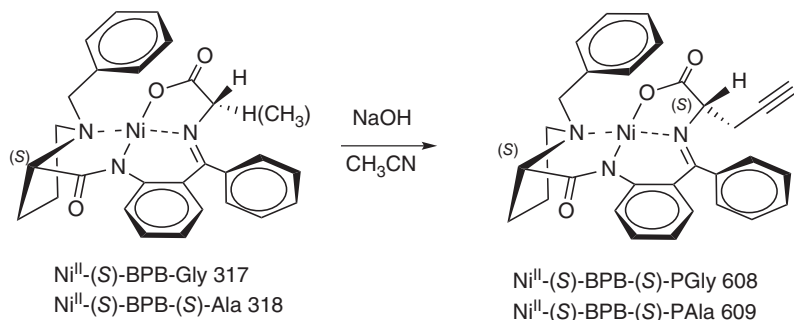
Alkynylated amino acids represent attractive target compounds which are not readily available in enantiomerically pure form. The Sonogashira reaction of free (*S*)-2-aminopent-4-ynoic acid has been previously reported to be successful only when highly reactive iodobenzenes were employed [279]. Bromobenzenes can be used after protecting the carboxyl and amino groups [280].

In this chapter, we report the synthesis of enantiomerically enriched derivatives of (*S*)-propargylglycine substituted at both α -carbon moiety and acetylenic group of propargyl moiety by C-alkylation of chiral Ni^{II} complex of Schiff bases of (*S*)-propargylglycine and (*S*)-BPB[Ni^{II} -(*S*)-BPB-(*S*)-PGly].

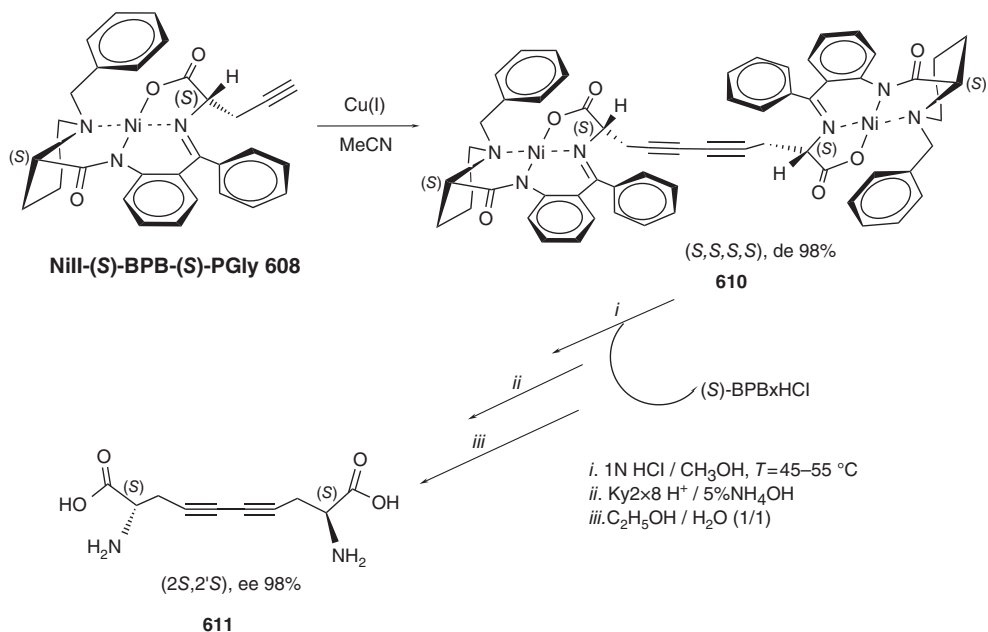
To perform asymmetric synthesis of nonprotein unsaturated (*S*)- α -amino acids, square-planar Ni^{II} ion complexes of propargylglycine and propargylalanine Schiff bases with chiral auxiliary reagent (*S*)-BPB were used as starting amino acid synthons [(*S*)-BPB Ni^{II} -(*S*)-BPB-(*S*)-PGly, **608**, (*S*)-BPB Ni^{II} -(*S*)-BPB-(*S*)-PGly, **609**] (Scheme 9.117).

The synthesis of **608** is in good yield and with >95% diastereomeric excess (Scheme 9.118) [281]. The cleavage of complex **608** in MeOH/HCl leads to (*S*)-2-aminopent-4-ynoic acid.

To obtain dimer of (*S*)-propargylglycine, the oxidative dimerization of complex Ni^{II} -(*S*)-BPB-(*S*)-PGly (**608**) was carried out at the acetylenic group in $\text{CH}_3\text{CN}/\text{K}_2\text{CO}_3$ in the presence of CuCl catalyst (Scheme 9.118).



Scheme 9.117



Scheme 9.118

We succeeded in obtaining crystals of dimeric complex **611** and confirmed (*S*)-absolute configuration of its amino acid moiety in Figure 9.58.

The next stage was the study of the reaction of C-alkylation of propargylglycine fragment of complex **608** by alkylhalogenides (Scheme 9.119). Allyl bromide, benzyl bromide and its halogen-substituted analogs were used as alkyl halogenides (RX).

The reaction of C-alkylation of amino acid moiety of complex **608** was conducted in DMF/NaOH and MeCN/ K_2CO_3 /Cu(I).

As a result, it was detected that when conducting the reactions of alkyl halogenides, condensation to complex **608** in MeCN/ K_2CO_3 in the presence of CuCl,

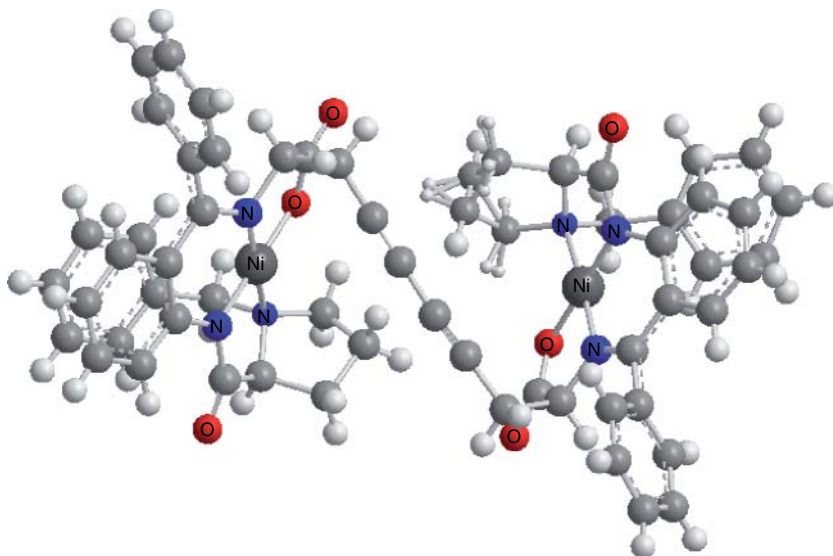
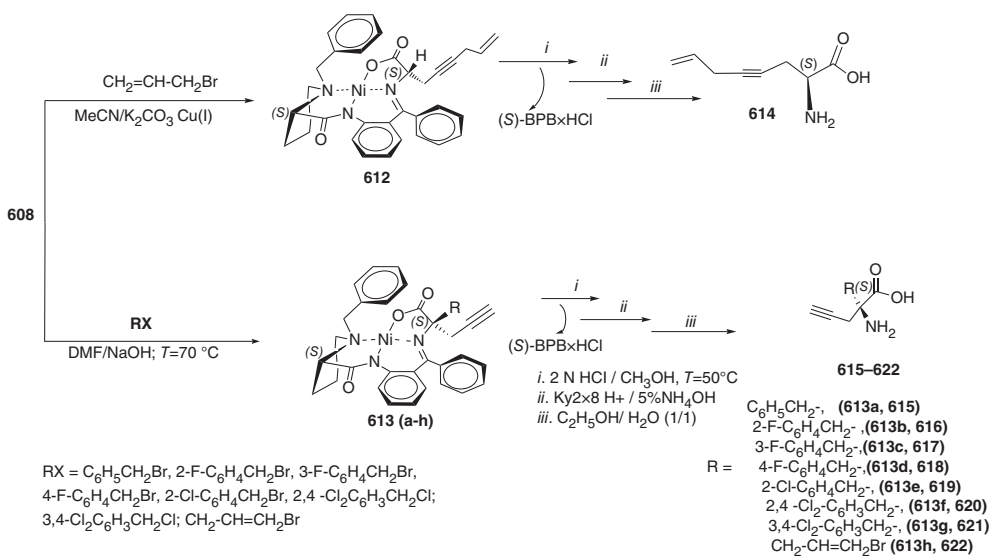


Figure 9.58 X-Ray of the product of oxidative dimerization of **611** complex.



Scheme 9.119

substitution at the acetylenic hydrogen atom occurs only in the case of using allyl bromide with the formation of (*S*)-4-allylpropargylglycine complex (**612**). When the reaction of alkylation is carried out in DMF in the presence of NaOH, substitution of α -H-amino acid residue with the formation of complexes of α -alkyl substituted (*S*)-propargylglycines (**613a–h**) is observed for all halogenides [282, 283].

The major fractions of synthesized complexes (**612**, **613a–h**) were chromatographed and their structures confirmed by spectral methods. Absolute configuration of α -carbon atom of amino acid moieties of complexes was assigned by polarimetric measuring.

Isolation of the target enantiomerically enriched amino acids (**615–622**) from the major diastereomeric complexes (**612**, **613a–h**) was conducted according to a general procedure [174]. Their structures and absolute configurations were determined by spectral methods.

The ratio of (*S,S*)- and (*S,R*)-diastereomers of alkylation products was evaluated by ^1H NMR analysis of the mixture of diastereomeric complexes (before chromatography) by the ratio of the integral intensities of the signals of methylene protons of *N*-benzylproline moiety in the range of 2.55–4.40 ppm. Besides, the ratio of diastereomeric complexes was additionally verified by chiral HPLC analysis of the mixture of amino acids obtained after acidic decomposition of the mixture of diastereomeric complexes (before chromatography) and ion-exchange demineralization. The results are given in Table 9.29.

The target α -alkyl and aryl substituted propargylglycines (**615–622**) as well as (*S*)-2-aminoocta-7-en-4-ynoic acid (**614**) were isolated from the diastereomeric mixtures of alkylated complexes, according to the standard procedure and crystallized from aqueous alcoholic solutions. The structures and absolute configuration of synthesized amino acids were established by physicochemical methods.

Table 9.29 The results of asymmetric C-alkylation of $\text{Ni}^{\text{II}}\text{-(S)-BPB-(S)-PGly}$.^{a)}

RX	Alkylated complex			Target amino acid		
	Major diastereomer	de (%) ^{b)}	Chem. yield (%) ^{c)}	Amino acids	ee (%) ^{d)}	Chem. yield (%)
$\text{CH}_2=\text{CH}-\text{CH}_2-\text{Br}^{\text{e)}$	612	74	74	614	98.5	71
$\text{C}_6\text{H}_5\text{CH}_2\text{Br}$	613a	72	55	615	97.5	60
$2\text{-F-C}_6\text{H}_4\text{CH}_2\text{Br}$	613b	70	52	616	95.5	64
$3\text{-F-C}_6\text{H}_4\text{CH}_2\text{Br}$	613c	68	62	617	96.5	71
$4\text{-F-C}_6\text{H}_4\text{CH}_2\text{Br}$	613d	76	67	618	95.0	64
$2\text{-Cl-C}_6\text{H}_4\text{CH}_2\text{Br}$	613e	73	58	619	96.4	64
$2,4\text{-Cl}_2\text{-C}_6\text{H}_3\text{CH}_2\text{Cl}$	613f	69	68	620	97.8	64
$3,4\text{-Cl}_2\text{-C}_6\text{H}_3\text{CH}_2\text{Cl}$	613g	71	60	621	95.3	64
$\text{CH}_2=\text{CH}-\text{CH}_2-\text{Br}$	613h	75	55	622	96.4	59

a) Reaction conditions: DMF/NaOH, 70 °C.

b) de determined by NMR.

c) Chemical yield of diastereomeric complexes at the stage of alkylation.

d) Determined by the method of chiral HPLC of the amino acid obtained after decomposition of the mixture of diastereomeric complexes and ion-exchange demineralization.

e) Reaction conditions: $\text{CH}_3\text{CN}/\text{K}_2\text{CO}_3/\text{Cu(I)}/28\text{ °C}$.

Table 9.30 Optimization for the synthesis of **623**.

Pd source (mol%)	Cul (mol%)	Solvent	PhBr (equiv.)	Base (ml)	Temp. (°C)	Time (h)	Yield (%) ^{a)}
PdCl ₂ (PPh ₃) ₂ (5)	10	1,4-Dioxane	0.84	HNiPr ₂ (0.5)	90	6	46
Pd(PPh ₃) ₄ (5)	10	1,4-Dioxane	0.84	HNiPr ₂ (0.5)	90	6	70
Pd(PPh ₃) ₄ (5)	10	THF	0.84	HNiPr ₂ (0.5)	90	6	58
Pd(PPh ₃) ₄ (5)	10	DMF	0.84	HNiPr ₂ (0.5)	90	6	64
Pd(PPh ₃) ₄ (5)	10	MeCN	0.84	HNiPr ₂ (0.5)	90	6	59
Pd(PPh ₃) ₄ (5)	10	1,4-Dioxane	0.84	Et ₃ N (0.5)	90	6	45
Pd(PPh ₃) ₄ (5)	5	1,4-Dioxane	0.84	HNiPr ₂ (0.5)	90	6	57
Pd(PPh ₃) ₄ (2.5)	5	1,4-Dioxane	0.84	HNiPr ₂ (0.5)	90	6	40
Pd(PPh ₃) ₄ (5)	10	DMF	0.84	HNiPr ₂ (0.5)	140	6	69
Pd(PPh ₃) ₄ (5)	10	1,4-Dioxane	0.84	HNiPr ₂ (0.25)	90	6	33
Pd(PPh ₃) ₄ (5)	10	1,4-Dioxane	0.84	HNiPr ₂ (1.0)	90	6	83
Pd(PPh ₃) ₄ (5)	10	1,4-Dioxane	0.84	HNiPr ₂ (1.5)	90	6	71
Pd(PPh ₃) ₄ (5)	10	1,4-Dioxane	1	HNiPr ₂ (1.0)	90	6	70
Pd(PPh ₃) ₄ (5)	10	1,4-Dioxane	1.2	HNiPr ₂ (1.0)	90	6	79
Pd(PPh ₃) ₄ (5)	10	1,4-Dioxane	1.2	HNiPr ₂ (1.0)	90	3	76

a) Isolated yield.

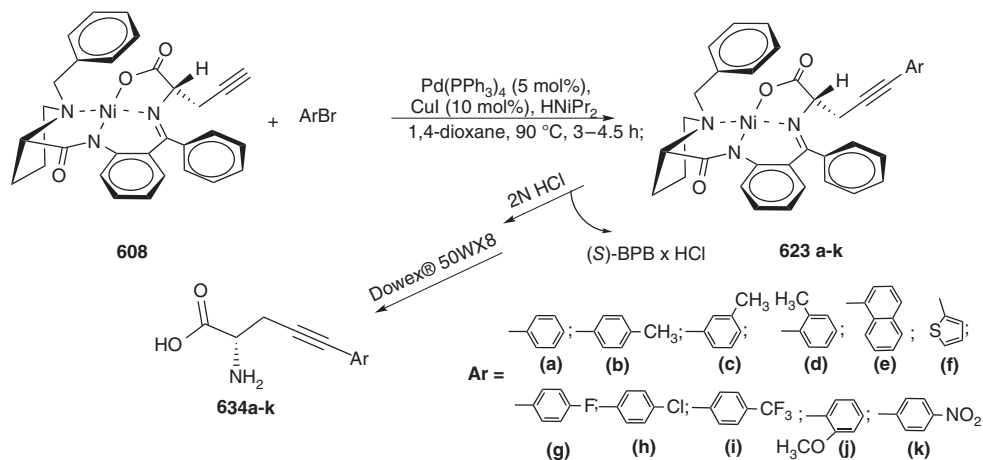
Also, there was developed a straightforward synthesis of alkynylated amino acids based on Sonogashira cross-coupling reaction of Ni complex **608** and subsequent deprotection (Table 9.30).

This process clearly proved advantageous in terms of yield, scope, and availability and costs of educts. The solvent of choice was 1,4-dioxane, while DMF, THF, and acetonitrile gave slightly lower yields. The base HNiPr₂ gave good yields, while Et₃N drastically decreased the yield (Table 9.30).

The Sonogashira cross-coupling reaction complex **608** with bromobenzenes afforded complexes **623a–k** in good to excellent yields using the inexpensive and commercially available catalyst Pd(PPh₃)₄ (Scheme 9.120).

The cleavage of complexes **623a–k** gave the corresponding free amino acids **624a–k** in very good yields (Table 9.31). The decomplexation was carried out by reflux in a MeOH/H₂O/HCl solvent mixture for 20 min. The free amino acids were obtained in very good to excellent yields. Electron donating and electron withdrawing groups on the benzene ring did not affect the yield. The enantiomeric excess was checked by chiral HPLC (Crownpak CR(–) column) and was estimated as >99%. This proved that the optical purity was not affected by the Sonogashira cross-coupling reaction or the cleavage step.

In addition, the twofold Sonogashira cross-coupling reaction could be successfully carried out using 1,4-dibromobenzene (Scheme 9.121). Compound **625** was obtained in 46% yield, which amounts to 68% for each coupling step. The deprotection afforded bis-amino acid **626**.

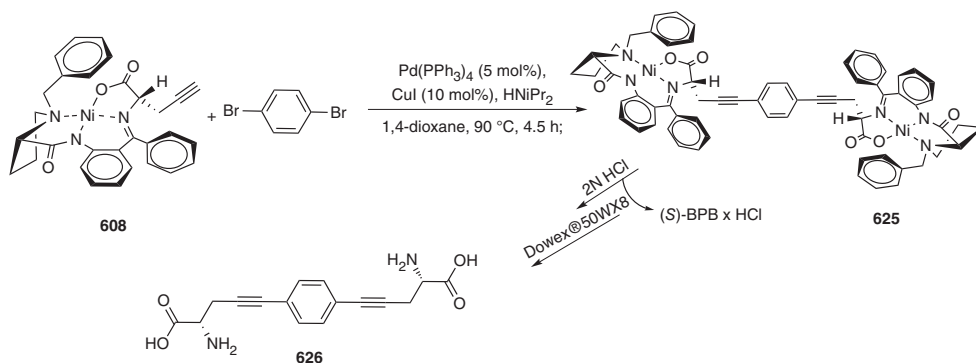


Scheme 9.120

Table 9.31 Derivatives 623a–k and 624a–k.

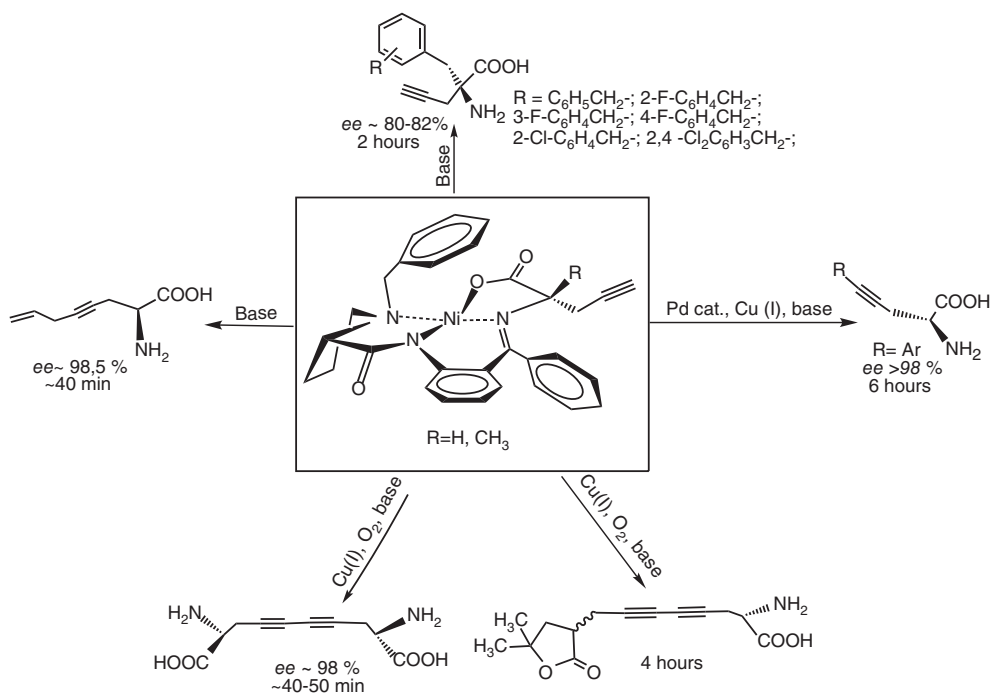
Ar	Time (h)	Yield (623a–k) (%) ^{a)}	Yield (624a–k) (%) ^{a)}
Phenyl (a)	3.0	79	87
4-Tolyl (b)	3.0	67	89
3-Tolyl (c)	3.0	71	86
2-Tolyl (d)	3.0	46	72
Naphth-1-yl (e)	4.5	68	52
Thiophen-2-yl (f)	3.5	78	88
4-Fluorobenzene (g)	3.0	71	90
4-Chlorobenzene (h)	3.0	72	84
4-(Trifluoromethyl)benzene (i)	3.0	76	92
3-Methoxybenzene (j)	3.5	67	99
4-Nitrobenzene (k)	3.0	7	7

a) Isolated yield



Scheme 9.121

Based on the scientific research results given in this section, obtaining of unsaturated (*S*)- α -amino acids is demonstrated in Scheme 9.122.



Scheme 9.122

In conclusion, the described straightforward strategy allowed preparation of a variety of optically pure unsaturated α -amino acids with a broad preparative scope.

9.6

Universal Technology for Small-Scale Production of Optically Active Non-Proteinogenic α -Amino Acids

Based on the scientific research results given in the previous sections, a universal method for the synthesis of nonproteinogenic optically active (*S*)- and (*R*)- α -amino acids containing various aliphatic, aromatic, and heterocyclic substituents in the side-chain radical has been developed. The method is based on the use of Ni^{II} complexes of Schiff bases of amino acids and dehydroamino acids with chiral auxiliary BPB (see Scheme 9.123).

For this, we used reactions of electrophilic alkylation of amino acid moieties that resulted in obtaining of α -substituted α -amino acids and addition reactions of nucleophiles to the $C=C$ bond of dehydroamino acid moieties of complexes with formation of β -substituted α -amino acids (Scheme 9.123).



Scheme 9.123

Analysis of the obtained results shows that Ni^{II} complexes of Schiff bases of amino acids and dehydroamino acids are good precursors to organize small-scale production of enriched nonproteinogenic amino acids as 90% stereoselectivity and 1–3 h duration are good technological parameters for the asymmetric reactions.

Based on the obtained data and effective technology for the preparative production of enantiomerically enriched nonproteinogenic amino acids have been developed. The developed technology has the following technological advantages:

- The technology is universal and makes it possible to obtain different nonproteinogenic amino acids on one production line using the same starting complex.
- High stereoselectivity. De of the main diastereomer of the alkylation product practically for all reactions is 90% and more. This allows producing optically pure amino acid with more than 98–99% enantiomeric purity by one crystallization.
- Regeneration of chiral auxiliary. After each synthesis, the starting chiral auxiliary BPB regenerates with a quantitative yield and complete retention of the starting optical activity. This allows using it many times in the reactions of asymmetric synthesis of amino acids.
- Profitability of the technology. The technology enables obtaining expensive and important nonprotein amino acids from available and inexpensive raw

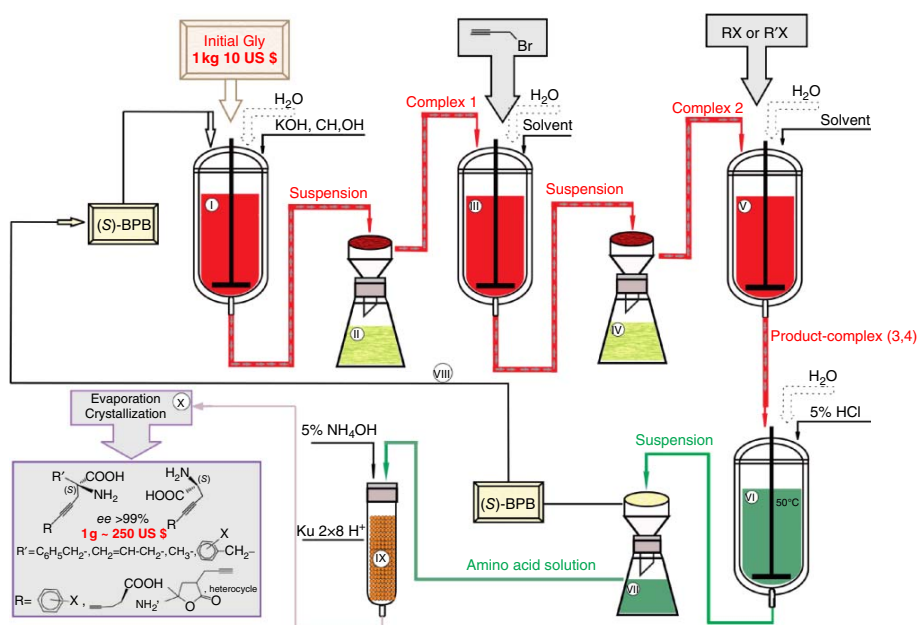


Figure 9.59 Technological scheme for preparative production of optically active α -amino acids.

material – glycine and D,L-alanine the cost of which is about 10 USD per 1 kg of the substance. And the cost of the products, I mean – synthesized amino acids are, in average, 350 USD per 1 g of the sample. By this price, we realize our amino acids in the European market.

Using the developed technology small-scale production for enantiomerically enriched nonproteinogenic (*S*)- and (*R*)- α -amino acids containing different aliphatic, aromatic, and heterocyclic substituents in the side-chain radical has been set up in the Scientific and Production Center “Armbiotechnology” of the National Academy of Sciences of the Republic of Armenia.

The technological scheme for preparative production of enantiomerically enriched nonproteinogenic (*S*)- α -amino acids in the example of those containing unsaturated bonds in the side-chain radical is shown in Figure 9.59.

Using this technology, more than 150 new, not described in the literature, non-proteinogenic optically active (*S*)- and (*R*)- α -amino acids containing aliphatic, aromatic, and heterocyclic substituents in the side-chain radicals have been synthesized in different countries (Armenia, Russia, USA, China, etc.).

By this technological line, about 15 names of nonproteinogenic amino acids are regularly produced and realized in the European market. Some of these compounds are included in the General Catalog of the Belgian “ACROSS ORGANICS” and German “Iris Biotech GmbH” Company.

The given scheme is universal and it can be used for small-scale production of other α - and β -substituted (*S*)- and (*R*)- α -amino acids presented in Scheme 9.123.

The studies were conducted with the financial support of the International Science and Technology Center (ISTC) within the framework of Projects #A-356, #2780, #A-1247, and #A-1677, commercialization initiative # CI-073, and Project-ID Az 86 223, Volkswagen Stiftung, Germany.

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