Asymmetric Synthesis in Organophosphorus Chemistry

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Synthetic Methods, Catalysis, and Applications

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Dedicated to my best friend and darling woman, Galina.

Contents

Preface

Chiral phosphorus compounds play an important role in many areas of science, including biologically active pharmaceuticals, agrochemicals, and ligands for transition metal complexes. In the last few years, enormous success has been achieved in the asymmetric synthesis of organophosphorus compounds and many new developments, finding considerable use in industry, have taken place,. Asymmetric synthesis and asymmetric catalysis have been, and remain, one of the most important research directions in chemistry, attracting the interest of many scientists and chemical groups. As a consequence, the asymmetric synthesis of organophosphorus compounds is studied extensively in many scientific centers, including academic and industrial research laboratories. Many methods for the preparation of enantiomerically pure organophosphorus compounds including classical resolution via diastereoisomers, chemical kinetic resolution, enzymatic resolution, asymmetric metallocomplex catalysis, and organocatalysis have been developed. Complexes with transition metals containing PAMP, DIPAMP, DIOP, CHIRAPHOS ligands are widely used for the asymmetric formation of C–H and C–C bonds. Over the last few years, great success has been achieved in the asymmetric synthesis of organophosphorus compounds, primarily with phosphine ligands for catalyzed asymmetric hydrogenation reactions, and many articles devoted to the synthesis of chiral organophosphorus compounds have been published. In the last 10 – 15 years, many excellent reviews and multivolume monographs dedicated to the stereochemistry of organophosphorus compounds have been published. Several journals dedicated to asymmetric synthesis and chirality, *Tetrahedron: Asymmetry* and *Chirality* being among the foremost, have also gained in popularity.

The importance of stereochemistry in drug action and differences in the physiologic action of enantiomeric antipodes is well-known and intensively studied now. The requirements stipulated for new drugs by the Food and Drug Administration in the United States and by similar regulating agencies in other countries has made this more obvious. Some amino- and hydroxyphosphonic acids, as well as synthetic phosphonic acids, have been found to have effective medicinal properties; they have been applied in pharmacology and medicine. Detailed information about these functionalized phosphonates and phosphonic acids can be found in the chapters of this monograph.

This book emphasize the importance of chiral organophosphorus compounds and their asymmetric synthesis. There has been no monograph devoted to the asymmetric synthesis of organophosphorus in the chemical literature although such a study would be of great interest. This is what encouraged and inspired us to prepare this book. Our book is intended to be used by chemistry experimenters, professors of universities, as

well as research students, as a source of basic knowledge and convenient reference. The literature covered is up to 2016.

Chapter 1 of this monograph is dedicated to the fundamentals of stereochemistry of organophosphorus compounds, including general theoretical concepts, common nomenclature, and analytical methods related to the stereochemistry of organophosphorus compounds. The other chapters of the book survey the various types of asymmetric reactions and chiral organophosphorus compounds.

Chapter 2 discusses methods for the synthesis of compounds with chiral phosphorus atoms, including compounds with dicoordinated phosphorus atom, three-coordinated trivalent compounds, compounds of tetracoordinated phosphorus, and also compounds of penta and hexacoordinated phosphorus, and so on.

Chapter 3 describes the methods for asymmetric synthesis of phosphorus compounds bearing chiral centers in side chains. These reactions are particularly important for the production of pharmaceutical products and intermediates.

Chapter 4 presents asymmetric catalysis with complexes of transition metals, that is, asymmetric catalytic hydrogenation and stoichiometric reduction of various unsaturated compounds. Asymmetric hydrogenation is the simplest way to create new chiral centers and the technology is a flagship for chiral synthesis. Because asymmetric synthesis is a highly application-oriented science, examples of industrial applications of the relevant technologies are appropriately illustrated throughout the text.

Chapter 5 is devoted to organocatalysis, which is especially intensively investigated. The most important principles of organocatalysis and examples of preparative and practical applications are discussed. In particular, the use of alkaloids of quinine and its derivatives, sparteine, proline, and amino acid and their derivatives as catalysts is described.

Chapter 6 considers the use of enzymes and others biological methods in asymmetric synthesis. Methods of kinetic resolution of racemic organophosphorus compounds, biocatalytic transesterification, dynamic kinetic resolution of α-hydroxyphosphonates, enzymatic resolution of aminophosphonates, and the biosynthesis of compounds with C–P bonds are discussed. Microbiological synthesis of chiral phosphorus compounds with yeast, bacteria, fungi are considered.

The book discusses methods for the asymmetric synthesis of chiral organophosphorus compounds with many applications in stereoselective synthesis and asymmetric catalysis with reference to updated literature findings as well as the author's original researches performed over the last 15–20 years.

Kolodiazhnyi O.

Abbreviations

Ac	acetyl group
AC	absolute configuration
AD mix-α	reagent for asymmetric dihydroxylation
AD mix-β	reagent for asymmetric dihydroxylation
ALB	Al-Li-bis(binaphthoxide)
Ar	Aryl
BCL	*Burkholderia cepacia* lipase
BINOL	2,20-dihydroxyl-1,10-binaphthyl
BINAP	2,20-bis(diphenylphosphino)-1,10-binaphthyl
Bn	benzyl group
BOC	*tert*-butoxycarbonyl group
Bz	benzoyl group
CALB	*Candida antarctica* lipase B
CBS	chiral oxazaborolidine compound developed by Corey, Bakshi, and Shibata
CCL	*Candida cyclindracea* lipase
CD	circular dichroism
CDA	chiral derivatizing agents
COD	1,5-cyclooctadiene
CIP	Cahn – Ingold – Prelog
Cp	cyclopentadienyl group
CPL	circularly polarized light
CRL	*Candida rugosa* lipase
CSR	chemical shift reagent
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DHQ	dihydroquinine
DHQD	dihydroquinidine
DIBAL-H	diisobutylaluminum hydride
DIPT	diisobutyl tartrate
DKR	dynamic kinetic resolution
DMAP	4-*N*,*N*-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide

DMT	dimethyl tartrate
l-DOPA	3-(3,4-dihydroxyphenyl)-L-alanin
DYKAT	dynamic kinetic asymmetric transformation
ee	enantiomeric excess
GC	gas chromatography
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
Ipc	isocamphenyl
IR	infrared spectroscopy
L*	chiral ligand
LDA	lithium diisopropylamide
LDBB	lithium 4,4′-di-*tert*-butyldiphenylide
LLB	Ln-Li-is(binaphthoxide)
LHMDS	$LiN(SiMe_3)_2$
MEM	methoxyethoxymethyl group
Mnt	menthyl
MOM	methoxymethyl group
MPA	methoxyphenylacetic acid
Ms	methanesulfonyl, mesyl group
MTPA	α-methoxyltrifluoromethyl-phenylacetic acid
NAD(P)H	nicotinamide adenine dinucleotide (phosphate)
NHMDS	$NaN(SiMe_3)_2$
NME	*N*-methylephedrine
NMMP	*N*-methylmorpholine
PFL	*Pseudomonas fluorescences* lipase
PLE	pig liver esterase
PTC	phase transfer catalyst
R*	chiral group
RAMP	(*R*)-1-amino-2-(methoxymethyl) pyrrolidine
Salen	*N,N′*-disalicylidene-ethylenediaminato
TBAF	tetrabutylammonium fluoride
Tf	trifluoromethanesulfonyl group
THF	tetrahydrofuran
TMS	trimethylsilyl group
TMSCN	cyanotrimethylsilane
Ts	tosyl group
TS	transition state

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Fundamentals of the Stereochemistry of Organophosphorus Compounds

1.1 Historical Background

Natural processes are subordinate to geometrodynamics – the theory describing physical objects, geometrical spacetime, and associated phenomena completely in terms of geometry, and her elder sister – symmetry. Symmetry/asymmetry is one of the basic concepts in modern natural science [1]. Research into this field began in the Middle Ages, when the birefringent properties of calcite were discovered. In 1669, Bartholinus observed the double refractive properties of the calcite Iceland spar. Later, in 1801, the mineralogist Haui found that quartz crystals are enantiomorphic, representing mirror images of one another. In 1815, another French naturalist J.-B. Biot discovered that certain chemical compounds rotate the plane of a beam of polarized light [2]. Biot constructed the first polarimeter and he also discovered that many natural compounds exhibit optical activity, that is, they rotate the plane of circularly polarized light. Studying crystals under a microscope, Biot discovered two types of crystals. The sample consisting of crystals of one type turned polarized light clockwise and that from another type in the opposite direction. A mixture of the two types of crystals had a neutral effect on polarized light. The nature of this property remained a mystery until 1848, when Louis Pasteur proposed that it had a molecular basis originating from some form of dissymmetry [3]. Pasteur separated the left and right hemihedral crystals of the sodium-ammonium salt of D,L-tartaric acid under a microscope, and connected the opposite optical activity to the mirror image of these crystals. Pasteur termed the mixture creating polarization as dissymetric and the phenomenon as dissymmetry (asymmetry). The term *chirality* was proposed by Lord Kelvin in 1894 and introduced into chemistry by Mislow in 1962. Dissimmetry, as discovered by Pasteur, is found in nature, whereas compounds obtained from living organisms are chiral or nonracemic. In 1852, Pasteur discovered that resolution could also be achieved by using a chiral base (quinine and brucine) and by using microorganisms. He discovered that paratartaric acid could be separated under the influence of optically active natural bases such as quinine or brucine. Pasteur developed a method for the separation of paratartaric acid with the help of *Penicillium glaucum*, leading to the formation of levorotatory tartaric acid, thus creating the basis for microbiological separation of racemates. J. Wislicenus came to the conclusion that the right- and non-superimposable levorotatory lactic acids have an identical structure, and he noticed that the only difference between the isomers is the order in which the radicals are distributed in space [4]. The origin of chirality itself was finally discovered in 1874, when van't Hoff and Le Bel independently proposed that this phenomenon of optical activity can be explained by the assumption that the four saturated chemical

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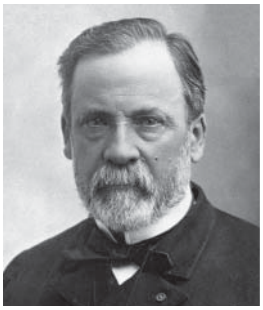
bonds between carbon atoms and their neighbors are directed toward the corners of a regular tetrahedron [5]. This concept led to the explanation for the observed optical activity by recognizing that a carbon atom with four different substituents exists in two mirror images: that is, it is chiral. The study of enantioselective reactions began with Emil Fisher [6], who studied the addition of hydrogen cyanide to sugars. In 1912, Bredig and Fiske [7] described the first catalytic enantioselective reaction. They studied the addition of hydrogen cyanide to benzaldehyde catalyzed by cinchona alkaloids. Although the mandelic acid that they obtained after hydrolysis of the initially formed benzcyanohydrin was of low optical purity (3–8%), Bredig and Fiske showed that it was possible to synthesize optically active compounds out of achiral precursors by using a chiral catalyst. Unlike Fischer, Marckwald performed an enantioselective reaction upon an achiral, unnatural starting material, although with a chiral organocatalyst [8]. In a paper titled "Ueber asymmetrische Syntheses," Marckwald gave the following definition of asymmetric synthesis: "Asymmetric syntheses are those reactions which produce optically active substances from symmetrically constituted compounds with the intermediate use of optically active materials but with the exclusion of all analytical processes." Fifty years later, Horst Pracejus reported the asymmetric organocatalytic reaction of methyl(phenyl)ketenes with alcohols catalyzed by alkaloids, leading to the formation of enantiomerically enriched esters of α-phenyl-propionic acid [9].



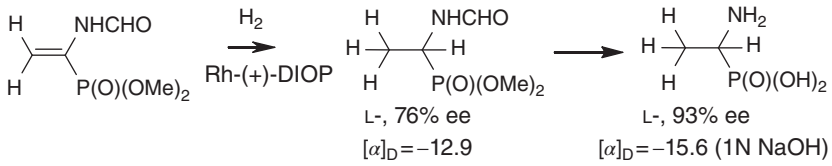
Louis Pasteur (1822–1895)

Hermann Emil Fischer (1852–1919)

The first work devoted to the asymmetric synthesis of aminophosphonates by catalytic hydrogenation of unsaturated phosphonates was published approximately 30 years ago. The development of enantioselective synthesis was initially slow, largely owing to the limited range of techniques available for their separation and analysis. It was not until the 1950s that real progress began with the development of new techniques. The first of these was X-ray crystallography, which was used to determine the absolute configuration (AC) of an organic compound by Bijvoet *et al.* [10]. During the same period, methods were developed to allow the analysis of chiral compounds by NMR, either using chiral derivatizing agents (CDAs), such as Mosher's acid [11], or europium-based shift reagents, of which $Eu(DPM)_3$ was the earliest [12]. Chiral auxiliaries were introduced by Corey and Ensley in 1975 [13] and featured prominently in the work of D. Enders. Around the same time, enantioselective organocatalysis was developed and enzyme-catalyzed enantioselective reactions became more and more common during the 1980s, particularly in industry, with their applications including asymmetric ester hydrolysis with pig-liver esterase. The emerging technology of genetic engineering has allowed the tailoring of enzymes to specific processes, permitting an increased range of selective transformations.

Today, the asymmetric synthesis of organophosphorus compounds is an extremely dynamic research domain in modern chemistry. Contributions to the development of asymmetric synthesis was made by many outstanding chemists.

Thus, L. Horner studied the electrochemical cleavage of quaternary phosphonium salts leading to the discovery that tertiary phosphines with three different substituents are chiral [14, 15]. This knowledge formed the basis of the pioneering work of Horner on enantioselective catalysis, especially enantioselective homogeneous hydrogenation [15], which was published independently in the same year as the work of W. S. Knowles [16] – work that was honored by the Nobel Prize and which was based on the chiral phosphines discovered by Horner [15]. Knowles developed one of the first asymmetric hydrogenation catalysts by replacing the achiral triphenylphosphine ligands in Wilkinson's catalyst with chiral phosphine ligands. He developed an enantioselective hydrogenation step for the production of L-DOPA (3-(3,4-dihydroxyphenyl)-L-alanine), utilizing the DIPAMP ligand. L-DOPA later became a mainstay for treating Parkinson's disease. Noyori Ryōji won the Nobel Prize in Chemistry together with W. S. Knowles for the development of the atropoisomeric ligand BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) and study of chirally catalyzed hydrogenation [17]. In 1985, Schöllkopf *et al.* [18] reported asymmetric hydrogenation of *N*-[1-(dimethoxyphosphoryl)-ethenyl] formamide, using a rhodium catalyst with (+)-DIOP chiral ligand to afford the L-(1-aminoethyl) phosphonate in good yields and 76% ee enantioselectivity. The initially formed formamide was hydrolyzed with concentrated hydrochloric acid to give the aminophosphonic acid. Crystallization from water/methanol increased the enantiomeric purity of the product up to 93% ee.



Significant contribution to the development of asymmetric synthesis of organophosphorus compounds was made by Henry Kagan, a member of the French Academy of Sciences. He developed C_2-symmetric phosphinic ligands, including DIOP, for asymmetric catalysis. These ligands have wide practical applications in the chemical industry [19].

The Japanese chemist Imamoto developed many types of phosphine ligands, which found practical applications [20]. The French chemist Juge created the accessible "ephedrine" method for the preparation of chiral phosphines named "the Juge-Stephan method." Together with Imamoto, he developed phosphine-boranes [21]. The American chemist William McEwen developed the fundamentals of the stereochemistry of organophosphorus compounds [22]. The Polish chemists Kafarsky [23] and Mikolajchyk [24] conducted important research studies in the application of phospha and sulfur reactants for the preparation of bioactive and natural compounds. Pietrusiewicz *et al.* [25], Kielbasisky and Drabowich [24, 26] are now continuing these studies. Methods for asymmetric synthesis and the synthesis of chiral organophosphorus compounds are of great interest to a number of powerful industrial firms and scientific research institutes, notable among them being the Leibniz Institute for Catalysis at the University of Rostock (LIKAT), the largest publicly funded research institute in

Europe. Professor A. Börner of the Institute has been working on the development of new phosphinic chiral ligands and their practical applications [27]. In addition to those mentioned above, hundreds of highly professional chemists in many scientific centers are working in the domain of asymmetric synthesis of organophosphorus compounds. Their names and achievements can be found in the chapters of this monograph.

1.2 Some Common Definitions in Stereochemistry

Some common terms in the field of stereochemistry are explained in this section. These terms appear repeatedly throughout this book. Therefore, it is essential that we establish common definitions for these frequently used terms [28].

Absolute configuration. The spatial arrangement of the atoms of a physically identified chiral molecular entity (or group) and its stereochemical description (e.g., (*R*) or (*S*), (P) or (M), (D) or (L)).

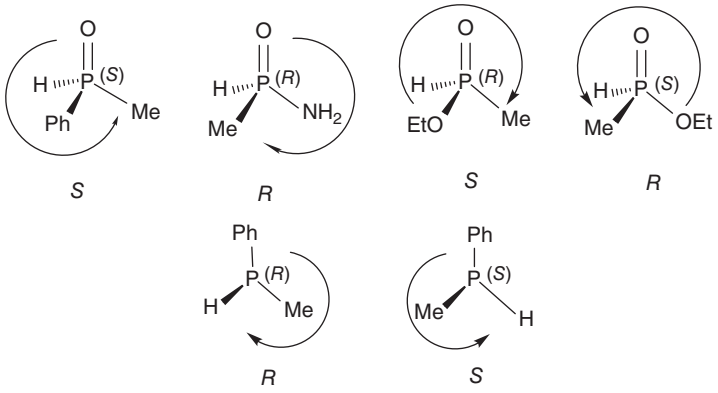
Absolute configuration. A chemist's term that refers to chiral molecules. Note particularly that this refers to both the entity under consideration, namely, the crystal structure versus molecule, as well as the symmetry restrictions.

Asymmetric compounds. Absence of all elements of symmetry. An asymmetric molecule is optically active. It has an additional molecule which is its non-superimposable mirror image. Together they are termed a *pair of enantiomers*. Some asymmetric molecules may exist not only as enantiomers but also exist as diastereomers.

Assigning the absolute configuration - the R–S sequence rules. In order to assign the stereochemistry of a stereocenter, the priority of the groups attached to the stereocenter must be determined.

The CIP (**C**ahn–**I**ngold–**P**relog) priority rules are a standard process to name the stereoisomer of a molecule. *R*/*S* descriptors are assigned by using a system for ranking priority of the groups attached to each stereocenter. The atomic numbers (*Z*) of the atoms directly attached to the stereocenter are compared. The group having the atom with the higher atomic number receives higher priority. Priority increases as the atomic number increases: I > Br > Cl > S > P > O > N > C > H > electron pair.

After the substituents of a stereocenter have been assigned their priorities, the molecule is oriented in space so that the group with the lowest priority is pointed away from the observer. A center with a clockwise sense of rotation is an (*R*) or rectus center and a center with a counterclockwise sense of rotation is an (*S*) or sinister center. The order of substituent priority in tetrahedral phosphorus compounds differs from that in carbon compounds with a true C=O multiple bond (Alk < R–O–C < C=O). The P=O bond in phosphates, phosphonates, and related compounds is traditionally represented as a double bond, although it is more correct to treat it as a single bond with two electron pairs localized on the oxygen atom. This is the reason that substituents at tetrahedral phosphorus have the following priority order: Alk < P=O < R–O–P [29, 30]. In tricoordinate phosphorus compounds, the group with the lowest priority is the electron pair.



Biocatalysis. Biocatalysis is the chemical process through which enzymes or other biological catalysts perform reactions between organic components. Biocatalysis makes use of biological compounds ranging from isolated enzymes to living cells to perform chemical transformations. The advantages of these reagents include very high ee and reagent specificity, as well as mild operating conditions and low environmental impact.

Chirality. The geometric property of a rigid object (or spatial arrangement of points or atoms) of being nonsuperposable on its mirror image. Such an object does not have symmetry operations of the second kind. If the object is superposable on its mirror image, the object is described as being achiral, and is modified for H-M symbols. Hermann–Mauguin notation is used to represent the symmetry elements in point groups, plane groups and space groups [28].

Chiral auxiliaries. A chiral auxiliary is an organic compound that couples to the starting material to form a new compound which can then undergo enantioselective reactions via intramolecular asymmetric induction. At the end of the reaction, the auxiliary is removed under conditions that will not cause racemization of the final product. It is typically then recovered for future use.

Dissymmetric compounds. Compounds lacking an alternating axis of symmetry and usually existing as enantiomers. Dissymmetry is the property of non-superimposability of a molecule on its mirror image. A dissymmetric molecule may have a simple axis of symmetry, yet it will be optically active and exist as a pair of enantiomers. Both asymmetric and dissymmetric molecules are optically active.

Prefixes d or l. Dextrorotatory or levorotatory according to the experimentally determined rotation of the plane of monochromatic plane-polarized light to the right or left.

Prefixes D *or* L. Absolute configurations assigned to a molecule through experimental chemical correlation with the configuration of D- or L-glyceraldehyde; often applied to amino acids and sugars, although (*R*) and (*S*) are preferred.

Diastereoisomer. Stereoisomers with two or more chiral centers, where the molecules are not mirror images of one another, for example, derythrose and *d*-threose. The term diastereoisomer is often contracted as diastereomer.

Enantiomerically pure/enantiopure. A sample in which all molecules have (within the limits of detection) the same chirality sense. The use of homochiral as a synonym is strongly discouraged (Moss [28]).

Enantioselective synthesis, also called *chiral synthesis* or *asymmetric synthesis*. This is defined by IUPAC as "a chemical reaction (or reaction sequence) in which one or more new elements of chirality are formed in a substrate molecule and which produces the stereoisomeric (enantiomeric or diastereoisomeric) products in unequal amounts."

Enantioselective organocatalysis. Organocatalysis refers to a form of catalysis where the rate of a chemical reaction is increased by an organic compound consisting of carbon, hydrogen, sulfur, and other nonmetal elements. When the organocatalyst is chiral, enantioselective synthesis can be achieved; for example, a number of carbon–carbon bond-forming reactions become enantioselective in the presence of proline with the aldol reaction being a prime example. Organocatalysis often employs natural compounds as chiral catalysts.

Enantiomer. Two stereoisomers that are non-superimposable mirror images of each other.

Enantiomer excess (ee). Enantiomeric excess (ee) is a measurement of purity used for chiral substances. It reflects the percentage by which one enantiomer is in excess over the other in a mixture of the two. A racemic mixture has an ee of 0%, while a single completely pure enantiomer has an ee of 100%: $\text{ee} = [(E_1 - E_2)/[(E_1 + E_2)] \times 100\%$.

Enantiotopic. The stereochemical term enantiotopic refers to the relationship between two groups in a molecule which, if one or the other were replaced, would generate a chiral compound. The two possible compounds resulting from that replacement would be enantiomers.

Erythro/threo. Terms derived from carbohydrate nomenclature used to describe the relative configuration at adjacent stereocenters. Erythro refers to a configuration with identical or similar substituents on the same side of the vertical chain in Fischer projection. Conversely, a *threo*-isomer has these substituents on opposite sides. These terms came from the nomenclature of two carbohydrate compounds, threose and erythrose.

Flack parameter. The parameter x in the structure-amplitude equation G:

$$I(hkl) = (1 - x)\left[F(hkl)\right]^2 + x\left[F(-h - k - l)\right]^2$$

Homotopic groups. Groups that can be exchanged by a symmetry axis. It follows that any achiral or chiral molecule which has an axis of symmetry contains at least one set (usually a pair) of homotopic groups.

Meso compounds. Compounds whose molecules not only have two or more centers of dissymmetry but also have plane(s) of symmetry. They do not exist as enantiomers, for example, *meso*-tartaric acid.

Optical activity. Experimentally observed rotation of the plane of monochromatic plane-polarized light to the observer's right or left. Optical activity can be observed with a polarimeter.

Optical isomer. Synonym for enantiomer, now disfavored, because most enantiomers lack optical activity at some wavelengths of light.

Optical purity. The optical purity of a sample is expressed as the magnitude of its optical rotation as a percentage of that of its pure enantiomer (which has maximum rotation).

Optical rotation. Enantiomers that rotate the plane-polarized light clockwise (to the right) are said to be dextrorotatory and are indicated with a lowercase "*d*" or a positive

sign (+). Those that rotate the plane counterclockwise are called *levorotatory* and are indicated with a lowercase "*l*" or a negative sign (−).

P-Chirogenic. In the literature, a phosphorus atom bonded to three different substituents is called *P-stereogenic*, *P-chirogenic*, or *P-chiral*. It should noted that "P-chiral" is not strictly correct because chirality is a property of a molecule as a whole.

Prochirality. Refers to the existence of stereoheterotopic ligands or faces in a molecule that, upon appropriate replacement of one such ligand or addition to one such face in an achiral precursor, gives rise to chiral products.

Pro-R and Pro-S. Refer to heterotopic ligands present in the system. It is arbitrarily assumed that the ligand to be introduced has the highest priority, and replacement of a given ligand by this newly introduced ligand creates a new chiral center. If the newly created chiral center has the (*R*)-configuration, that ligand is referred to as *pro-R*,; while pro-S refers to the ligand replacement that creates an (*S*)-configuration.

Racemate. An equimolar mixture of a pair of enantiomers. It does not exhibit optical activity. The chemical name or formula of a racemate is distinguished from those of the enantiomers by the prefix rac- (or racem-) or by the symbols *RS* and *SR*.

Racemization: The process of converting one enantiomer to a 50 : 50 mixture of the two.

Re and Si. Labels used in stereochemical descriptions of heterotopic faces. If the CIP priority of the three ligands a, b, and c is assigned as $a > b > c$, the face that is oriented clockwise toward the viewer is called *Re*, while the face with a counterclockwise orientation of $a < b < c$ is called *Si*.

Scalemic. Compounds existing as a mixture of two enantiomers in which one is in excess. The term was coined in recognition of the fact that most syntheses or resolutions do not yield 100% of one enantiomer.

Stereoisomer. Molecules consisting of the same types and same number of atoms with the same connections but different configurations.

1.3 Determination of Enantiomer Composition

Stereochemistry and chirality are of great importance in many different fields as the molecular properties and biological effects of the stereoisomers are often significantly different. Determination of ee's of the drug samples may allow for individualization and tracking of drug distribution routes. Aside from the classical methods of polarimetry and chemical resolution, some of the most popular current methods for ee. determination include chromatography (i.e., gas chromatography (GC), high performance liquid chromatography (HPLC)), and other techniques that may be considered related variants, such as capillary zone electrophoresis, micellar electrokinetic chromatography, and supercritical fluid chromatography (SFC). These techniques can be applied directly to the samples, or some achiral reagent may be used for sample modification, for instance, the acylation of an amine for improved chromatographic separation. To determine how much one isomer is in excess over the other, analytical methods based on HPLC or GC on a chiral column have proved to be most reliable. Chiral chemical shift reagents and chiral solvating agents for NMR analysis are also useful, and so are optical methods [31–34].

The enantiomer composition of a chemical compound may be described by the ee, which describes the excess of one enantiomer over the other. Correspondingly, the

diastereomer composition of a sample can be described by the diastereomer excess (de), which refers to the excess of one diastereomer

$$\text{enantiomeric excess } (\%\text{ee}) = \frac{[R]-[S]}{[S]+[R]} \times 100\%$$

$$\text{diastereomeric excess } (\%\text{de}) = \frac{[S^*S]-[S^*R]}{[S^*S]+[S^*R]} \times 100\%$$

where (*R*) and (*S*) are the composition of *R* and *S* enantiomers, respectively, (*S*,*S*) and (*S*,*R*) are the composition of the diastereomers.

A variety of methods are also available wherein the compound under investigation can be converted with a chiral reagent to diastereomeric products, which have readily detectable differences in physical properties. If a derivatizing agent is employed, it must be ensured that the reaction with the subject molecule is quantitative and that the derivatization reaction is carried out to completion [31].

1.3.1 Method of Nuclear Magnetic Resonance

Spectroscopic techniques, primarily NMR, are highly useful for determination of ee's by the observation of ^{1}H, ^{13}C, ^{19}F, or other nuclei. NMR methods have employed direct methods, using chiral lanthanide shift reagents or chiral solvating agents, but also can use indirect methods [32–39]. One typical indirect NMR method is the use of a chiral reagent to transform substrate enantiomers into stable diastereomeric derivatives. Any NMR approach hinges on observing separate absorptions (different chemical shifts) for corresponding nuclei in the substrate enantiomers.

1.3.1.1 Chiral Solvating Agents

In organophosphorus chemistry, the chiral solvating agents (CSA), quinine, cinchonine, derivatives of amino acids, chiral phosphonic acids, and Kagan's amides are most often applied (Table 1.1) [35–55]. Use of cinchona alkaloids (quinine and cinchonidine) as chiral solvating agents is a convenient method for determination of the enantiomeric composition of hydroxyphosphonates [32–34]. Determinations are carried out by the addition of an alkaloid solvent in $CDCl_3$ to a hydroxyphosphonate placed in the NMR tube and subsequent recording of NMR ^{31}P-[^{1}H] spectra. The signals of diastereomers in the spectrum are well resolved, thus allowing the integration. The optimal magnitude of $\Delta\delta_P$ signals was attained at a 1 : 4 molar ratio of hydroxyphosphonate/alkaloid (Figure 1.1) [40].

It was found that the determination can also be achieved in achiral solvents in the presence of certain chiral compounds, namely, chiral solvating agents. In these cases, the determination is achieved on the basis of diastereomeric interaction between the substrate and the chiral solvating agent. It is possible to use such deuterated solvents as C_6D_6 or $CDCl_3$ which do not interfere with the solvating action of the alkaloid; however, the use solvents such as deuteromethanol leads to negative results that play a key role in the formation of hydrogen bridges between the alkaloid and the hydroxyphosphonate, leading to discrimination of the enantiomers in the NMR spectra. (*S*)-(1)-*N*-(3,5-dinitrodibenzoyl)-1-phenylethylamine and the corresponding (*S*)-(1)-1-naphthyl derivative (Kagan's amide) are effective CSAs for tertiary phosphine oxides and phospholene oxides. Association with 2-phospholene-1-oxide derivatives causes characteristic perturbations of the ^{31}P resonance that correlate with the AC [41–43].