

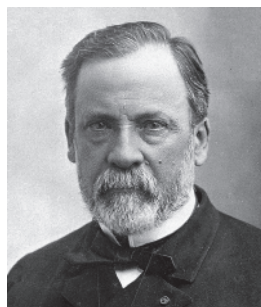
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Fundamentals of the Stereochemistry of Organophosphorus Compounds

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 dissymmetric and the phenomenon as dissymmetry (asymmetry). The term *chirality* was proposed by Lord Kelvin in 1894 and introduced into chemistry by Mislow in 1962. Dissymmetry, 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

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 Synthesen,” 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)

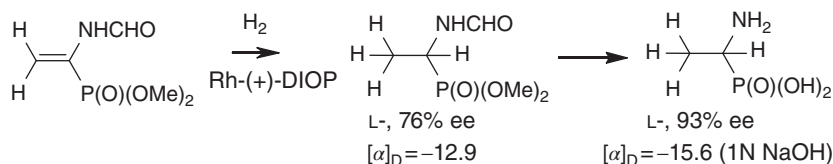


Hermann Emil Fischer
(1852–1919)

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 atropisomeric 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 Mikolajchuk [24] conducted important research studies in the application of phosphorus 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*)).

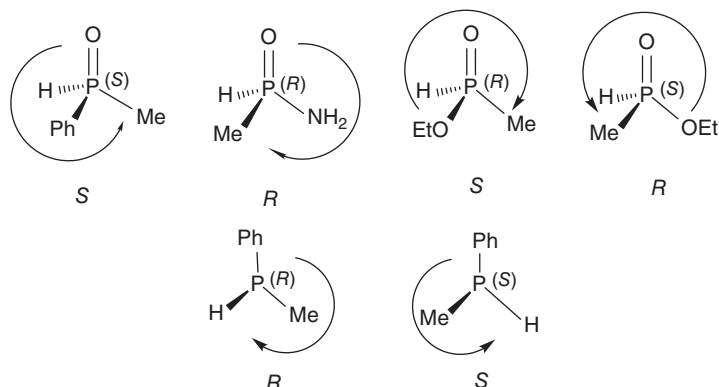
Absolute configuration. A chemist's term that refers to chiral molecules. Note particularly that this refers to both the entity under consideration, namely, the crystal structure versus molecule, as well as the symmetry restrictions.

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 (Cahn–Ingold–Prelog) 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: $I > Br > Cl > S > P > O > N > C > H > \text{electron pair}$.

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 ($\text{Alk} < R-O-C < C=O$). 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: $\text{Alk} < P=O < R-O-P$ [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%: $ee = [(E_1 - E_2)/(E_1 + E_2)] \times 100\%$.

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 :

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

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 be 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

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

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

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

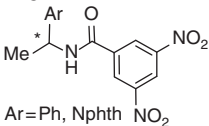
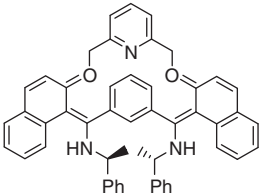
Spectroscopic techniques, primarily NMR, are highly useful for determination of ee's by the observation of ^1H , ^{13}C , ^{19}F , or other nuclei. NMR methods have employed direct methods, using chiral lanthanide shift reagents or chiral solvating agents, but also can use indirect methods [32–39]. One 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 - ^1H spectra. The signals of diastereomers in the spectrum are well resolved, thus allowing the integration. The optimal magnitude of $\Delta\delta_{\text{p}}$ 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].

Table 1.1 Some CSA used for determinations of enantiomeric excesses.

Entry	Reagent	Types of phosphorus compounds	References
1	<i>N</i> -Fmoc- <i>N'</i> -Boc-L-tryptophan	Phosphonates, phosphinates, phosphates, phosphine oxides, and amidophosphonates	[35]
2	Quinine	Hydroxyphosphonates	[36–39]
3	Cinchonidine	Hydroxyphosphonates	[40]
4	Kagan's amides  Ar = Ph, Npht, NO ₂	Tertiary phosphine oxides, phosphine oxides	[41–43]
5	Macrocycles 	Phosphinic, phosphonic, and phosphorus acids	[44]
6	<i>t</i> -Bu(Ph)P(S)OH	P-chiral phosphonates and α -substituted phosphonates, tertiary phosphine oxides, phosphinamides, phosphinates, phosphinthioates, phosphinites	[45–47]
7	Cyclodextrins	Hydroxyphosphonates, aminophosphonates	[48–54]

The enantiomeric discrimination is usually larger with a greater shielding naphthyl derivative. (*R*)-(1) or (*S*)-(2)-*tert*-butylphenylphosphinothioic acid is also an effective chiral NMR-solvating agent that associates with compounds containing a phosphine oxide unit. A similar association occurs with phosphinate esters and phosphorus thioacids and thionates. In each case, shielding from the phenyl group causes consistent trends in the ¹H and ³¹P NMR spectra that correlate with the AC. The same occurs with (*R*)-(1) and (*S*)-(2)-(N-phenyl)methylphenyl phosphinic amide, which associates with other phosphinic amides through hydrogen bonds [47]. Kafarski *et al.* used α - and β -cyclodextrins as chiral selectors for the ³¹P NMR determination of the ee of aminoalkanephosphonic and aminoalkanephosphinic acids. Most of these acids form inclusion complexes with α - and β -cyclodextrins and upon increasing the cyclodextrin to aminophosphonic acid molar ratio, the ³¹P NMR signals for (*R*)- and (*S*)-enantiomers separate. When a racemic mixture of an aminophosphonic acid was dissolved in a solution containing cyclodextrin, two diastereomeric complexes were formed and in most cases two signals were observed in the ³¹P NMR spectra [48–54].

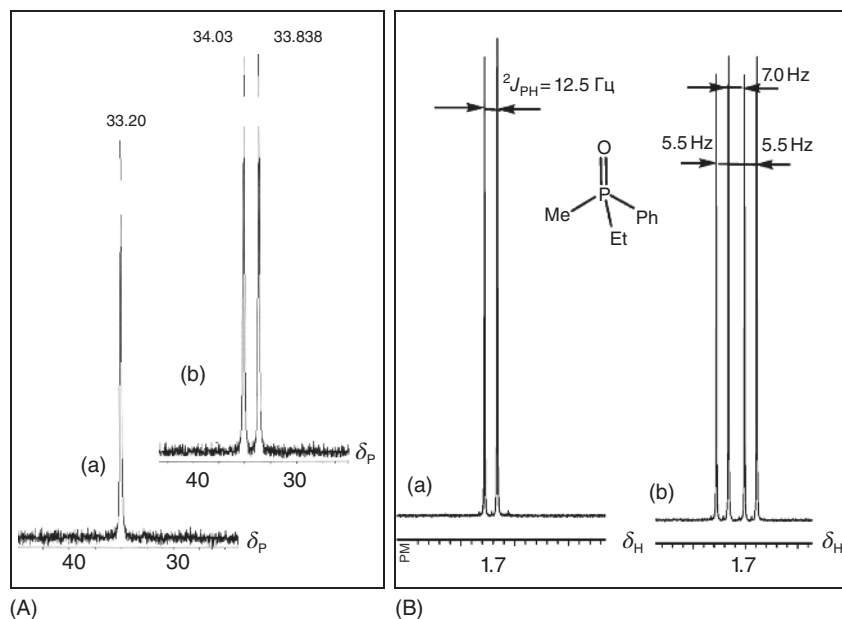
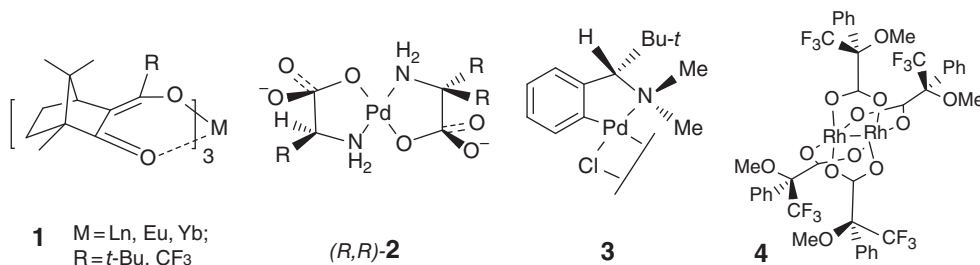


Figure 1.1 ^{31}P - ^1H NMR spectra of racemic $(\text{EtO})_2\text{P}(\text{O})\text{CH}(\text{Cl})\text{Bu-}t$ without solvating reagent and with cinchonidine (A). NMR spectra of racemic methyl-ethyl-phenylphosphine oxide without a solvating reagent and with Kagan's amide (B).

1.3.1.2 Complexes of Metals (Shift Reagents)

One of the most useful applications of lanthanide shift reagents is in the determination of optical purity by the use of chiral ligands on the lanthanide. Two of the more effective reagents developed are $\text{Eu}(\text{facam})_3$ (tris(3-trifluoroacetyl-D-camphorato)europium(III)) and $\text{Eu}(\text{hfc})_3$ (tris(3-heptafluorobutyryl-D-camphorato)europium(III)). Chiral chemical shift reagents (CSR) may be used to enhance the anisochrony of diastereomeric mixtures to facilitate their quantitative analysis. CSR are paramagnetic complexes of certain lanthanides, such as europium and ytterbium, with ligands designed to make them soluble in organic solvents. They are also chemically inert and, in some cases, improve the solubility of compounds in nonaqueous solvents. When added to NMR samples, they coordinate weakly to polar functional groups, such as amines, esters, ketones, and alcohols, and create a strong local magnetic field that produces large chemical shift changes. Examples of chiral CSRs (which are commercially available) are shown in Scheme 1.1. If a CSR binds a substrate possessing a stereocenter, two diastereomeric complexes can be formed from its enantiomers, which, in principle, will exhibit different chemical shifts. This leads to distinct resonance peaks (^1H or ^{13}C) of the two enantiomeric forms of the sample. Chiral shift reagents usually form adducts with enantiomeric substrates containing diastereomeric protons showing well-resolved NMR signals; for example, complexes of lanthanides such as camphor derivatives, in particular tris-(3-3-(+)-camphorato) lanthanum (III) ($\text{R}=\text{C}(\text{CH}_3)_3$, C_3F_7 , and others) or $\text{Eu}(\text{hfc})_3$ (europium tris[3-(heptafluoropropyl-hydroxymethylene)-(+)-camphorate]) **1**. The resolution in NMR spectra of an (*R*)/(*S*)-isomeric mixture in the presence of chiral shift reagent of europium tris[3(heptafluoropropylhydroxymethylene)-(-)-camphorate] is



Scheme 1.1 The metal complexes increasing anisochronous signals of tested materials.

sufficient for determination of their enantiomeric ratio [56–59]. Lanthanide complexes can serve as weak Lewis acids. In nonpolar solvents (e.g., CDCl₃, CCl₄, or CS₂), these paramagnetic salts are able to bind Lewis bases, such as amides, amines, esters, ketones, and sulfoxides. As a result, protons, carbons, and other nuclei are usually deshielded relative to their positions in the uncomplexed substrates, and the chemical shifts of those nuclei are altered. The extent of this alteration depends on the strength of the complex and the distance of the nuclei from the paramagnetic metal ion. Therefore, the NMR signals of different types of nuclei are shifted to different extents, and this leads to spectral simplification. The spectral nonequivalence observed in the presence of chiral CSR can be explained by the difference in geometry of the diastereomeric CSR-chiral substrate complexes, as well as the different magnetic environment of the coordinated enantiomers that causes the anisochrony. For example, it was found by NMR that the interaction of Pd(II) ions with 1-aminophosphonate ligands (L) yields, in a non-diastereoselective manner, diastereoisomeric chelate pairs (PdL₂) observable in alkaline D₂O solutions [56]. The chelate complexes **2** give two peaks in the ³¹P NMR spectra; one corresponds to the chiral species (both ligands are (*R*) or (*S*) enantiomers) and the second to the *meso*-forms (*R*) and (*S*)-ligands). Under the experimental conditions used, values in the range 0.03–0.18 ppm were observed. Enantiomers of the monodentate phosphine *t*-BuP(Ph)C₆H₄Br-4 were resolved by chromatographic separation of their diastereomeric adducts with a homochiral *ortho*-palladated resolving agent **3** derived from α -*tert*-Bu-substituted tertiary benzylamine. The conformation of the palladacycle and the AC of the phosphine were determined using ¹H NMR spectroscopy and confirmed by an X-ray diffraction study of both diastereomeric complexes [60]. The enantiomerically pure dirhodium complex (*R*)Rh₂(MTPA)₄ **4** is a good auxiliary for chiral recognition of a variety of organic compounds by using ¹H or ¹³C NMR spectroscopy. The dirhodium method works particularly well with functional groups which are soft bases. Therefore, it is a good supplement to the methods using CSR, which are known to complex rather hard bases. The diastereomeric complexes of **4** with the P=S and P=Se derivatives exhibit significant differences in the chemical shifts which allows their determination by ¹H, ¹³C, and ³¹P NMR spectroscopy [59].

1.3.1.3 Chiral Derivatizing Agents for NMR

CDAs are optically active reactants that react with the enantiomers that are to be analyzed. CDAs are chiral auxiliaries used to convert a mixture of enantiomers into diastereomers in order to analyze the quantities of each enantiomer present within the mixture. Analysis can be conducted by spectroscopy or by chromatographic methods.

Typically, the reaction involves the formation of a covalent bond, although in some cases it may involve the formation of a soluble salt. In many cases, the diastereomeric complexes exhibit chemical shift patterns that correlate with the AC. For the CDA to be useful in determining ee, it is essential that no kinetic resolution occur during the derivatization reaction.

Dale and Mosher [11] proposed α -methoxy- α -phenyl- α -trifluoromethyl acetic acid (MTPA) in both the (*R*)- and (*S*)-forms. MTPA is now known as *Mosher's acid*. The chloride of MTPA reacts with chiral alcohols (mostly secondary alcohols) to form diastereomeric mixtures called *MTPA esters* or *Mosher's esters*. There are two advantages in using MTPA: The epimerization of the chiral α -C is avoided because of the absence of the α -proton; and the introduction of a CF_3 group makes it possible to analyze the derivatives by means of ^{19}F NMR, which simplifies the analysis process. The presence of a second NMR active nucleus (^{19}F) provides another way to determine ee and possibly the AC. Peak overlapping is generally not observed, and the ^{19}F NMR signals are far better separated than are the ^1H NMR peak configurations [61]. The derivatization of amino- and hydroxyphosphonates with MTPA (Mosher acid) [61–64], camphoric acid [63], mandelate acid [64], phosphono-dipeptides [65, 66], diazaphospholidine chloride [67], and others has been described. (*S*)-Naproxene[®] chlorides and (*S*)-ibuprofen[®] chlorides are convenient chiral derivatizing reagents for determination of the enantiomeric purity of α - and β -hydroxyalkylphosphonates by ^{31}P NMR spectroscopy [68]. ^1H NMR spectroscopy of chiral 1-(1-naphthyl)ethylamine salts of hydroxyphosphonic acids [55], NMR in chiral medium, GLC with chiral stationary phase [69], and other methods were also used (Figure 1.2).

N-Substituted (L)-amino acids were used for the determination of the enantiomeric composition of chiral 1-hydroxyalkylphosphonic acids by means of ^{31}P NMR spectroscopy (Scheme 1.2) [11, 61–65]. The ^1H NMR spectroscopy of chiral 1-(1-naphthyl)ethylammonium salts of hydroxy phosphonic acids, NMR in chiral media, and other methods were also used [51, 70–77]. The diastereomeric esters formed can be analyzed by ^1H , ^{19}F , and ^{31}P NMR spectroscopy. The signals of the P atoms in ^{31}P NMR spectra of (*S*)-hydroxyphosphonate esters are usually located in a lower field than those of (*R*)-hydroxyphosphonates.

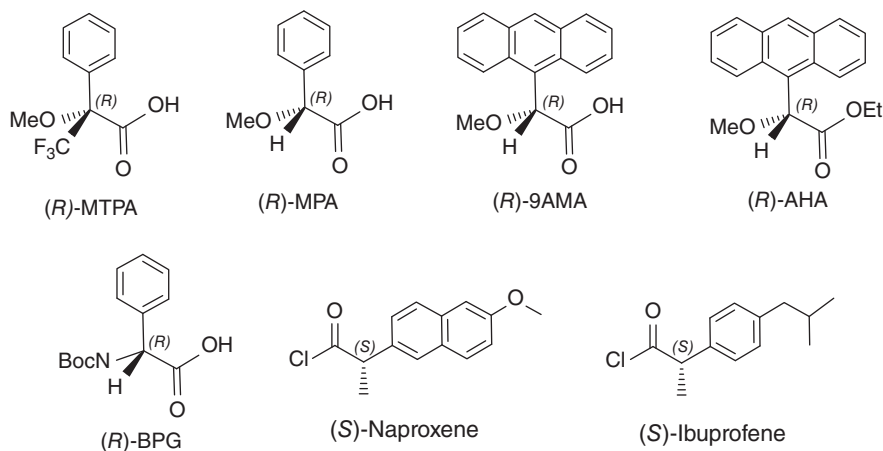
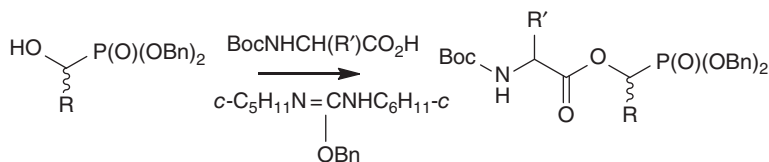
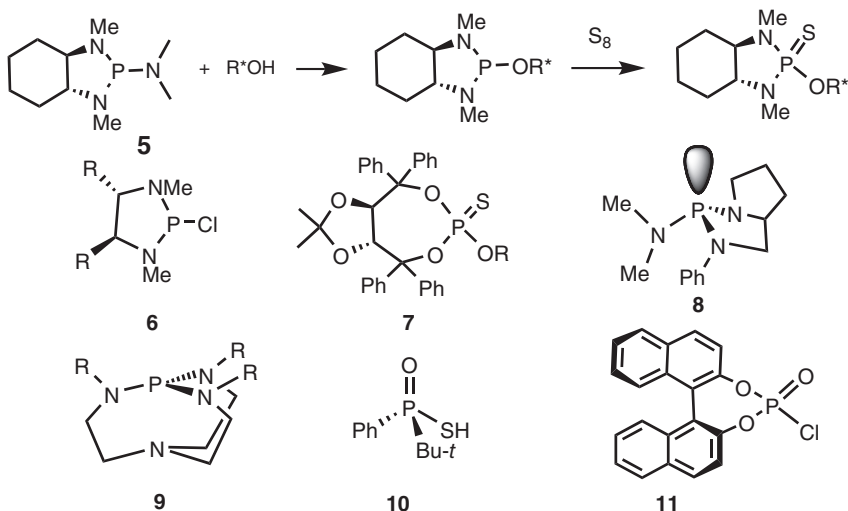


Figure 1.2 Some chiral derivatizing agents.



Scheme 1.2 Determination of optical purity by means of N-substituted L-amino acids.

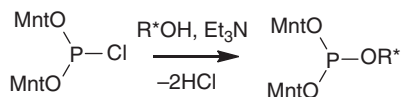


Scheme 1.3 Phosphorus-containing CDA.

A number of chiral phosphorus derivatizing agents **5–11** were described and used for the determination of enantiomeric purity of organophosphorus compounds by NMR [70–76] (Scheme 1.3). For example, the phosphorus derivative of TADDOL **7** was used for the enantiomeric discrimination of alcohols and carboxylic acids by ^1H and ^{31}P NMR spectra. P(III) and P(V)-phosphorus derivatives of C_2 -symmetric ligands (1,2-diphenyl-1,2-bis(*N*-methylamino)ethane or 1,2-bis(*N*-methylamino)cyclohexane) are suitable for the determination of the optical purity of carboxylic acid. Cyclic phosphorochloridites prepared by reaction of PCl_3 with chiral butane-2,3-diol or hydrobenzoin were used to measure the ee of chiral alcohols. A phosphorus derivative of (*S*)-2-anilinomethylpyrrolidine was useful for the enantiomeric discrimination of halohydrins (Scheme 1.3).

Derivatized diastereomers of various alcohols and amines allow to exactly define the diastereomeric ratio and optical purity of samples by ^{31}P NMR spectra, even in reaction mixtures. For example, the derivatizing reagent obtained from tartrates or from 1,2-diaminocyclohexane allow to attain the $\Delta\delta$ of derivatizing compounds in several ppm.

Dimethylchlorophosphite is a convenient chemical derivatizing agent for the determination of the enantiomeric purity of hydroxyphosphonates, aminophosphonates, amino acids, and alcohols by ^{31}P NMR. The diastereomeric hydroxy phosphonate derivatives formed upon the reaction with this reagent differ appreciably in the



Scheme 1.4 Dimethylchlorophosphite as derivatizing reagent.

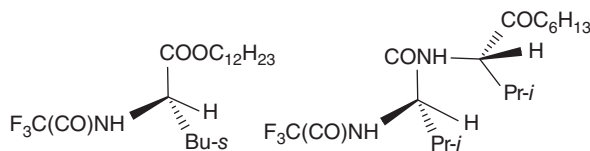
chemical shifts δ_{P} ; therefore, the enantiomeric ratio can be easily determined by integrating the ^{31}P NMR signal intensities [77] (Scheme 1.4).

1.3.2 Chromatographic Methods of Analysis

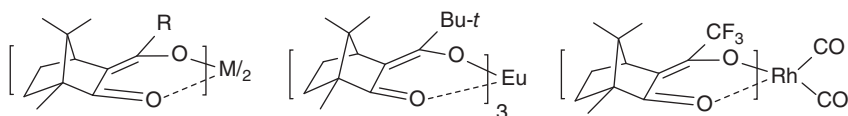
Both GC and HPLC provide fast and accurate methods for enantiomeric separation of chirogenic organophosphorus compounds and allow quantitation of both mass and even optical rotation for HPLC, if appropriate detection devices are used. Chromatographic methods are among the most useful for chiral separation. There are two approaches: indirect, which utilizes derivatizing agents and direct, which uses chiral stationary phases or chiral mobile phase additives. In the indirect method, a racemic mixture is made to react with a chiral reagent to form a pair of diastereomers and then chromatographed using an achiral column. Because diastereomers possess different physiochemical properties, they can be separated in an achiral environment. The following are the advantages of the indirect approach: (i) it is less expensive, that is, conventional chromatographic columns can be used, (ii) it is more flexible because various achiral columns and mobile phase conditions, as in HPLC, can be used, and (iii) numerous types of derivatization chemistry are available. On the other hand, the following are the disadvantages of this method: (i) it involves a long analysis time that includes sample preparation and verification of the derivatization chemistry. (ii) There is inconvenience, specifically in preparative chromatography, when reversal of derivatization is needed to recover the pure enantiomers. (iii) The need arises to synthesize noncommercially available pure derivatizing reagent. (iv) Biased results are obtained for enantiomeric composition due to partial racemization of the derivatizing agent or unequal reaction rate.

Direct separation of enantiomers on an achiral column using a chiral mobile phase additive is applied only in HPLC. In GC, the mobile phase is an inert carrier gas, where the possibility of selective interactions with the analyte or the stationary phase is minimal. However, in HPLC, the mobile phase is a dynamic part of the system that influences both analyte and stationary phase interaction. In this method, enantiomeric separation is accomplished by the formation of a pair of transient diastereomeric complexes between the racemic analyte and the chiral mobile phase additive.

Many racemic mixtures can be separated on conventional achiral LC columns by using an appropriate chiral mobile phase additive. Additives such as β - and γ -cyclodextrins have been successful. The advantages of this technique are as follows: (i) it is less expensive conventional LC columns can be used. (ii) A wide variety of possible additives are available. (iii) Different selectivities can be obtained from the chiral phases. However, the problems with this technique include the following: (i) many chiral additives are expensive and sometimes have to be synthesized. (ii) The mode of operation is complex and inconvenient for preparative applications because the chiral additive must be removed from the enantiomeric solutes.

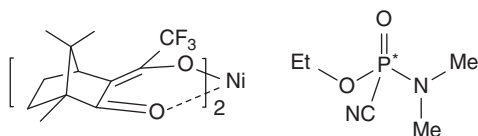


Scheme 1.5 Chiral stationary phases for gas chromatography.



M = Ni, Mn; R = CF₃, C₃F₇

Scheme 1.6 Chiral metallochelates for gas chromatography.



Scheme 1.7 Structure of the chiral metal chelate Ni(II)bis[(1R)-3-(heptafluorobutyl) camphorate].

1.3.2.1 Gas Chromatography

Chiral GC is a very commonly used method for the analysis of mixtures of enantiomers. The method is based on the principle that molecular association between the chiral stationary phase and the sample may lead to some chiral recognition and sufficient resolution of the enantiomers. The chiral stationary phase contains an auxiliary resolving agent of high enantiomeric purity (Schemes 1.5–1.7). The enantiomers to be analyzed undergo rapid and reversible diastereomeric interactions with the stationary phase and hence may be eluted at different rates. Separation of enantiomeric or diastereomeric mixtures by GC is a good method for determining enantiomer compositions. However, this method is limited to samples that are both volatile and thermally stable. Normally, if the compound to be separated has a low boiling point (e.g., <260 °C), or it can be converted to a low boiling substance, and no racemization occurs during the analysis, it is possible to analyze it by GC. If the compound has a high boiling point, or the compound tends to decompose or racemize at high temperature, HPLC would be the choice of separation [78, 79].

Benschop [80] reported the gas chromatographic separation of the stereoisomers of several chiral organophosphorus compounds using the glass capillary columns coated with the nonchiral phases SE-30 and Carbowax 20 M, or with the chiral in OV-phases Chirasil-Val and Ni(II)bis[(1R)-3-(heptafluorobutyl) camphorate]. The Chirasil-Val column was extended with a Carbowax 20M column, thus giving complete separation of the four Soman stereoisomers. Besides Soman, the enantiomers of isopropyl methylphosphonofluoridate (Sarin) and cyclohexyl methylphosphono-fluoridate (cyclohexylsarin) were resolved. The enantiomers of O-ethyl N,N-dimethylphosphoramidocyanide (Tabun) were separated by GC on

a capillary column coated with Ni(II)-bis[(1*R*)-3-(heptafluorobutyl)camphorate] in OV-101 (L = 14 m, i.d. = 0.44 mm, T. oven = 120 °C). Keglevich *et al.* resolved the 1-*n*-butyl-3-methyl-3-phospholene 1-oxide with TADDOL derivatives by chiral GC on a 30 m capilar column Supelco BETA DEX 120 [81].

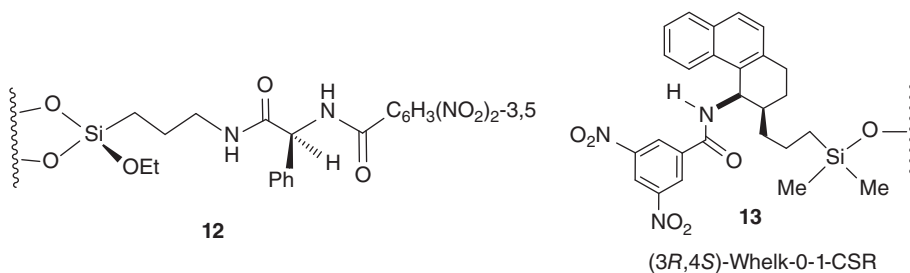
1.3.2.2 Liquid Chromatography

Chiral HPLC is one of the most powerful tools to prepare enantiopure standards of chiral compounds. HPLC procedures were developed and successfully employed for the separation of a high number of organic and organophosphorus compounds. Because of their specific adsorption character, cyclodextrins and cyclodextrin derivatives immobilized on silica gel have been frequently applied for the improvement of the separation parameters of various chromatographic methods [82–89]. Aryl(hydroxymethyl) phosphonates were separated by HPLC on chiral stationary phase **12**. It was noted that (*R*)-(+)-hydroxyphosphonates are retained by the chiral stationary phase (3*R*,4*S*)-Whelk-O-1 **13** more strongly than (*S*)-(–)-hydroxyphosphonates [90]. This is due to the formation of a stronger hydrogen bond between the oxygen atom of the P=O group and the hydrogen atom of the amide NH group in the case of (*R*)-isomers than between the hydroxyl and NH-groups in the case of (*S*)-hydroxyphosphonates. For example, the enantiomers of diethyl α-hydroxybenzylphosphonate containing para, or ortho substituents or other aromatic rings (1-naphthyl, 2-naphthyl, and 2-thienyl) were separated by HPLC on a Whelk-O-1 chiral stationary phase **13**, which is superior to other CSPs (Scheme 1.8) [84].

In order to study the retention and chiral recognition mechanism, the method of quantitative structure-enantioselectivity retention relationships (QSERRs) has been investigated from the quantitative equations established between the chromatographic retention of enantiomers and their molecular descriptors of physicochemical properties [88, 89]. The separation of enantiomers of a series of 18 novel nitrogen mustard-linked phosphoryl diamide derivatives was investigated on the phenyl carbamate derivative β-cyclodextrin bonded phase in normal-phase HPLC. Some of the enantiomers were separated in baseline. The retention and separation mechanism involves the external association and inclusion between the substituent *R*² and the hydrophobic pocket [89].

The stationary Pirkle's phase for the super- and subcritical fluid chromatography separations of enantiomeric pairs of phosphine oxides was successfully used [90].

Kobayashi [91] reported the chromatographic resolution of racemic compounds containing phosphorus as chiral center. The compounds were resolved by HPLC on optically active (+)-poly(triphenylmethyl methacrylate). The resolved compounds



Scheme 1.8 Effective chiral phase for resolution of amino acids [86, 90].

include insecticides such as *O*-ethyl *O*-(4-nitrophenyl) phenylphosphonothionate (EPN), *O*-(4-cyanophenyl)-*O*-ethyl phenylphosphono-thionate (cyanofenfos), and 2-methoxy-4*H*-1,3,2-benzo-dioxaphosphorin 2-sulfide (salithion).

The separation of a number of P-chiral racemates and C-chiral organophosphorus pairs of enantiomers was achieved on a commercial cellulosic tris-(3,5-dimethylphenyl-carbamate) stationary phase (Lux Cellulose-1, Phenomenex) in SFC [92].

1.4 Determination of the Absolute Configuration

In the area of asymmetric synthesis, one of the most important parameters is the configuration of the major product of an asymmetric reaction [93]. The methodologies to determine the ACs of the chiral compounds are classified into nonempirical methods for determining ACs and the relative methods using an internal reference with known AC. The main nonempirical methods are the Bijvoet method [10] by X-ray crystallography and the circular dichroism (CD) exciton chirality method. In X-ray crystallography, the anomalous dispersion effect of heavy atoms can be measured very accurately under proper conditions and the absolute stereostructure obtained is clear and unambiguous. However, the X-ray method needs crystals of suitable quality for good X-ray diffraction, and there is the problem how to obtain such single crystals.

The CD method for determination of chirality is also useful because the AC can be determined in a nonempirical manner, which does not require crystallization. Moreover, chirality of some biological reactions can be monitored by CD, and even the ACs of unstable compounds can be determined by this method [94].

The ACs of secondary alcohols and hydroxyphosphonates can be determined by the Mosher's method using MTPA. This method is very convenient as it does not require crystallization of compounds. Although this method was first applied to the secondary alcohols, it can be used for other kinds of compounds. The AC of new compounds can also be determined by the method of chemical correlation and comparison of optical rotation, $[\alpha]_D$, or CD spectra with reference compounds.

1.4.1 X-ray Crystal Analysis

There are several ways to determine the absolute structure by X-ray crystallography. For example, a comparison of the intensities of Bijvoet pairs [10] or of the *R* factors for the two possible structures can suggest the correct absolute configuration (AC). One of the most effective approaches is application of the Flack parameter, because this parameter unambiguously indicates the AC of molecule. In this case, the AC can be easily defined using the chirality of the auxiliary introduced as an internal reference. Consequently, the samples do not need to contain heavy atoms for an anomalous dispersion effect. The result obtained is one-valued, even when the final *R*-value is not small enough owing to poor quality of the single crystal. The AC can be determined, even if only the relative configuration is obtained. A number of methods to link an internal reference to the target molecule have been developed and described, for example, ionic acidic or basic salts, covalent esters or amides, or various inclusion complexes.

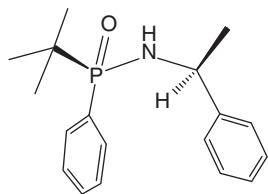
Normal X-ray crystallography cannot distinguish between enantiomers. If the sample includes only light nuclei, the interference pattern is determined only by intermolecular separation, and the phase coincidence is independent of the spatial orientation

of these nuclei. Thus, from the diffraction pattern, it is possible to calculate various internuclear distances and constitutions in the molecule and to deduce the relative positions of these nuclei in space. One can build the relative configuration of a compound, but it is normally difficult to distinguish enantiomers or to get the ACs for chiral compounds containing only light atoms. Because of a phase delay or abnormal dispersion, the interference pattern depends not only on interatomic distances but also on their relative positions in space, thus allowing to define the AC of molecules containing heavy atoms. The AC of a compound can be obtained by determining the relative configuration at the position of interest against a reference compound or a substituent with known AC. A typical example is the X-ray crystallography taken after the introduction of a chiral auxiliary with known absolute configuration. In this case the absolute configuration can be determined using the chirality of the auxiliary introduced as an internal reference. For a molecule without a heavy atom, the AC can be determined by attaching another chiral moiety of known configuration to the sample.

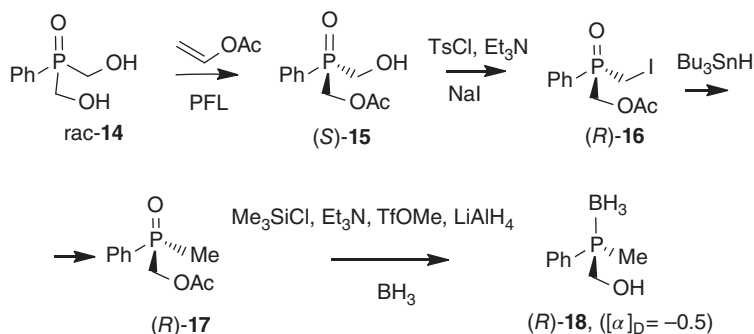
Thus, the AC of the phosphor atoms in the quinoline salt of (+)-(*R*)-*O*-ethyl-*O*-phenylphosphorothioic acid and the brucine salt of (–)-(*S*)-ethyl phenylthiophosphonous acid were determined by X-ray single-crystal diffraction analysis (Scheme 1.9) [92, 96].

In X-ray crystallography, the Flack parameter is used to estimate the AC which is determined by single-crystal X-ray structural analysis. This parameter, introduced by H. D. Flack, became one of a standard set of values being checked for structures with noncentrosymmetric space groups. This approach determines the absolute structure of a noncentrosymmetric crystal. The Flack parameter can be calculated during structural refinement using the following equation: $I(hkl) = (1 - x)[F(hkl)]^2 + x[F(-h-k-l)]^2$, where x is the Flack parameter, I is the square of the scaled observed structure factor, and F is the calculated structure factor [97]. The value x determined for all data usually should lie between 0 and 1. In the case when the value of the Flack parameter is near 0, the absolute structure determined by structural analysis is evidently correct; if the value is near 1, then the inverted structure is correct. However, if the value is near 0.5, the crystal should be racemic or twinned. The technique is most effective when the crystal contains both lighter and heavier atoms. Light atoms usually show only a small anomalous dispersion effect. In this case, the Flack parameter can refine to a physically unrealistic value (<0 or >1) and has no meaning.

For example, Scheme 1.9 shows an example of X-ray structural analysis of the molecule for which the Flack parameter was refined to $-0.05(8)$, which is close to 0, that is, the determined AC (R_P , S) is correct. Crystallographic data should to be registered in the Crystallographic center, and the registration number should be obtained without which it is not possible to publish the article. The crystallographic data (excluding the structure factors) for the structure were deposited at the Cambridge Crystallographic Data Centre, as supplementary publication no. CCDC 195666 [95].



Scheme 1.9 Example of single-crystal X-ray structural analysis of *t*-Bu(Ph)P(O)NHCH(Me)Ph [95].



Scheme 1.10

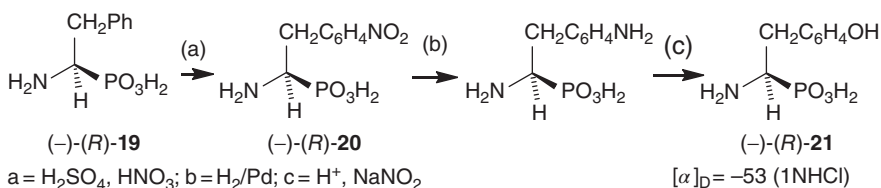
1.4.2 Method of Chemical Correlation

AC can be determined relatively by chemical correlation, or by comparison of the optical rotation or CD spectrum of the compound in question with that of reference compounds with known AC. Although this method is frequently used, a careful selection of reference compounds is necessary for reliable analysis [98, 99]. For example, the biocatalytic acetylation of prochiral bis(hydroxymethyl) phenylphosphine oxide **14** in the presence of lipase PFL (*Pseudomonas fluorescences* lipase) led to the formation of chiral compound (*S*)-**15** in 50% yield and with 79% ee. The AC of compound (*S*)-**15** was determined by chemical correlation (Scheme 1.10). To this end, alcohol (*S*)-**15** was converted to iodide (*R*)-**16** which was then reduced to phosphinate (*R*)-**17** whose transformation resulted in a borane complex of phosphinic acid (*R*)-**18** with known AC [100].

Mastalerz *et al.* [99] have established the ACs of a number of optically active phosphonic analogs of serine, α -chloroalanine, phenylalanine, tyrosine, and 2-aziridinephosphonic acid via chemical correlations with phosphonic analogs of alanine or aspartic acid of known configuration. For example, by conversion of (–)-PheP **19** to TyrP **21**, the configuration of TyrP as (*R*)-(–) was established. The conversion was accomplished by nitration, reduction, and diazotization. Specific rotations indicate that the *p*-nitro **20**, and *p*-amino congeners of TyrP **21** also have the (*R*)-(–) configuration (Scheme 1.11).

1.4.3 The Assignment of Absolute Configuration by NMR

The ACs of secondary alcohols are frequently determined by an advanced Mosher method developed by Kusumi *et al.* [101, 102]. In this case, the ACs of chiral



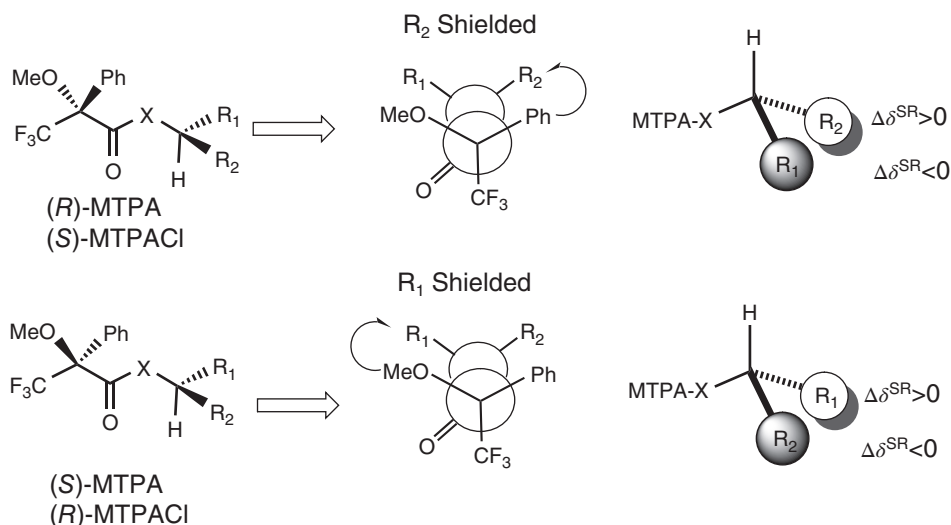
Scheme 1.11 Determination of absolute configurations by chemical correlation.

auxiliaries, such as α -methoxy- α -trifluoromethylphenylacetic acid (MTPA) or α -methoxyphenylacetic acid (MPA)], are known, and the preferred conformation of the esters formed with chiral secondary alcohols and MTPA or MPA acid is rationalized. Moreover, the phenyl group generates the effect of magnetic anisotropy because of the ring current that is induced by an external magnetic field, and therefore the NMR signals of alcohol shielded by the phenyl group are displaced to a higher magnetic field. By observing the ^1H NMR or ^{31}P anisotropy effect, we can determine the AC of the chiral compound. This method is particularly convenient because it does not require special purification of compounds [101, 102]. This method involves converting of chiral hydroxyphosphonates to their corresponding MTPA esters, followed by NMR analysis of the resulting derivatives. Mosher proposed that the carbonyl proton and ester carbonyl, as well as the trifluoromethyl group of an MTPA moiety, lie in the same plane. Calculations on this MTPA ester demonstrate that the proposed conformation is just one of two stable conformations. As a result of the diamagnetic effect of the benzene ring, the NMR signals of protons of the (*R*)-MTPA ester should appear upfield relative to those of the (*S*)-MTPA ester. Therefore, for $\Delta\delta = \delta\text{S} - \delta\text{R}$, protons on the right side of the MTPA have positive values ($\Delta\delta > 0$) and protons on the left side of the plane have negative values ($\Delta\delta < 0$).

Determination of the absolute configuration of hydroxyphosphonates (or secondary alcohols) by the Mosher-Kusumi method (Scheme 1.13). To a solution of 0.1 mmol of any hydroxyphosphonate in CH_2Cl_2 , 0.2 mmol of anhydrous pyridine is added. Then 0.1 mmol of (*R*)-(-)-MTPA-Cl is added to the first sample (marked A), and 0.1 mmol of (*S*)-(+)-MTPA-Cl to the second sample (marked B). The progress of the reaction is monitored by thin-layer chromatography, by eluting with a solvent (usually, hexane-ethyl acetate in a 4:1 ratio) and visualizing the plate using ultraviolet light or using any other appropriate method. The MTPA esters will have a higher R_f value compared to the starting alcohol. The product can be isolated by partitioning the reaction mixtures between diethyl ether and water, followed by extraction of the aqueous phase with ether. The ether phases are dried and the residues are dissolved in CDCl_3 for NMR analysis. Then ^1H NMR spectra of both esters are recorded and the chemical shift differences ($\Delta\delta = \delta\text{S} - \delta\text{R}$) between the diastereomers **22** and **23** are calculated by gathering the positive and negative $\Delta\delta$ values together. The AC of the hydroxyphosphonate can then be determined by using the formula shown below with $\Delta\delta < 0$ and $\Delta\delta > 0$ replaced by the actual structure fragments that exhibit positive and negative differences, respectively.

Kakisawa *et al.* [102] described the application of a modified Mosher's method to the N-MTPA derivatives of amino acid esters and acyclic amines, indicating that this method may be generally used to determine the ACs of the α -carbons of amino compounds. For the assignment of AC of hydroxy-, aminophosphonates, as well as of secondary alcohols or amines, the model of the target molecule should be constructed and it should be confirmed that all assigned nuclei with positive and negative $\Delta\delta$ values are actually found on the right and left sides of the MTPA plane, respectively (Scheme 1.12).

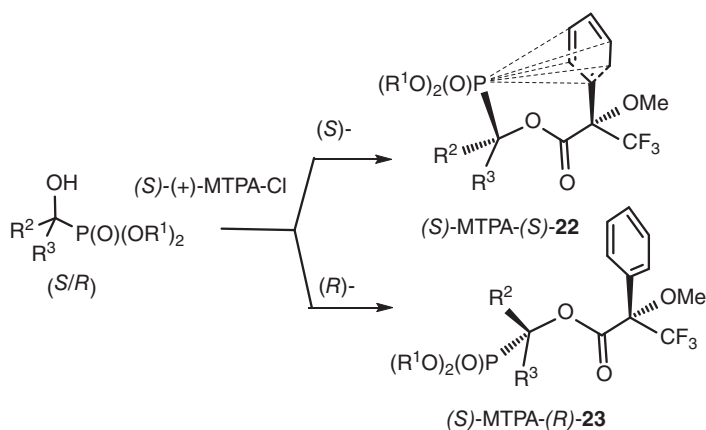
The absolute values of $\Delta\delta$ must be proportional to the distance from the MTPA moiety. Evidently, to correlate the information obtained from the NMR spectra with the AC, a detailed understanding of the structure as well as the strength and direction of



Scheme 1.12 Model to predict the absolute configurations of secondary alcohols, hydroxyphosphonates (X = O), primary amines or aminophosphonates (X = NH).

the anisotropic effect of Ph on R₁ and R₂ in each conformation is necessary. When these conditions are fulfilled, the model should indicate the correct AC of the target compound.

The AC of many α -hydroxyphosphonates was determined by derivatization with MTPA and application of ¹H, ¹⁹F, and ³¹P NMR spectroscopy [32, 33, 39]. Chemical shifts δ_p of derivatized (S)-hydroxyphosphonates **22** are usually in downfield relationship to signals of the corresponding (R)-hydroxyphosphonates **23**. The difference in chemical shifts δ_p (0.40–1.09 ppm) allows us to determine ACs of hydroxyphosphonates (Scheme 1.13).



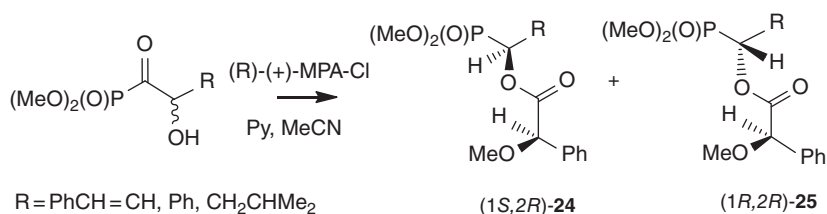
Scheme 1.13 Determination of configuration of hydroxyphosphonates by means of MTPA.

The conformation model of Mosher's esters derived from α -hydroxyphosphonates shows that the trifluoromethyl group and the carbonyl hydrogen at the C=O group ($R_2 = H, D$) are eclipsed by the carbonyl oxygen. The phosphorus atom in the (*R*)-MTPA ester is shielded by the phenyl group if the chiral alcohol has an (*R*)-configuration at C-1 relative to alcohol having an (*S*)-configuration. Therefore, the chemical shift of the phosphorus atom in the ^{31}P NMR spectra of the (*R*)-MTPA derivatives of (*R*)-hydroxyphosphonates will be upfield when compared with those of the (*S*)-alcohol.

The ^{31}P NMR spectra of (*R*)-MTPA esters with (*S*)-hydroxyphosphonates **24** confirmed that their signals δ_p are indeed downfield and that signals δ_p of (*R*)-hydroxyphosphonates **25** derivatized with (*R*)-MTPA esters are upfield. The shift differences were within 0.28–0.50 ppm (Table 1.2) [61]. In another work, Hammett and Wuggenig [103] have analyzed the resolution of phosphonates catalyzed by enzymes and confirmed Mosher's assumption that signals δ_p of (1*R*,2*R*)-esters and (*R*)-MTPA should be upfield in relation to (*S*)-MTPA esters (Scheme 1.14). The different orientation of the aromatic shielding cone effect in the diastereomeric derivatives leads to a selective shielding or deshielding of the R^1 or R^2 substituents at the asymmetric center. The AC of α -hydroxyphosphonates can be determined by ^1H and ^{31}P NMR spectroscopy of the mandelate ester derivatives. The observed chemical shifts allow assignment of the AC of the hydroxyphosphonates depending on the position of the phenyl group in the compounds and its shielding effect. Thus, the ^1H NMR spectra of (1*S*,2*R*)-diastereomers showed a downfield shift of signals for the *O*-methyl protons relative to the parent alcohol. The AC of compounds was additionally determined by

Table 1.2 Chemical shifts (δ_p) in the ^{31}P NMR spectra of Mosher's esters (Scheme 1.13).

Mosher ester			δ_p (ppm)		$\Delta\delta$	References
R^1	R^2	R^3	(<i>S</i>)	(<i>R</i>)	$[\delta(S) - \delta(R)]$	
Et	H	Me	22.21	21.77	0.44	[61]
Pr	H	Me	21.9	21.5	0.40	[61]
<i>i</i> -Pr	H	Et	19.33	18.93	0.40	[61]
Bu	H	Me	19.80	19.39	0.41	[61]
C_5H_{11}	H	Et	19.90	19.43	0.47	[61]
Et	H	Et	19.85	19.37	0.48	—
PhCH_2CH_2	H	<i>i</i> -Pr	17.42	17.01	0.41	[61]

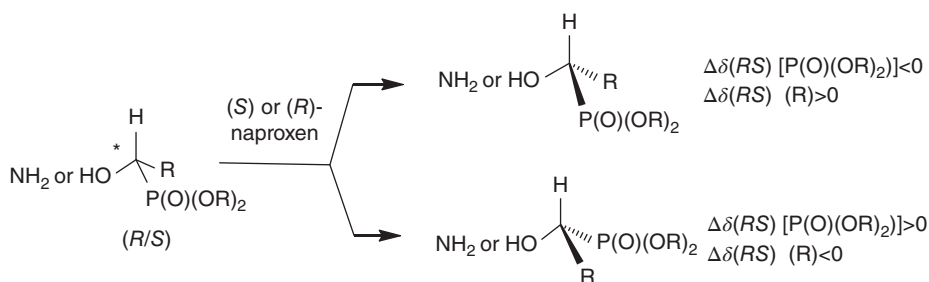


Scheme 1.14 Determination of absolute configuration by derivatization of hydroxyphosphonates with MPA.

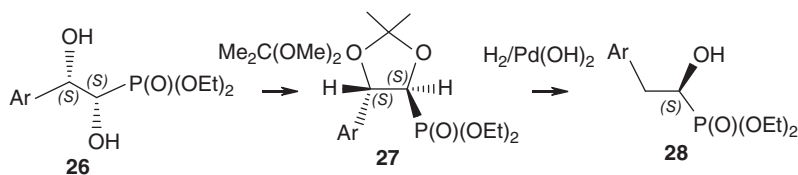
X-ray analysis. Kozłowski and Ordóñez [63, 64] determined the enantiomeric purity and the AC of α -hydroxy phosphonates **24** using esterification with mandelic acid. The spatial relationship between R^1/R^2 and the aryl ring is correlated to the observed chemical shift change. The R^1 substituent of the (*R,R*)-diastereomer is at higher field than the R^2 substituent. Inversely, R^2 in the (*S,R*)-derivative shifts more upfield relative to R^1 . The upfield or downfield shifts of the signals for the methyl-group protons in the ^1H NMR spectra of compounds depend on the arrangement of the phenyl group in the molecule and its shielding effect (Scheme 1.14).

Blazewska *et al.* [104, 105] have described the assignment of the AC of hydroxy- and aminophosphonates by their double derivatization with commercially available naproxen as CDA. They have shown that the diethoxyphosphoryl group is deshielded in esters of (*R*)- α -aminophosphonates with (*S*)-naproxen and in esters of (*S*)-1-aminophosphonates with (*R*)-naproxen. The correlation between the spatial arrangement around the stereogenic carbon center and the signs of the $\Delta\delta_{RS}$ allows determination of the AC of hydroxy- and aminophosphonates by comparison of the ^1H and ^{31}P NMR spectra of the (*R*)- and (*S*)-naproxen ester or amide derivatives. The proposed model is also valid for 2-aminophosphonates on consideration of the change in the order of the initial substituent. The analysis can be carried out by ^1H or ^{31}P NMR; however, the determination of AC is essentially simplified in case of ^{31}P NMR. This method was applied for the determination of the AC for a series of hydroxyphosphonates (Scheme 1.15).

Yokomatsu *et al.* [106] determined the AC of dihydroxyphosphonates **26** by converting them into the cyclic acetonides [107, 108]. The dihedral angles between HCCP were calculated by the MOPAC semiempirical program. On the basis of these calculations and the phosphorus version of the Karplus equations, a large vicinal proton–phosphorus coupling constant ($^3J_{\text{PH}} = 17.2\text{ Hz}$) was expected for *trans*-**27**, while a small coupling constant ($^3J_{\text{PH}} = 1.7\text{ Hz}$) was assumed for the *cis*-isomer. Careful analysis of the ^1H NMR spectrum of the *cis*- and *trans*-isomers established the vicinal coupling constant to be 10.1 and 9.8 Hz, respectively, suggesting their *trans*-stereochemistry. The (*S*)-AC of compounds was confirmed also by means of ^{31}P NMR analysis of their (*R*)-MTPA esters. The δ_{P} chemical shifts of (*S*)-diastereomers in the low field of the ^{31}P NMR spectra were assigned to the (*S*)-configuration. Hence the results obtained by the two alternative methods coincided and consequently the AC of initial compounds **26** was unambiguously established as (1*S*,2*S*) (Scheme 1.16).



Scheme 1.15 Determination of absolute configuration of hydroxy- or aminophosphonates, using naproxen as CDA.



Scheme 1.16 Modification of dihydroxyphosphonate for determination of absolute configuration
 Ar = 3-MeOC₆H₄, 4-ClC₆H₄, furyl, 1-naphthyl.

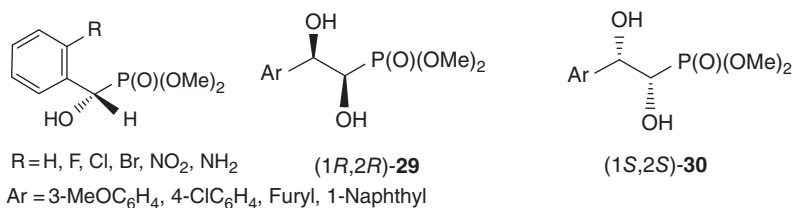
The AC of a series of 3,3'-disubstituted-MeO-BIPHEP derivatives was determined by the ¹H NMR spectra of the methoxyl group when the 3,3'-disubstituted-MeO-BIPHEP derivative was mixed with (–)-(2*R*,3*R*)-dibenzoyltartaric acid ((–)-DBTA) (1 : 2) and its NMR spectrum was run in CDCl₃. The chemical shift of the methoxyl group in the *S*_{ax} enantiomer occurred at higher field than that in the corresponding *R*_{ax} enantiomer [109].

The CD method is successfully used for determination of the AC of hydroxyphosphonates [106, 110, 111]. CD involves circularly polarized light. Left-hand circular (LHC) and right-hand circular (RHC) polarized light represent two possible spin angular momentum states for a photon, and so CD is also referred to as dichroism for spin angular momentum. It is exhibited in the absorption bands of optically active chiral molecules. For example, Wynberg and co-workers [110] used the CD spectra to determine the AC of a number of chiral α-hydroxy phosphonates. The enantiomers having (*S*)-configuration show a negative Cotton effect at 225 nm. Yokomatsu *et al.* [106] used the CD spectra to determine the AC of 1,2-dihydroxyphosphonates. It was found that α,β-dihydroxy phosphonates having the (1*S*,2*S*)-configuration show a positive Cotton effect at 210 – 230 nm, whereas (1*R*,2*R*)-isomers show a negative Cotton effect at these wavelengths (Scheme 1.17). Keglevich determined successfully the AC of 3-phospholene oxides by CD spectroscopy using quantum chemical calculations for the analysis of the spectra [81].

1.5 Asymmetric Induction and Stereochemistry

1.5.1 Asymmetric Induction

Asymmetric induction in stereochemistry describes the preferential formation in a chemical reaction of one enantiomer or diastereoisomer over the other as a result of the influence of a chiral inductor present in the substrate, reagent, catalyst, or reaction medium [1, 6]. There are three types of asymmetric induction: (i) internal asymmetric



Scheme 1.17 Examples of 1,2-dihydroxyphosphonates the absolute configuration of which was defined by means of CD-spectra.

induction, which uses a chiral center bound to the reactive center through a covalent bond and remains so during the reaction, (ii) relayed asymmetric induction, which uses a chiral information that is introduced in a separate step and then removed in a separate chemical reaction, and (iii) external asymmetric induction, in which chiral information is introduced in the transition state through a chiral catalyst or chiral auxiliary. A chiral auxiliary is a chemical compound or unit that is temporarily incorporated into an organic synthesis in order to control the stereochemical outcome of the synthesis. Asymmetric induction can involve chiral features in the substrate, reagent, catalyst, or environment and it works by making the activation energy required to form one enantiomer lower than that of the opposing enantiomer [112]. Asymmetric induction can occur intramolecularly when given a chiral starting material. This behavior can be exploited, especially when the goal is to make several consecutive chiral centers to give a specific enantiomer of a specific diastereomer. When two reactants of a reaction are stereogenic, the stereogenic elements of each reactant may operate either in concert (matched pair) or in opposition (mismatched pair). This phenomenon is known [113–115] as double asymmetric induction or double diastereoselection. See Section 3.5.

1.5.2 Asymmetric Synthesis

This involves a reaction that selectively creates one configuration of one or more new stereogenic elements by the action of a chiral reagent or auxiliary, acting on heterotopic faces, atoms, or groups of a substrate. The stereoselectivity is primarily influenced by the chiral catalyst, reagent, or auxiliary, despite any stereogenic elements that may be present in the substrate.

1.5.3 Asymmetric Transformation

This involves the conversion of a racemic mixture of stereoisomers into a single stereoisomer or a mixture in which one isomer predominates. An “asymmetric transformation of the first kind” involves such a conversion without separation of the stereoisomers, whereas in an “asymmetric transformation of the second kind,” separation, such as an equilibration, is accompanied by selective crystallization of one stereoisomer.

1.5.4 An Enantioselective Reaction

An enantioselective reaction is one in which one enantiomer is formed in preference to the other, in a reaction that creates an optically active product from an achiral starting material, using either a chiral catalyst, an enzyme, or a chiral reagent. An important variant is the *kinetic resolution*, in which a pre-existing chiral center undergoes reaction with a chiral catalyst, an enzyme, or a chiral reagent such that one enantiomer reacts faster than the other and leaves behind the less reactive enantiomer, or in which a pre-existing chiral center influences the reactivity of a reaction center elsewhere in the same molecule.

1.5.5 Enantioselective Synthesis

Enantioselective synthesis (or asymmetric synthesis), is defined by IUPAC as “a chemical reaction 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 synthesis is a key process in modern chemistry and is particularly important in the field of pharmaceuticals, as the different enantiomers or diastereomers of a molecule often have different biological activity.

Enantiomers possess identical enthalpies and entropies, and hence should be produced in equal amounts by an undirected process – leading to a racemic mixture. The solution is to introduce a chiral feature which will promote the formation of one enantiomer over another via interactions at the transition state. Reactions giving unequal amounts of stereoisomers are called stereo differentiating and prefixed according to the nature of the substrate as enantiomer- and diastereomer-, enantiotopos- and diastereotopos-, and further enantioface- and diastereoface-differentiating reactions, according to whether stereoisomers, groups, or faces are differentiated. Note that the first two types cover substrate-selective transformations, while the last four product-selective ones. Izumi’s classification is rather appealing because the conditions of selectivity can be defined very simply: enantio-differentiation requires chiral means, whereas diastereo-differentiation does not. The development of chiral catalysts is the most significant success in asymmetric synthesis in the last decades, which is capable to invoke transformation of achiral substrates in chiral products. Asymmetric catalysis, in which one molecule of chiral catalyst can yield many molecules of chiral product, has significant potential advantages over these older procedures. The catalysts are typically rendered chiral by using chiral ligands; however, it is also possible to generate chiral-at-metal complexes using simpler achiral ligands. Most enantioselective catalysts are effective at low concentrations making them well suited to industrial-scale synthesis, as even exotic and expensive catalysts can be used affordably. Compounds with a center of prochirality as well as a center of chirality can be transformed to a mixture of diastereomers without the interference of an additional source of chirality. In an enantioselective synthesis, the differentiation between the two enantiomers is possible by the same principle of diastereomeric transition states created under influence of additional sources of chirality (e.g., chiral catalyst). These methods are especially valuable for reactions in which two new stereocenters are formed stereoselectively in one step as, for example, in the case of multistereoselectivity [114, 115].

1.6 Summary

This chapter provides general information concerning stereochemistry, nomenclature of chiral systems, determination of enantiomer composition, determination of AC as well as some other stereochemical terms used in organophosphorus chemistry. As the purpose of this book is asymmetric synthesis, the remaining chapters provide details of asymmetric syntheses of chiral organophosphorus compounds.

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