PRINCIPLES AND APPLICATIONS OF ASYMMETRIC SYNTHESIS

Guo-Qiang Lin
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Dedicated to Professors
Chung-Kwong Poon and Wei-Shan Zhou

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PREFACE

Asymmetric synthesis has been one of the important topics of research for chemists in both industrial laboratories and the academic world over the past three decades. The subject matter is not only a major challenge to the minds of practicing scientists but also a highly fertile field for the development of technologies for the production of high-value pharmaceuticals and agrochemicals. The significant difference in physiologic properties for enantiomers is now well known in the scientific community. The recent guidelines laid down for new chiral drugs by the Food and Drug Administration in the United States and by similar regulating agencies in other countries serve to make the issue more obvious. In the past 10 years, many excellent monographs, review articles, and multivolume treatises have been published. Journals specializing in chirality and asymmetric synthesis have also gained popularity. All these attest to the importance of chiral compounds and their enantioselective synthesis.

As practitioners of the art of asymmetric synthesis and as teachers of the subject to postgraduate and advanced undergraduate students, we have long felt the need for a one-volume, quick reference on the principles and applications of the art of asymmetric synthesis. It is this strong desire in our daily professional life, which is shared by many of our colleagues and students, that drives us to write this book. The book is intended to be used by practicing scientists as well as research students as a source of basic knowledge and convenient reference. The literature coverage is up to September 1999.

The first chapter covers the basic principles, common nomenclatures, and analytical methods relevant to the subject. The rest of the book is organized based on the types of reactions discussed. Chapters 2 and 3 deal with carbon–carbon bond formations involving carbonyls, enamines, imines, enolates, and so forth. This has been the most prolific area in the field of asymmetric synthesis in the past decade. Chapter 4 discusses the asymmetric C–O bond formations including epoxidation, dihydroxylation, and aminohydroxylation. These reactions are particularly important for the production of pharmaceutical products and intermediates. Chapter 5 describes asymmetric synthesis using the Diels-Alder reactions and other cyclization reactions. Chapter 6 presents the asymmetric catalytic hydrogenation and stoichiometric reduction of various unsaturated functionalities. Asymmetric hydrogenation is the simplest way of creating new chiral centers, and the technology is still an industrial 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 7 records the applications of the asymmetric synthetic methods in the total synthesis of natural products. Chapter 8 reviews the use of enzymes and other methods and concepts in asymmetric synthesis. Overall, the book is expected to be useful for beginners as well as experienced practitioners of the art.

We are indebted to many of our colleagues and students for their assistance in various aspects of the preparation of this book. Most notably, assistance has been rendered from Jie-Fei Cheng, Wei-Chu Xu, Lu-Yan Zhang, Rong Li, and Fei Liu from Shanghai Institute of Organic Chemistry (SIOC) and Cheng-Chao Pai, Ming Yan, Ling-Yu Huang, Xiao-Wu Yang, Sze-Yin Leung, Jian-Ying Qi, Hua Chen, and Gang Chen from The Hong Kong Polytechnic University (PolyU). We also thank Sima Sengupta and William Purves of PolyU for proofreading and helping with the editing of the manuscript. Strong support and encouragement from Professor Wei-Shan Zhou of SIOC and Professor Chung-Kwong Poon of PolyU are gratefully acknowledged. Very helpful advice from Prof. Tak Hang Chan of McGill University and useful information on the industrial application of ferrocenyl phosphines from Professor Antonio Togni of Swiss Federal Institute of Technology and Dr. Felix Spindler of Solvias AG are greatly appreciated.

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ABBREVIATIONS

2ATMA	2-anthrylmethoxyacetic acid
Ac	acetyl group
AD mix-α	commercially available reagent for asymmetric dihydroxylation
AD mix-β	commercially available reagent for asymmetric dihydroxylation
AQN	anthraquinone
Ar	aryl group
ARO	asymmetric ring opening
BINAL–H	BINOL-modified aluminum hydride compound
BINOL	2,2′-dihydroxyl-1,1′-binaphthyl
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BLA	Brønsted acid–assisted chiral Lewis acid
Bn	benzyl group
BOC	*t*-butoxycarbonyl group
Bz	benzoyl group
CAB	chiral acyloxy borane
CAN	cerium ammonium nitrate
CBS	chiral oxazaborolidine compound developed by Corey, Bakshi, and Shibata
CCL	*Candida cyclindracea* lipase
CD	circular dichroism
CE	capillary electrophoresis
CIP	Cahn-Ingold-Prelog
COD	1,5-cyclooctadiene
Cp	cyclopentadienyl group
m-CPBA	*m*-chloroperbenzoic acid
CPL	circularly polarized light
CSA	camphorsulfonic acid
CSR	chemical shift reagent
DAIB	3-*exo*-(dimethylamino)isoborneol
DBNE	*N*,*N*-di-*n*-butylnorephedrine
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone

de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DHQ	dihydroquinine
DHQD	dihydroquinidine
DIBAL–H	diisobutylaluminum hydride
DIPT	diisopropyl tartrate
DIBT	diisobutyl tartrate
DMAP	4-*N*,*N*-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMI	dimethylimidazole
DMSO	dimethyl sulfoxide
DMT	dimethyl tartrate
L-DOPA	3-(3,4-dihydroxyphenyl)-L-alanine
DPEN	1,2-diphenylethylenediamine
EDA	ethyl diazoacetate
EDTA	ethylenediaminetetraacetic acid
ee	enantiomeric excess
GC	gas chromatography
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
Ipc	isocamphenyl
IR	infrared spectroscopy
KHMDS	$KN(SiMe_3)_2$
L*	chiral ligand
LDA	lithium diisopropylamide
LHMDS	$LiN(SiMe_3)_2$
LICA	lithium isopropylcyclohexylamide
LPS	lipopolysaccharide
LTMP	lithium tetramethylpiperidide
MAC	methyl α-(acetamido)cinnamate
MEM	methoxyethoxymethyl group
(*R*)-MNEA	*N*,*N*-di-[(1*R*)-(α-naphthyl)ethyl]-*N*-methylamine
MOM	methoxymethyl group
MPA	methoxyphenylacetic acid
Ms	methanesulfonyl, mesyl group
MTPA	α-methoxyltrifluoromethylphenylacetic acid

NAD(P)H	nicotinamide adenine dinucleotide (phosphate)
NHMDS	$NaN(SiMe_3)_2$
NLE	nonlinear effect
NME	*N*-methylephedrine
NMI	1-methylimidazole
NMMP	*N*-methylmorpholine
NMO	4-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
ORD	optical rotatory dispersion
Oxone®	commercial name for potassium peroxomonosulfate
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PLE	pig liver esterase
4-PPNO	4-phenylpyridine *N*-oxide
PTAB	phenyltrimethylammonium bromide
PTC	phase transfer catalyst
R*	chiral alkyl group
RAMP	(*R*)-1-amino-2-(methoxymethyl)pyrrolidine
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
Salen	*N*,*N*′-disalicylidene-ethylenediaminato
SAMEMP	(*S*)-1-amino-2-(2-methoxyethoxymethyl)pyrrolidine
SAMP	(*S*)-1-amino-2-(methoxymethyl)pyrrolidine
S/C	substrate-to-catalyst ratio
SRS	self-regeneration of stereocenters
TAPP	$\alpha\alpha\beta\beta$-tetrakis(aminophenyl)porphyrin
TBAF	tetrabutylammonium fluoride
TBHP	*t*-butyl hydrogen peroxide
TBDPS	*t*-butyldiphenylsilyl group
TBS	*t*-butyldimethylsilyl group
TCDI	1,1-thionocarbonyldiimidazole
Teoc	2-trimethylsilylethyl *N*-chloro-*N*-sodiocarbamate
TES	triethylsilyl group
Tf	trifluoromethanesulfonyl group
THF	tetrahydrofuran
TMS	trimethylsilyl group
TMSCN	cyanotrimethylsilane, Me_3SiCN
TPAP	tetrapropylammonium perruthenate
Ts	toluenesulfonyl, tosyl group

CHAPTER 1

Introduction

> The universe is dissymmetrical; for if the whole of the bodies which compose the solar system were placed before a glass moving with their individual movements, the image in the glass could not be superimposed on reality.... Life is dominated by dissymmetrical actions. I can foresee that all living species are primordially, in their structure, in their external forms, functions of cosmic dissymmetry.
>
> —Louis Pasteur

These visionary words of Pasteur, written 100 years ago, have profoundly influenced the development of stereochemistry. It has increasingly become clear that many fundamental phenomena and laws of nature result from dissymmetry. In modern chemistry, an important term to describe dissymmetry is *chirality** or *handedness*. Like a pair of hands, the two enantiomers of a chiral compound are mirror images of each other that cannot be superimposed. Given the fact that within a chiral surrounding two enantiomeric biologically active agents often behave differently, it is not surprising that the synthesis of chiral compounds (which is often called *asymmetric synthesis*) has become an important subject for research. Such study of the principles of asymmetric synthesis can be based on either intramolecular or intermolecular chirality transfer. Intramolecular transfer has been systematically studied and is well understood today. In contrast, the knowledge base in the area of intermolecular chirality transfer is still at the initial stages of development, although significant achievements have been made.

In recent years, stereochemistry, dealing with the three-dimensional behavior of chiral molecules, has become a significant area of research in modern organic chemistry. The development of stereochemistry can, however, be traced as far back as the nineteenth century. In 1801, the French mineralogist Haüy noticed that quartz crystals exhibited hemihedral phenomena, which implied that certain facets of the crystals were disposed as nonsuperimposable species showing a typical relationship between an object and its mirror image. In 1809, the French physicist Malus, who also studied quartz crystals, observed that they could induce the polarization of light.

In 1812, another French physicist, Biot, found that a quartz plate, cut at the

* This word comes from the Greek word *cheir*, which means *hand* in English.

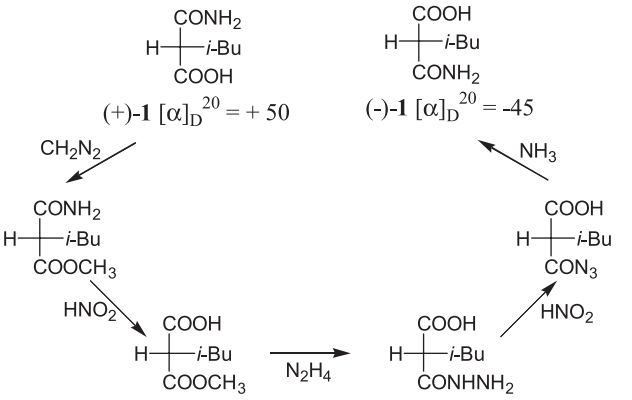
right angles to one particular crystal axis, rotated the plane of polarized light to an angle proportional to the thickness of the plate. Right and left forms of quartz crystals rotated the plane of the polarized light in different directions. Biot then extended these observations to pure organic liquids and solutions in 1815. He pointed out that there were some differences between the rotation caused by quartz crystals and that caused by the solutions of organic compounds he studied. For example, he noted that optical rotation caused by quartz was due to the whole crystal, whereas optical rotation caused by a solution of organic compound was due to individual molecules.

In 1822, the British astronomer Sir John Herschel observed that there was a correlation between hemihedralism and optical rotation. He found that all quartz crystals having the odd faces inclined in one direction rotated the plane of polarized light in one direction, while the enantiomorphous crystals rotate the polarized light in the opposite direction.

In 1846, Pasteur observed that all the crystals of dextrorotatory tartaric acid had hemihedral faces with the same orientation and thus assumed that the hemihedral structure of a tartaric acid salt was related to its optical rotatory power. In 1848, Pasteur separated enantiomorphous crystals of sodium ammonium salts of tartaric acid from solution. He observed that large crystals were formed by slowly evaporating the aqueous solution of racemic tartaric acid salt. These crystals exhibited significant hemihedral phenomena similar to those appearing in quartz. Pasteur was able to separate the different crystals using a pair of tweezers with the help of a lens. He then found that a solution of enantiomorphous crystals could rotate the plane of polarized light. One solution rotated the polarized light to the right, while the other one rotated the polarized light to the left.

Pasteur thus made the important deduction that the rotation of polarized light caused by different tartaric acid salt crystals was the property of chiral molecules. The (+)- and (−)-tartaric acids were thought to be related as an object to its mirror image in three dimensions. These tartaric acid salts were dissymmetric and enantiomorphous at the molecular level. It was this dissymmetry that provided the power to rotate the polarized light.

The work of these scientists in the nineteenth century led to an initial understanding of chirality. It became clear that the two enantiomers of a chiral molecule rotate the plane of polarized light to a degree that is equal in magnitude, but opposite in direction. An enantiomer that rotates polarized light in a clockwise direction is called a dextrorotatory molecule and is indicated by a plus sign (+) or italic letter "*d*". The other enantiomer, which rotates the plane of polarized light in a counterclockwise direction, is called levorotatory and is assigned a minus sign (−) or italic letter "*l*". Enantiomers of a given molecule have specific rotations with the same magnitude but in opposite directions. This fact was first demonstrated experimentally by Emil Fischer through a series of conversions of the compound 2-isobutyl malonic acid mono amide (**1**, see Scheme 1–1). As shown in Scheme 1–1, compound (+)-**1** can be converted to (−)-**1** through a series of reactions. From their projections, one can see that these two



Scheme 1–1. Enantiomers of 2-isobutyl malonic acid mono amide have opposite optical rotations.

compounds are mirror images of each other. Fischer's experimental result easily showed that these two compounds have an opposite specific rotation. The amount of the specific rotation is nearly the same, and the difference may be the result of experimental deviation.

An equal molar mixture of the dextrorotatory and levorotatory enantiomers of a chiral compound is called a racemic mixture or a racemate. Racemates do not show overall optical rotation because the equal and opposite rotations of the two enantiomers cancel each other out. A racemic mixture is designated by adding the prefix (±) or *rac*- before the name of the molecule.

Within this historical setting, the actual birth of stereochemistry can be dated to independent publications by J. H. van't Hoff and J. A. Le Bel within a few months of each other in 1874. Both scientists suggested a three-dimensional orientation of atoms based on two central assumptions. They assumed that the four bonds attached to a carbon atom were oriented tetrahedrally and that there was a correlation between the spatial arrangement of the four bonds and the properties of molecules. van't Hoff and Le Bell proposed that the tetrahedral model for carbon was the cause of molecular dissymmetry and optical rotation. By arguing that optical activity in a substance was an indication of molecular chirality, they laid the foundation for the study of intramolecular and intermolecular chirality.

1.1 THE SIGNIFICANCE OF CHIRALITY AND STEREOISOMERIC DISCRIMINATION

Chirality is a fundamental property of many three-dimensional objects. An object is chiral if it cannot be superimposed on its mirror image. In such a case, there are two possible forms of the same object, which are called *enantiomers*,

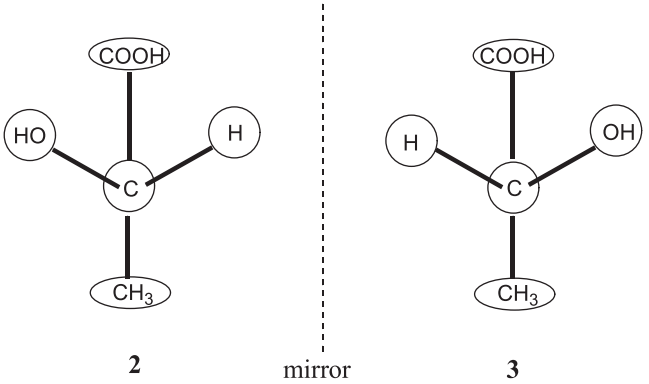


Figure 1–1. Mirror images of lactic acid.

and thus these two forms are said to be enantiomeric with each other. To take a simple example, lactic acid can be obtained in two forms or enantiomers, **2** and **3** in Figure 1–1, which are clearly enantiomeric in that they are related as mirror images that cannot be superimposed on each other.

Enantiomers have identical chemical and physical properties in the absence of an external chiral influence. This means that **2** and **3** have the same melting point, solubility, chromatographic retention time, infrared spectroscopy (IR), and nuclear magnetic resonance (NMR) spectra. However, there is one property in which chiral compounds differ from achiral compounds and in which enantiomers differ from each other. This property is the direction in which they rotate plane-polarized light, and this is called *optical activity* or *optical rotation*. Optical rotation can be interpreted as the outcome of interaction between an enantiomeric compound and polarized light. Thus, enantiomer **3**, which rotates plane-polarized light in a clockwise direction, is described as (+)-lactic acid, while enantiomer **2**, which has an equal and opposite rotation under the same conditions, is described as (−)-lactic acid.

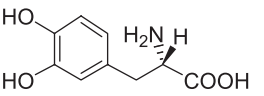
Readers may refer to the latter part of this chapter for the determination of absolute configuration.

Chirality is of prime significance, as most of the biological macromolecules of living systems occur in nature in one enantiomeric form only. A biologically active chiral compound interacts with its receptor site in a chiral manner, and enantiomers may be discriminated by the receptor in very different ways. Thus it is not surprising that the two enantiomers of a drug may interact differently with the receptor, leading to different effects. Indeed, it is very important to keep the idea of chiral discrimination or stereoisomeric discrimination in mind when designing biologically active molecules.

As human enzymes and cell surface receptors are chiral, the two enantiomers of a racemic drug may be absorbed, activated, or degraded in very different ways, both in vivo and in vitro. The two enantiomers may have unequal degrees

or different kinds of activity.[1] For example, one may be therapeutically effective, while the other may be ineffective or even toxic.

An interesting example of the above difference is L-DOPA **4**, which is used in the treatment of Parkinson's disease. The active drug is the achiral compound dopamine formed from **4** via in vivo decarboxylation. As dopamine cannot cross the blood–brain barrier to reach the required site of action, the "prodrug" **4** is administered. Enzyme-catalyzed in vivo decarboxylation releases the drug in its active form (dopamine). The enzyme L-DOPA decarboxylase, however, discriminates the stereoisomers of DOPA specifically and only decarboxylates the L-enantiomer of **4**. It is therefore essential to administer DOPA in its pure L-form. Otherwise, the accumulation of D-DOPA, which cannot be metabolized by enzymes in the human body, may be dangerous. Currently L-DOPA is prepared on an industrial scale via asymmetric catalytic hydrogenation.



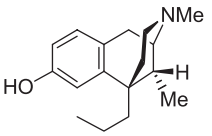
4

From the above example one can see that stereoisomeric discrimination is very striking in biological systems, and for this reason chirality is recognized as a central concept. If we consider the biological activities of chiral compounds in general, there are four different behaviors: (1) only one enantiomer has the desired biological activity, and the other one does not show significant bioactivity; (2) both enantiomers have identical or nearly identical bioactivity; (3) the enantiomers have quantitatively different activity; and (4) the two enantiomers have different kinds of biological activity. Table 1–1 presents a number of examples of differences in the behavior of enantiomers. The listed enantiomers may have different taste or odor and, more importantly, they may exhibit very different pharmacological properties. For example, D-asparagine has a sweet taste, whereas natural L-asparagine is bitter; (*S*)-(+)-carvone has an odor of caraway, whereas the (*R*)-isomer has a spearmint smell; (*R*)-limonene has an orange odor, and its (*S*)-isomer has a lemon odor. In the case of disparlure, a sex pheromone for the gypsy moth, one isomer is active in very dilute concentration, whereas the other isomer is inactive even in very high concentration. (*S*)-propranolol is a β-blocker drug that is 98 times as active as its (*R*)-counterpart.[2]

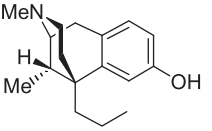
Sometimes the inactive isomer may interfere with the active isomer and significantly lower its activity. For example, when the (*R*)-derivative of the sex pheromone of a Japanese beetle is contaminated with only 2% of its enantiomer, the mixture is three times less active than the optically pure pheromone. The pheromone with as little as 0.5% of the (*S*)-enantiomer already shows a significant decrease of activity.[3]

A tragedy occurred in Europe during the 1950s involving the drug thalidomide. This is a powerful sedative and antinausea agent that was considered

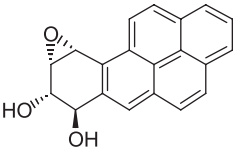
TABLE 1–1. Examples of the Different Behaviors of Enantiomers



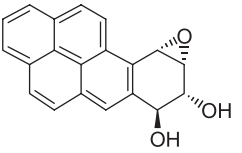
(-)-Benzomorphia
(eases pain, unhabituational)



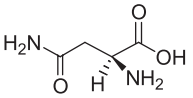
(+)-Benzomorphia
(faintly pain-easing, habituational)



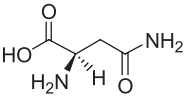
(-)-Benzopyryldiol
(strong carcinogenicity)



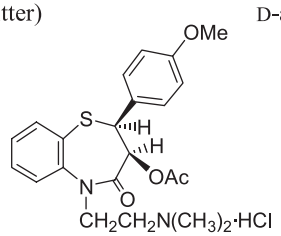
(+)-Benzopyryldiol
(no carcinogenicity)



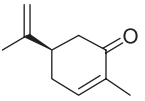
L-asparagine (bitter)



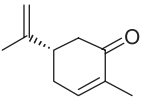
D-asparagine (sweet)



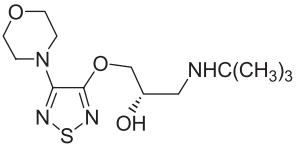
diltiazem
(the (*S*, *S*)-form is effective in relieving myocardial infarction[4])



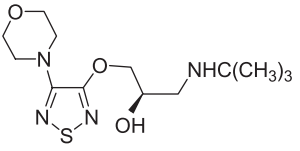
(*R*)-carvone (spearmint odor)



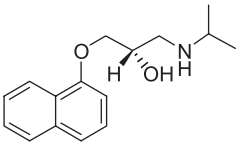
(*S*)-carvone (caraway odor)



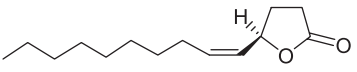
(*R*)-timolol (adrenergic blocker)



(*S*)-timolol (ineffective)



(*S*)-propranolol
[98 times the activity of its (*R*)-isomer]



Sex pheromone of the Japanese beetle
(its enantiomer is inactive)

especially appropriate for use during early pregnancy. Unfortunately, it was soon found that this drug was a very potent teratogen and thus had serious harmful effects on the fetus. Further study showed that this teratogenicity was caused by the (*S*)-isomer (which had little sedative effect), but the drug was sold in racemic form. The (*R*)-isomer (the active sedative) was found not to cause deformities in animals even in high doses.[5] Similarly, the toxicity of naturally occurring (−)-nicotine is much greater than that of unnatural (+)-nicotine. Chiral herbicides, pesticides, and plant growth regulators widely used in agriculture also show strong biodiscriminations.

In fact, stereodiscrimination has been a crucial factor in designing enantiomerically pure drugs that will achieve better interaction with their receptors. The administration of enantiomerically pure drugs can have the following advantages: (1) decreased dosage, lowering the load on metabolism; (2) increased latitude in dosage; (3) increased confidence in dose selection; (4) fewer interactions with other drugs; and (5) enhanced activity, increased specificity, and less risk of possible side effects caused by the enantiomer.

Now it is quite clear that asymmetry (or chirality) plays an important role in life sciences. The next few sections give a brief introduction to the conventions of the study of asymmetric (or chiral) systems.

1.2 ASYMMETRY

1.2.1 Conditions for Asymmetry

Various chiral centers, such as the chiral carbon center, chiral nitrogen center, chiral phosphorous center, and chiral sulfur center are depicted in Figure 1–2.

Amines with three different substituents are potentially chiral because of the pseudotetrahedral arrangement of the three groups and the lone-pair electrons. Under normal conditions, however, these enantiomers are not separable because of the rapid inversion at the nitrogen center. As soon as the lone-pair electrons are fixed by the formation of quaternary ammonium salts, tertiary amide *N*-oxide, or any other fixed bonding, the inversion is prohibited, and consequently the enantiomers of chiral nitrogen compounds can be separated.

In contrast to the amines, inversion of configuration for phosphines is generally negligibly slow at ambient temperature. This property has made it possible for chiral phosphines to be highly useful as ligands in transition metal-catalyzed asymmetric syntheses.

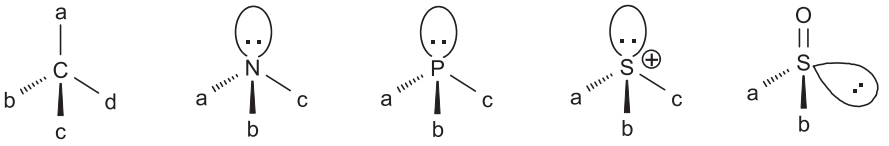


Figure 1–2. Formation of asymmetry.

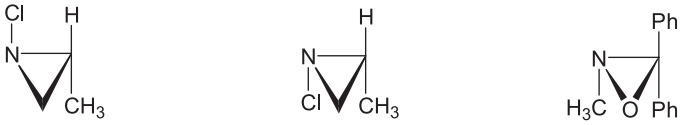


Figure 1–3. Solution stable three-membered heterocyclic ring systems.

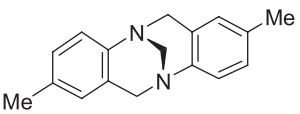
As a result of the presence of lone-pair electrons, the configuration of organosulfur species is pyramidal, and the pyramidal reversion is normally slow at ambient temperature. Thus two enantiomers of chiral sulfoxides are possible and separable.

As a general rule, asymmetry may be created by one of the following three conditions:

1. Compounds with an asymmetric carbon atom: When the four groups connected to a carbon center are different from one another, the central carbon is called a *chiral center*. (However, we must remember that the presence of an asymmetric carbon is neither a necessary nor a sufficient condition for optical activity.)
2. Compounds with another quaternary covalent chiral center binding to four different groups that occupy the four corners of a tetrahedron:

   Si, Ge, N (in quaternary salts or *N*-oxides)

   Mn, Cu, Bi and Zn—when in tetrahedral coordination.
3. Compounds with trivalent asymmetric atoms: In atoms with pyramidal bonding to three different groups, the unshared pair of electrons is analogous to a fourth group. In the case of nitrogen compounds, if the inversion at the nitrogen center is prevented by a rigid structural arrangement, chirality also arises. The following examples illustrate this phenomenon.
   a. In a three-membered heterocyclic ring, the energy barrier for inversion at the nitrogen center is substantially raised (Fig. 1–3).
   b. The bridgehead structure completely prevents inversion.



Irreversible

1.2.2 Nomenclature

If a molecule contains more than one chiral center, there are other forms of stereoisomerism. As mentioned in Section 1.1, nonsuperimposable mirror images are called *enantiomers*. However, substances with the same chemical constitution may not be mirror images and may instead differ from one another

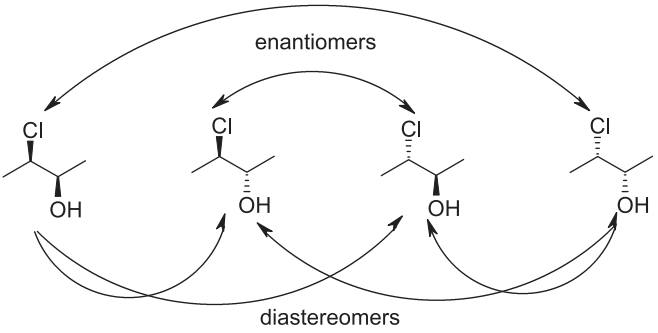


Figure 1–4. Enantiomers and diastereomers.

in having different configurations at one or more chiral centers in the molecule. These substances are called *diastereomers*. Thus, for 2-chloro-3-hydroxylbutane, one can draw four different structures, among which one can find two pairs of enantiomeric and four pairs of diastereomeric relations (Fig. 1–4).

For the unambiguous description of the various isomers, it is clearly necessary to have formal rules to define the structural configurations. These rules are explained in the following sections.

1.2.2.1 Fischer's Convention. Initially, the absolute configurations of optical isomers were unknown to chemists working with optically active compounds. Emil Fischer, the father of carbohydrate chemistry, decided to relate the possible configurations of compounds to that of glyceraldehyde of which the absolute configuration was yet unknown but was defined arbitrarily.

In Fischer's projection of glyceraldehyde, the carbon chain is drawn vertically with only the asymmetric carbon in the plane of the paper. Both the carbonyl and the hydroxylmethyl groups are drawn as if they are behind the plane, with the carbonyl group on the top and the hydroxylmethyl group at the bottom of the projection. The hydroxyl group and the hydrogen atom attached to the asymmetric carbon atom are drawn in front of the plane, the hydroxyl group to the right and the hydrogen atom to the left. This configuration was arbitrarily assigned as the D-configuration of glyceraldehyde and is identified by a small capital letter D. Its mirror image enantiomer with the opposite configuration is identified by a small capital letter L.

The structure of any other optically active compound of the type $R-CHX-R'$ is drawn with the carbon chain

in the vertical direction with the higher oxidative state atom (R or R') on the top. If the X group (usually –OH, $-NH_2$, or a halogen) is on the right side, the relative configuration is designated D; otherwise the configuration is designated L.

Although the D-form of glyceraldehyde was arbitrarily chosen as the dextrorotatory isomer without any knowledge of its absolute configuration, the choice was a fortuitous one. In 1951, with the aid of modern analytical methods, the D-configuration of the dextrorotatory isomer was unambiguously established.

The merit of Fischer's convention is that it enables the systematic stereochemical presentation of a large number of natural products, and this convention is still useful for carbohydrates or amino acids today. Its limitations, however, become obvious with compounds that do not resemble the model reference compound glyceraldehyde. For example, it is very difficult to correlate the terpene compounds with glyceraldehyde. Furthermore, selection of the correct orientation of the main chain may also be ambiguous. Sometimes different configurations may even be assigned to the same compound when the main chain is arranged in a different way.

1.2.2.2 The Cahn-Ingold-Prelog Convention. The limitations of Fischer's convention made it clear that in order to assign the exact orientation of the four connecting groups around a chiral center it was necessary to establish a systematic nomenclature for stereoisomers. This move started in the 1950s with Cahn, Ingold, and Prelog establishing a new system called the Cahn-Ingold-Prelog (CIP) convention[6] for describing stereoisomers. The CIP convention is based on a set of sequence rules, following which the name describing the constitution of a compound is accorded a prefix that defines the absolute configuration of a molecule unambiguously. These prefixes also enable the preparation of a stereodrawing that represents the real structure of the molecule.

In the nomenclature system, atoms or groups bonded to the chiral center are prioritized first, based on the sequence rules. The rules can be simplified as follows: (1) An atom having a higher atomic number has priority over one with a lower atomic number; for isotopic atoms, the isotope with a higher mass precedes the one with the lower mass. (2) If two or more of the atoms directly bonded to the asymmetric atom are identical, the atoms attached to them will be compared, according to the same sequence rule. Thus, if there is no heteroatom involved, alkyl groups can be sequenced as tertiary > secondary > primary. When two groups have different substituents, the substituent bearing the highest atomic number on each group must be compared first. The sequence decision for these groups will be made based on the sequence of the substituents, and the one containing prior substituents has a higher precedence. A similar rule is applicable in the case of groups with heteroatoms. (3) For multiple bonds, a doubly or triply bonded atom is duplicated or triplicated with the atom to which it is connected. This rule is also applicable to aromatic systems. For example,