

Introduction

1.1 Why we do asymmetric syntheses

The world is chiral [1-3]. Most organic compounds are chiral. Chemists working with perfumes, cosmetics, nutrients, flavors, pesticides, vitamins, and pharmaceuticals, to name a few examples [4-8], require access to enantiomerically pure compounds. In the pharmaceutical industry [8,9], more than half of the drugs available on the market in 1990 (worldwide) were chiral, and roughly half of those were sold as a single enantiomer. But of those drugs sold as a single enantiomer, roughly 90% were natural products or semisynthetic derivatives. By contrast, nearly 90% of all chiral synthetic drugs sold at that time were racemic [10].

As our ability to produce enantiomerically pure compounds grows, so does our awareness of the differences in pharmacological properties that a chiral compound may have when compared with its enantiomer or even its racemate [11,12]. We easily recognize that all biological receptors are chiral, and as such can distinguish between the two enantiomers of a ligand or substrate. Enantiomeric compounds often have different odors or tastes [13-15].¹ Thus, it is obvious that two enantiomers should be considered different compounds when screened for pharmacological activity [8,12,16]. The demand for enantiomerically pure compounds as drug candidates is not likely to let up in the foreseeable future.

How might we obtain enantiomerically pure compounds? Historically, the best answer to that question has been to isolate them from natural sources. Hence the dependence on natural product isolation for the production of enantiomerically pure pharmaceuticals. Derivatization of natural products or their use as synthetic starting materials has long been a useful tool in the hands of the synthetic chemist, but it has now been raised to an art form by practitioners of the “Chiron” approach to total synthesis, wherein complex molecules are dissected into chiral fragments that may be obtained from natural products [17-25].

So if the objective is to obtain an enantiomerically pure compound, one has a choice to make: synthesize the molecule in racemic form and resolve it [26], find a plant or bacterium that will make it for you, start with the appropriate chiron (but beware of racemic or partly racemic natural products), or plan an asymmetric synthesis. Among the factors to consider in weighing the alternatives are the amount of material required, the cost of the starting materials, length of synthetic plan, etc., factors which have long been important to synthetic design [27,28]. For the purposes of biological evaluation, it may be *desirable* to include a resolution so that one synthesis will provide both enantiomers. But for the production of a single

¹ For example, the enantiomers of limonene smell and taste like oranges or lemons, the enantiomers of phenylalanine taste bitter or sweet, the enantiomers of carvone taste like spearmint or caraway, all depending on the absolute configuration.

enantiomer, resolution will have a maximum theoretical yield of 50% unless the unwanted enantiomer can be recovered and recycled. In most cases, the chiron and enzyme/organism approaches will be restricted to the production of only one enantiomer by a given route, notwithstanding the talent of some investigators to produce both enantiomers of a target from the same chiral starting material. The chiron approach consumes the chiral natural product, while the asymmetric synthesis routes (historically) do not. However, the lines of distinction between these categories are fading.

1.2 What is an asymmetric synthesis?

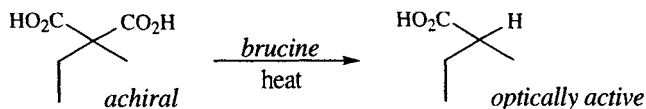
The most quoted definition of an asymmetric synthesis is that of Marckwald [29]:

‘Asymmetrische’ Synthesen sind solche, welche aus symmetrisch constituirten Verbindungen unter intermediärer Benutzung optisch-activer Stoffe, aber unter Vermeidung jedes analytischen Vorganges, optisch-activ Substanzen erzeugen.²

In modern terminology, the core of Marckwald’s definition is the conversion of an achiral substance into a chiral, nonracemic one by the action of a chiral reagent. By this criterion, the chiron approach falls outside the realm of asymmetric synthesis. Marckwald’s point of reference of course, was biochemical processes, so it follows that modern enzymatic processes [30-32] are included by this definition. Marckwald also asserted that the nature of the reaction was irrelevant, so a self-immolative reaction or sequence³ such as an intermolecular chirality transfer in a Meerwein-Ponndorf-Verley reaction would also be included:



Interestingly, the Marckwald definition is taken from a paper that was rebutting a criticism [33] of Marckwald’s claim to have achieved an asymmetric synthesis by a group-selective decarboxylation of the brucine salt of 2-ethyl-2-methylmalonic acid [34,35]:



Thus from the very beginning, the definition of what an asymmetric synthesis might encompass, or even if one was possible, has been a matter of debate. On the latter point, the idea that a chemist could synthesize something in optically active form from an achiral precursor was doubted in some circles, even in Marckwald’s

² ‘Asymmetric’ syntheses are those which produce optically active substances from symmetrically constituted compounds with the intermediate use of optically active materials, but with the avoidance of any separations.

³ Self-immolative processes are those that generate a new stereocenter at the expense of an existing one, either in a single reaction or in a sequence whereby the controlling stereocenter is deliberately destroyed in a subsequent step.

time. That doubt, expressed in a published lecture in 1898 [36] was one of the last tenets of the vitalism theory to die.

When one considers that historically, isolated natural products were the major source of chiral nonracemic chemicals, and when the labor of extraction was also considered, it is no wonder that recovery of the chiral reagent was important. Nowadays, the source of a reagent is the nearest chemical catalog, and it makes little difference if the chiral substance, whether to be used as a chiron or as a recoverable or consumable reagent, is obtained by isolation, enzymatic synthesis, or resolution. For the purposes of synthetic planning, the most important variable is the cost of the process relative to the value of the product. Also, the scale of the planned synthesis must be considered: an affordable cost for the preparation of a few grams of product may not be feasible for the production of several hundred kilos. It may also be important to consider the availability of either enantiomer of the chiral reagent.

In 1974, Eliel proposed the following criteria for judging an asymmetric synthesis [37]:

1. The synthesis must be highly stereoselective.
2. If the chiral auxiliary (adjuvant) is an integral part of the starting material, the chiral center (or other chirality element) generated in the asymmetric synthesis must be readily separable from the auxiliary without racemization [of the new stereocenter].
3. The chiral auxiliary or reagent must be recoverable in good yield and without racemization.
4. The chiral auxiliary or catalyst should be readily and inexpensively available in enantiomerically pure form.

Several comments [38] are appropriate regarding these guidelines. The first is obviously the most important, and is universally applicable to all synthetic strategies. Chromatographic or other purification techniques often provide a practical solution to low selectivity in unfavorable cases, however. Points 2 and 3 address auxiliary-based techniques, and are predicated on the higher cost of chiral reagents. Condition 3 is less important when a chiral catalyst has a high turnover number or when the chiral auxiliary is very inexpensive. Point 4 also becomes less important in catalytic processes as the turnover number increases.

The simplicity of the Marckwald definition has been its most enduring feature, but our understanding of structure and mechanism has evolved since Marckwald's time,⁴ and spectroscopic and chromatographic techniques have displaced polarimetry as the primary determinant of enantiomeric purity. In light of these

⁴ As a point of reference, consider that in Marckwald's time the van't Hoff - le Bel theory of tetrahedral carbon was accepted, but what we now know as an sp^2 or trigonal carbon, was not. It was thought, at least by some, that the fourth site of a carbonyl carbon was an unoccupied site on a tetrahedron. For example, under the term 'asymmetric induction' in the first collective index of *Chemical Abstracts*, we find reference to a paper (8:3431¹) entitled "Preparation of *l*-benzaldehyde through asymmetric induction . . ." (E. Erlenmeyer, F. Landesberger, G. Hilgen-dorff *Biochem. Z.* **1914**, *64*, 382-392). The formula for benzaldehyde was PhCHL.Ol , where L indicates an unoccupied position.

developments, as well as the new applications of double asymmetric induction (*vide infra*) that are not addressed by the Marckwald definition, a broader definition is appropriate:

Asymmetric synthesis is a reaction or reaction sequence 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.

In 1933, two short monographs [39,40] summarized virtually everything known about asymmetric synthesis and asymmetric induction. By 1971, the field was summarized in another short monograph of about 450 pages [41], but by then the art of organic synthesis was ready for a rapid advance: ten years later, a five volume treatise [42] was necessary (~1800 pages). The literature continues to grow at such a rate that comprehensive coverage is increasingly difficult. Although not restricted to asymmetric synthesis, the recent nine volume *Comprehensive Organic Synthesis* encyclopedia [43] subtitled 'Selectivity, Strategy, and Efficiency in Modern Organic Chemistry' is ~7000 pages. In 1995, a 6000-page treatise entitled *Stereoselective Synthesis* and advertised as "the whole of organic stereochemistry" appeared as part of the Houben-Weyl series [44].

It is the primary aim of the present work to provide a *concise* analysis of the stereochemical features of transition states in a variety of reaction types. These control elements are only partly understood at present, but as the intra- and intermolecular forces that govern transition state assemblies come further into focus, the principles outlined in this book will be refined and improved. The ultimate (attainable?) goal is clear: the production of any relative and absolute configuration of one or more stereogenic units through the use of chiral catalysts that do not require consideration of chirality elements extant in the substrate.

1.3 Stereoselectivity: intraligand vs. interligand asymmetric induction

It is the primary goal of this book to analyze the factors that influence stereoselectivity when one stereoisomer predominates over others. For illustrative purposes, consider the addition of a nucleophile to a carbonyl. The faces of unsymmetric carbonyls are heterotopic, either enantiotopic (if there are no stereocenters in the molecule) or diastereotopic (if there are), as shown in Figure 1.1 (see also glossary, Section 1.6). In order to achieve a predominance of one stereoisomer (enantiomer or diastereomer) over the other, the transition states resulting from attack from the heterotopic *Re* or *Si* faces must be diastereomeric. This will be the case if either the carbonyl compound or the reagent (or both) is (are) chiral.

It is useful to classify stereoselective reactions as a preliminary step to identifying the factors influencing stereoselectivity. Metals are intimately involved in almost all highly stereoselective reactions,⁵ so our classification will begin there.

⁵ For a review of stereoselective reactions of free radicals, see ref. [45,46].

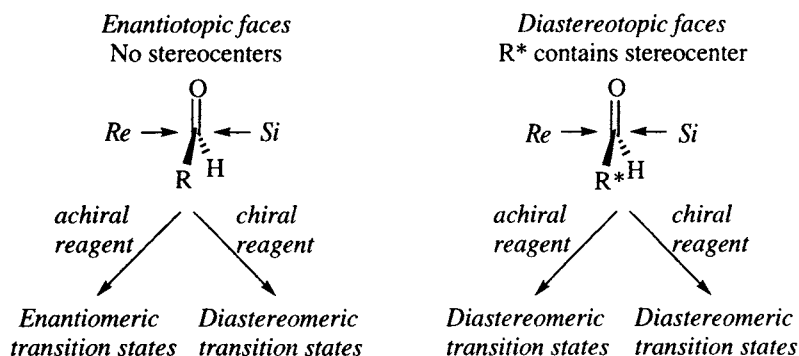
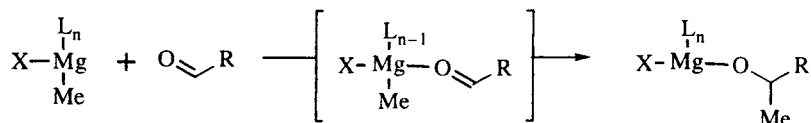


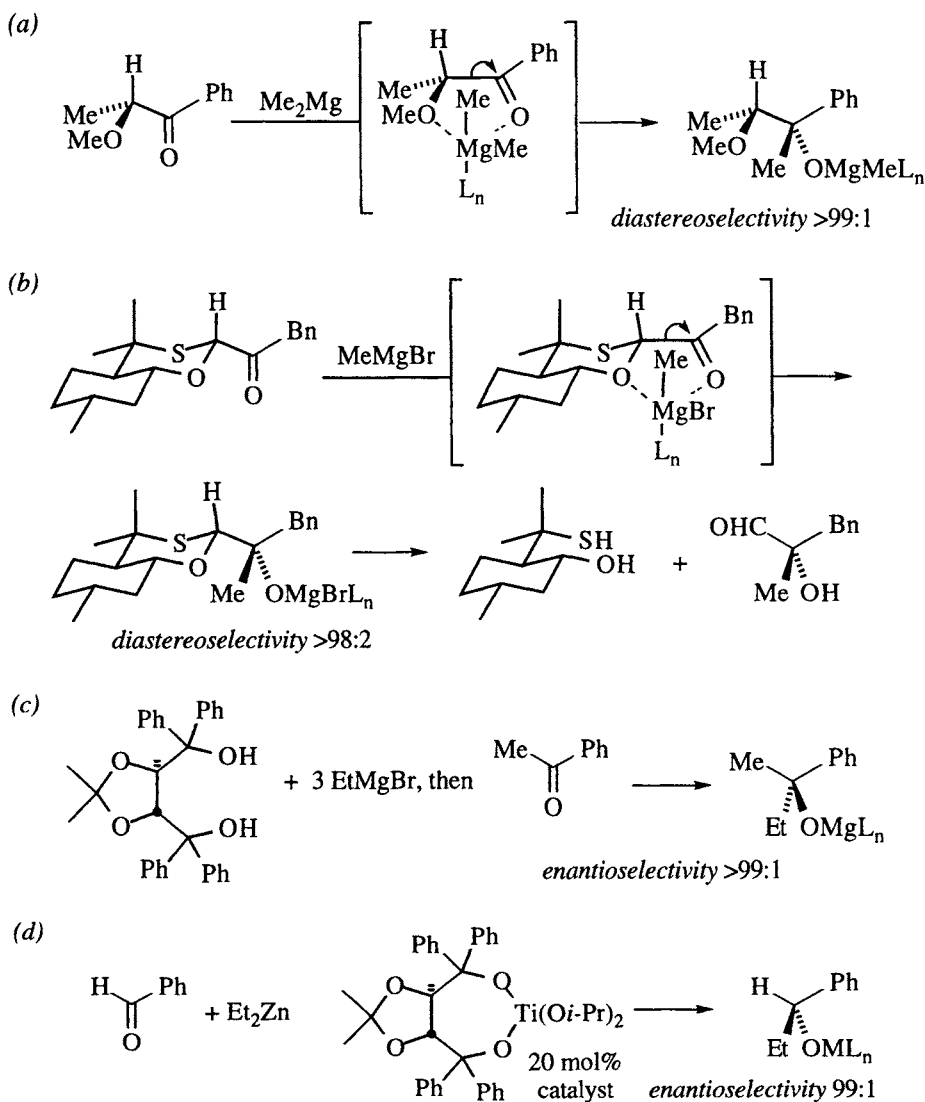
Figure 1.1. Additions to heterotopic faces of an aldehyde.

The first step is to examine the ligands on the metal. The most important ligand will be the substrate; other ligands may simply be solvent, monodentate or bidentate “spectator” ligands, or a ligand that is involved in the reaction (a “player”). Take the addition of a Grignard reagent to an aldehyde as an example (Scheme 1.1). The Grignard reagent (ignoring Schlenk processes) has an organic ligand (*e.g.*, Me), a halide (X), and several bound solvent molecules (L_n) in its coordination sphere. Addition to a carbonyl does not occur, however, until the aldehyde coordinates to the magnesium. Notice that four types of ligand are now apparent in the intermediate shown in brackets: the aldehyde substrate, the methyl group that adds to the carbonyl, the halide, and the bound solvent. The aldehyde and the methyl are the “players” while the halide and the solvent ligands are “spectators”.



Scheme 1.1. The addition of a Grignard reagent to an aldehyde.

Several examples of carbonyl additions (see also Chapter 4) serve to illustrate a further ligand classification that has tremendous bearing on stereoselectivity, and which illustrates in a nutshell the history of asymmetric synthesis while also pointing us toward its future. In the 1950s, Cram examined the influence of an adjacent stereocenter on the stereoselectivity of nucleophilic additions to carbonyls [47,48]. In the example illustrated (Scheme 1.2a, taken from Eliel’s later work, [49], one diastereomer is formed to the near exclusion of the other. The chirality sense (*R/S*) of the new stereocenter is determined by the chirality center adjacent to the carbonyl. Both the “old” and the “new” stereocenters are within the same ligand on the metal, however, so the asymmetric induction is *intraligand*. Later, the auxiliary shown in Scheme 1.2b was developed for use in an asymmetric synthesis of α -hydroxy aldehydes. Here, the oxathiane fragment is *removed* after directing the selective formation of one of two possible diastereomers [50]. Note, however, that this example is also a case of *intraligand* asymmetric induction, and that both of these examples have diastereomeric transition states because the carbonyl-containing substrate is chiral. Scheme 1.2c shows the addition of a Grignard to an ketone, after modifying the reagent with a chiral diol. Here, since the ketone is achiral, the two



Scheme 1.2. Intraligand vs. interligand asymmetric induction: (a) Diastereoselective addition *via* Cram's cyclic model ([49], *cf.*, Section 4.2). (b) Asymmetric synthesis of a pure enantiomer *via* diastereoselective addition to a carbonyl with a chiral auxiliary [50]. (c) Enantioselective addition of ethyl Grignard to an aldehyde using a chiral ligand on magnesium [51]. (d) Catalytic enantioselective addition of diethylzinc to an aldehyde using a chiral ligand on titanium [52].

faces of the carbonyl are enantiotopic, and the transition states are rendered diastereomeric by the chiral diol ligand. Although the details of the reaction are unknown, the only chirality element present in the reactants are in the diol ligand, making this *interligand* asymmetric induction.⁶

⁶ In principle a metal atom may also be stereogenic (and therefore influence the stereoselectivity), but a separate category is not needed since chiral nonracemic metal complexes containing achiral ligands are rare in asymmetric synthesis [53].

The mental process of “removing” the stereocenter from the substrate and putting it on another ligand of the metal allows the introduction of the element of asymmetric catalysis [54,55], as shown by the diethylzinc addition in Scheme 1.2d [56]. Here, the chiral reagent is used in less than stoichiometric quantities. Catalytic processes are, of course, more cost-effective than stoichiometric processes, and have the added advantage of decreasing the environmental impact of disposing of (or recycling) byproducts produced in stoichiometric quantities.

These four examples illustrate the progress made in stereoselective reactions in the last few decades, and which has evolved through several distinct phases: (i) Diastereoselective synthesis by addition of nucleophiles to carbonyls having a neighboring stereocenter; (ii) the extension of the same notion to the synthesis of a single enantiomer *via* diastereoselection and auxiliary removal; and (iii) enantioselective addition to an achiral substrate by a stoichiometric reagent; and (iv) enantioselective addition mediated by a chiral catalyst. Extrapolation of the trend that is apparent in these simple examples points inexorably toward the goal stated at the end of the previous section: the production of new stereogenic units through the use of chiral catalysts that do not require consideration of existing chirality elements.

1.4 Selectivity: kinetic and thermodynamic control

The means by which stereoselectivity is achieved in various reactions and processes are widely variable. However, the asymmetric induction that results in any given process must fall into one of only two categories: thermodynamic or kinetic control, the latter being the more common.

Consider a starting material, **A**, that may give two possible products, **B** and **C**. Figure 1.2a illustrates how equilibration might occur to afford an equilibrium mixture of **B** and **C** by one of two possible routes. The reactions $A \rightarrow B$ and $A \rightarrow C$ might be reversible, or **A** and **C** could equilibrate by a route that does not involve **A**. Either way, the product ratio (**C/B**) is given by

$$C/B = \frac{[C]}{[B]} = K = e^{-\Delta G/RT}, \quad (1.1)$$

where ΔG is the free energy difference between **C** and **B**: $\Delta G = G_B - G_C$. Processes such as this are under *thermodynamic control*.

Under conditions of *kinetic control* (Figure 1.2b), the conversion of **A** into either **B** or **C** is irreversible, the relative rates of formation of each product determine the outcome, and the product ratio (**C/B**) is given by

$$C/B = \frac{k_1}{k_2} = e^{-\Delta\Delta G^\ddagger/RT}, \quad (1.2)$$

where k_1 and k_2 are the rate constants for the formation of **B** and **C**, respectively.

$\Delta\Delta G^\ddagger$ is the difference in the transition state energies for each process:

$$\Delta\Delta G^\ddagger = \Delta G_B^\ddagger - \Delta G_C^\ddagger, \quad (1.3)$$

where ΔG_B^\ddagger and ΔG_C^\ddagger are the free energies of activation for the formation of **B** and **C**, respectively.

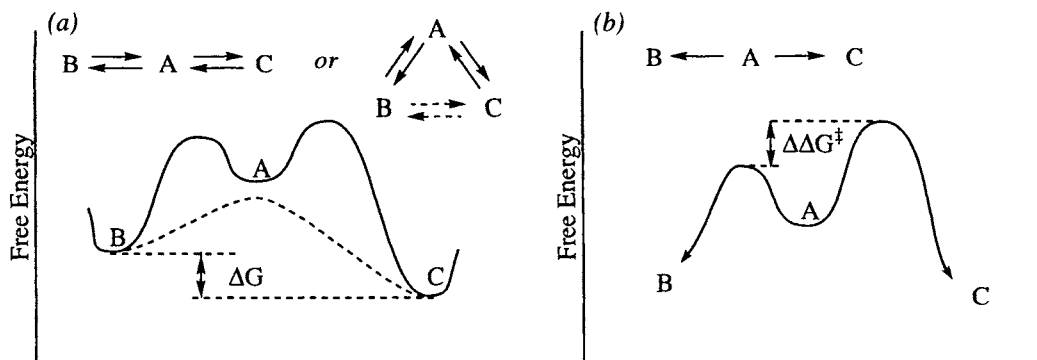


Figure 1.2. (a) Conversion of A into a mixture of B and C under *thermodynamic control*. Note that B and C may equilibrate via A or by another route (dashed line). (b) Conversion of A into B and C under *kinetic control*.

Two types of selectivity may be used to establish new stereogenic units in a molecule: *diastereoselectivity* and *enantioselectivity*. In *diastereoselective* reactions, either kinetic or thermodynamic control are possible, but in *enantioselective* reactions, the products are isoenergetic and only kinetic control is possible.⁷

Equations 1.1 and 1.2 establish the exponential dependence of selectivity on free energy and temperature. Figure 1.3 shows plots of these equations at three different temperatures.⁸ The curves of Figure 1.3 illustrate a number of points:

1. The steepest part of the curves occurs in the region where the selectivity (K or k_1/k_2) is ≤ 10 . Because of the exponential relationship, a doubling of the free energy difference at 10:1 will increase the selectivity to 100:1.
2. The total energy differences that afford 100:1 selectivity are not great. For comparison, recall that ΔG for the *cis* and *trans* isomers of the dimethylcyclohexanes or between the axial and equatorial conformations of methylcyclohexane is 1,600–1,700 cal/mole.
3. In the “flat” part of the curves, small differences in energy will produce large differences in selectivity. For example at 0°, an increase in ΔG or $\Delta\Delta G^\ddagger$ of 873 cal/mole increases selectivity from 20:1 to 100:1. By comparison, ΔG for the *gauche* and *anti* forms of butane is 900 cal/mole.
4. At lower temperatures, the selectivity curves “flatten out” more quickly. Thus for a given process, subtle changes in the stereochemical control elements will usually have a greater influence if the reaction is carried out at low temperature. Note that this does not necessarily mean that lowering the temperature of a reaction will result in increased selectivity (*vide infra*).
5. Selectivities may be expressed in any of several ways: as K or k_1/k_2 , % enantiomer excess (ee), % diastereomer excess (de), or the percentage of the major enantiomer (% es) or diastereomer (% ds).⁹ It is worth keeping these

⁷ Unless the reaction is conducted in a nonracemic chiral solvent.

⁸ Strictly speaking, these equations and the curves in Figure 1.3 are valid only for a unimolecular reaction in the gas phase, but to a first approximation they serve as useful tools for our purposes.

⁹ Use of enantiomer excess (the excess of one enantiomer over its racemate) to describe *selectivity* is inappropriate since it implies that the minor enantiomer and an equal amount of the major enan-

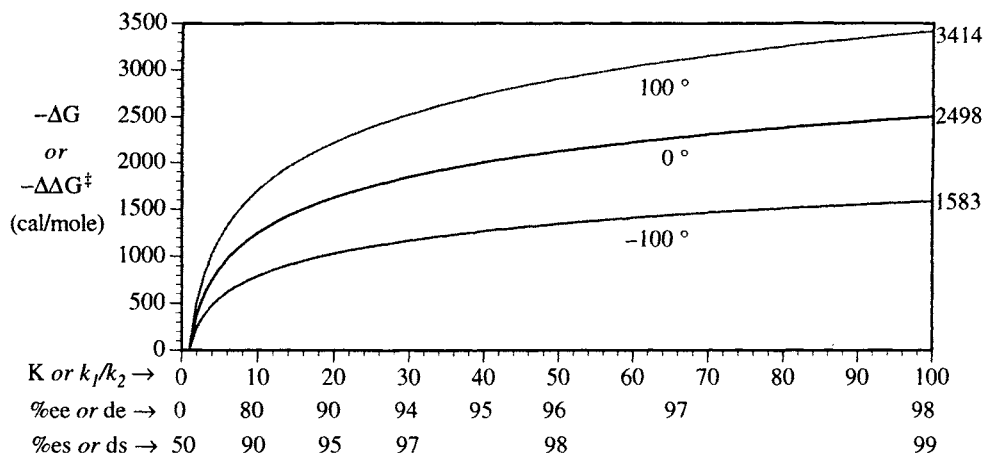


Figure 1.3. The relationship between selectivity and free energy (for the competitive formation of two products) at -100° , 0° , and 100° C. The free energy values for product ratios of 100:1 are labeled on the right ordinate (cal/mole).

parallel scales in mind when evaluating selectivities, as all are used interchangeably in the literature. Since routine purification techniques can often remove 5 to 10% of isomeric impurities, selectivities higher than 95% (ds or es) may not be required from a practical standpoint.

Regarding the effect of temperature on selectivity, reliance on equations such as 1.1 and 1.2 can be misleading, since free energy itself is temperature dependent:

$$G = H - T\Delta S. \quad (1.4)$$

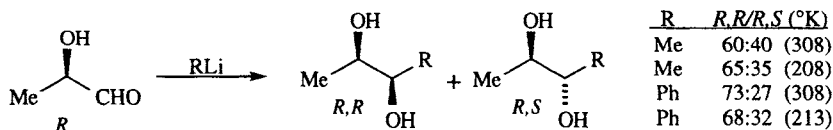
Combination of equations 1.2 and 1.4 [38] gives

$$\frac{k_1}{k_2} = \left(e^{-\Delta\Delta H^{\ddagger}/RT} \right) \left(e^{\Delta\Delta S^{\ddagger}/R} \right), \quad (1.5)$$

where $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ are the differences in enthalpy and entropy of activation for the formation of **B** and **C**, defined as was $\Delta\Delta G^{\ddagger}$ in equation 1.3.¹⁰ Equation 1.5 shows that only the enthalpy term is temperature dependent. An example of the effect this can have is shown in the additions of organolithiums to lactaldehyde shown in Scheme 1.3 [57]. The addition of methyllithium has $\Delta\Delta H^{\ddagger} = -260$ cal/mole and $\Delta\Delta S^{\ddagger} = 0$. Since $\Delta\Delta H^{\ddagger}$ is negative, the exponent of the first term is positive and lowering the temperature from 308° to 208° results in an increase in k_1/k_2 . In contrast, the addition of phenyllithium has $\Delta\Delta H^{\ddagger} = +340$ cal/mole and $\Delta\Delta S^{\ddagger} = +28$ e.u. With a positive $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$, **C** is favored by enthalpy and **B** is favored by entropy. In this case, the reaction is entropy controlled: since the exponent of the first term is negative, lowering the temperature decreases the preference for **B**;

tiomer are formed in a random process. In this book, percent enantioselectivity (% es) and percent diastereoselectivity (% ds) will be used to describe selectivity. These terms suffer the drawback that a process that forms two stereoisomers randomly is nevertheless 50% "selective." On the other hand, few of the processes discussed in this book are stereorandom, and the correlation with the familiar concept of "% yield" has obvious advantages.

¹⁰ $\Delta\Delta H^{\ddagger} = \Delta H^{\ddagger}_{\text{B}} - \Delta H^{\ddagger}_{\text{C}}$, negative if **B** is favored; $\Delta\Delta S^{\ddagger} = \Delta S^{\ddagger}_{\text{B}} - \Delta S^{\ddagger}_{\text{C}}$, positive if **B** is favored.



Scheme 1.3. Effect of temperature on addition of organolithiums to *R*-lactaldehyde [57].

nevertheless, the entropic preference prevails and **B** is still the major product, albeit in lower amount [57]. Thus, although lowering the temperature often increases selectivity, it does not necessarily do so in all cases.

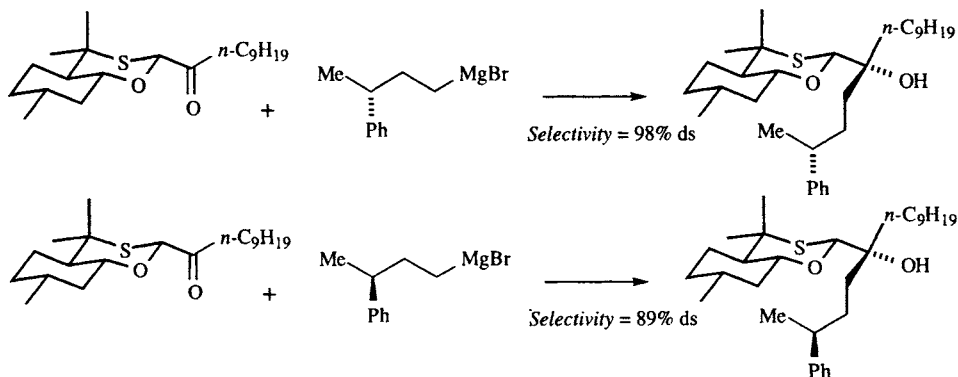
1.5 Single and double asymmetric induction

For the purposes of illustration, Figure 1.4 illustrates two reaction types in generic form. Single asymmetric induction occurs if a single chirality element directs the selective formation of one stereoisomer over another by selective reaction at one of the heterotopic (*Re/Si*) faces of a trigonal atom.



Figure 1.4. Two types of reactions that distinguish heterotopic faces.

An interesting circumstance develops when two of these techniques are combined in the same reaction, such as when the second reactant also contains a chirality element (*e.g.*, when a chiral nucleophile reacts with a chiral carbonyl compound): the chirality elements of each reactant may influence stereoselectivity either in concert or in opposition. This phenomenon is known [58,59] as double asymmetric induction. A simple illustration is shown in Scheme 1.4 and involves the reaction of



Scheme 1.4. Double asymmetric induction: changing the absolute configuration of a chiral nucleophile affects the stereoselectivity of addition to a chiral ketone [60].

the two enantiomers of a chiral Grignard reagent with a chiral ketone [60].¹¹ Note the difference in diastereoselectivity observed for the two reactions, clearly resulting from the change in absolute configuration of the remote stereocenter of the Grignard.

In order to understand the phenomenon of double asymmetric induction, we need to have a clear picture of the inherent selectivities of each of the chiral partners in closely related single asymmetric induction processes. Consider for example the kinetically controlled aldol addition reactions shown in Scheme 1.5 [58].¹² The first two illustrated reactions are examples of single asymmetric induction with inherently low selectivities. Scheme 1.5a is the reaction of a chiral *Z*(*O*)-enolate with an achiral aldehyde [61], and illustrates the *Si*-facial preference of the *S* enantiomer of the enolate of 78:22. In Scheme 1.5b, an achiral enolate that is structurally similar to the chiral enolate of Scheme 1.5a is allowed to react with a chiral aldehyde [62]. The 73:27 product ratio reflects the *Re*-facial preference of

major products are the same. Since both chiral reactants, the enolate of the first reaction and the aldehyde of the second both prefer the same absolute configuration in the addition product, we may expect that reaction of the chiral enolate with the chiral aldehyde would afford product having the same absolute configuration.

When the *S*-enolate and the *S*-aldehyde (Scheme 1.5c) were allowed to react, the expected product was indeed formed, but the selectivity was higher (89:11) than in either of the previous examples because the inherent selectivities of the two chiral species are mutually reinforcing [58]. This is an example of *matched pair* double asymmetric induction. A *mismatched* double asymmetric induction would result from reversing the absolute configuration of either of the two chiral reactants. For example, when the *S*-aldehyde and now the *R*-enolate (Scheme 1.5d) were allowed to react, the two products were formed in a ratio of 40:60 [58]. The higher selectivity of the enolate (78% ds) over the aldehyde (73% ds) is manifested in the absolute configuration obtained as the major isomer in Scheme 1.5d.

With this example in mind, let us reexamine the principles of selectivity presented earlier and apply them to the case of double asymmetric induction. In Figure 1.2b, two possible products are formed under kinetic control. This reaction diagram is applicable to the examples of Schemes 1.5a and 1.5b, in that *a single chirality element* operates to render the two transition structures diastereomeric. Now imagine what the effect of a second chirality element might be. Figure 1.5a illustrates the case of a matched pair: the second chirality element increases $\Delta\Delta G^\ddagger$ by lowering the energy of the already favored transition state ($A \rightarrow B$) and/or raising the energy of the disfavored one. The previously favored isomer is formed with increased selectivity. Figure 1.5b illustrates the mismatched case, wherein the second chirality element decreases $\Delta\Delta G^\ddagger$ by increasing the energy of the favored transition state and/or decreasing the energy of the disfavored one. In this example, the second chirality element decreases $\Delta\Delta G^\ddagger$ but does not change its sign. Obviously, additional perturbation of the transition states could reduce $\Delta\Delta G^\ddagger$ to zero, or reverse the selectivity by changing the sign of $\Delta\Delta G^\ddagger$.

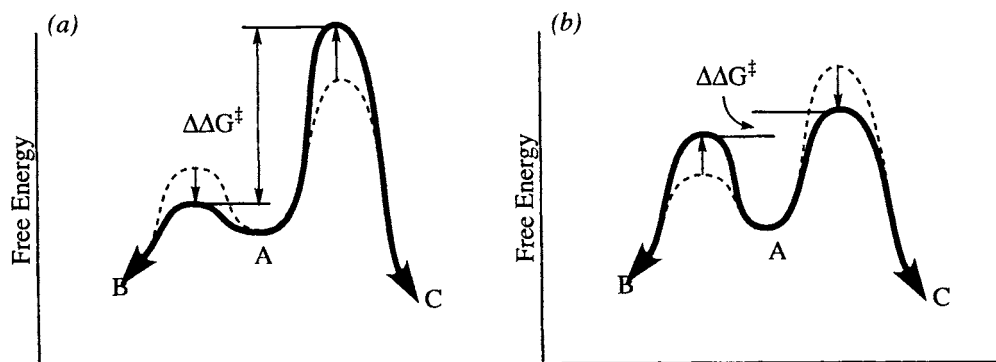


Figure 1.5. Double asymmetric induction. The dashed lines represent a hypothetical case of single asymmetric induction. (a) Matched pair: $\Delta\Delta G^\ddagger$ is increased by the influence of a second chirality element; (b) Mismatched pair: $\Delta\Delta G^\ddagger$ is decreased by the influence of a second chirality element.

There are two important lessons here. The first is that a matched pair will afford higher selectivities than either chiral reactant would afford on its own. The second lesson is more subtle. In considering the two single asymmetric induction reactions, suppose that one of the chiral reagents is much more selective than the other. In this instance, the mismatched pair may still be a highly selective reaction. Figure 1.6 illustrates an energy diagram wherein the stereoselectivity due to the second chirality element completely overwhelms that of the first. The dotted lines indicate a preference, in single asymmetric induction, for product B. Under the influence of a much more highly selective reagent, the double asymmetric induction (bold line) favors A by “changing the sign” of $\Delta\Delta G^\ddagger$. Even though this is a mismatched pair, it still may be very selective. In such cases, the chiral reagent is the primary determinant of the absolute configuration of the new stereocenter(s) in the product!

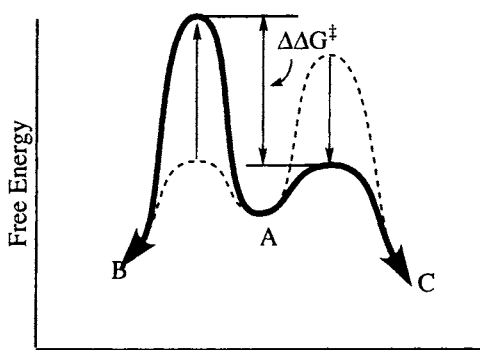
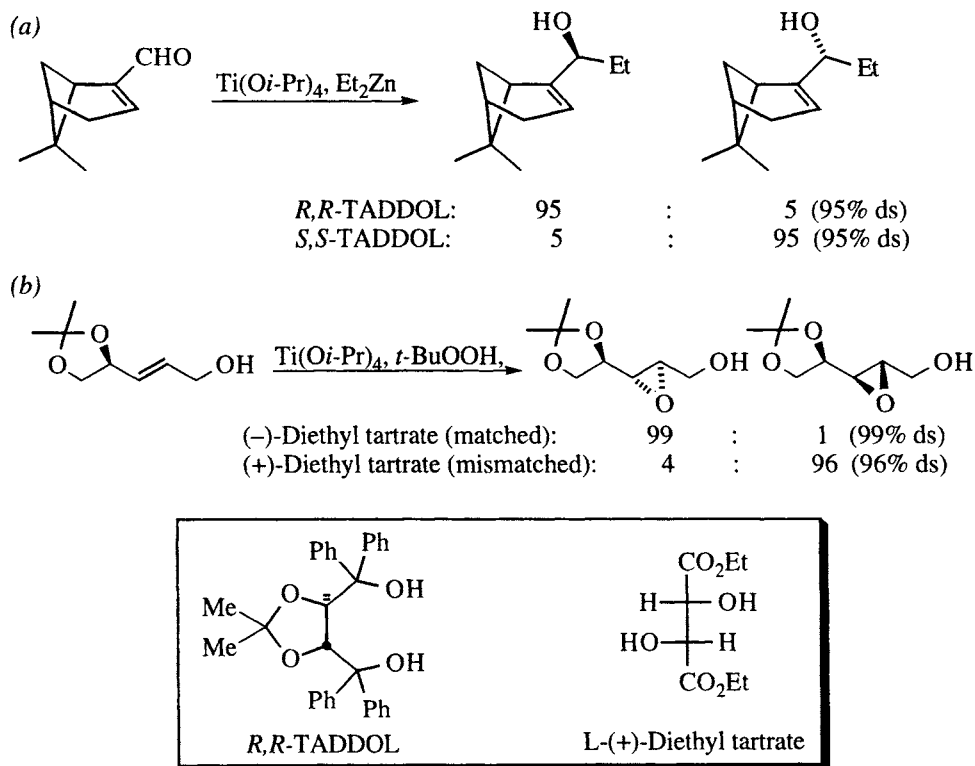


Figure 1.6. Reagent-based stereocontrol in double asymmetric induction.

In a general sense, if the species having an overwhelmingly higher “inherent selectivity” is the chiral auxiliary, chiral reagent or chiral catalyst, and the less selective species is a synthetic intermediate being carried on to a target, then *the reagent can be used to determine the absolute configuration of the product, independent of the chirality sense and bias of the substrate*. This concept is known as “*Reagent-Based Stereocontrol*” [58,59]. As we will see throughout this book, a number of reagents deliver high enough selectivities to achieve this important goal.

Two examples of such processes are shown in Scheme 1.6. One is the titanium TADDOLate-catalyzed addition of diethylzinc to myrtenal (see Section 4.3, [52]; the other is the Sharpless asymmetric epoxidation (see Section 8.2.2, [58,63]). In both cases, the diastereoselectivity for the reaction of the substrate with an achiral reagent is low (65-70% ds), while the catalysts have enantioselectivities of >95% with achiral substrates. In these cases of double asymmetric induction, the catalyst completely overwhelms the facial bias of the chiral substrate.



Scheme 1.6. Matched and mismatched double asymmetric induction demonstrating “Reagent-Based Stereocontrol”: (a) The diethylzinc addition catalyzed by titanium TADDOLates (Chapter 4, [52]). (b) The Sharpless asymmetric epoxidation (Chapter 8, [58,63]).

1.6 Glossary of stereochemical terms¹⁴

A values: The free energy difference ($-\Delta G^\circ$) between equatorial and axial conformations of a substituted cyclohexane, positive if equatorial is preferred. For a compilation of values, see ref. [64], and references cited therein.

A^{1,2}, A^{1,3} strain: see *allylic strain*.

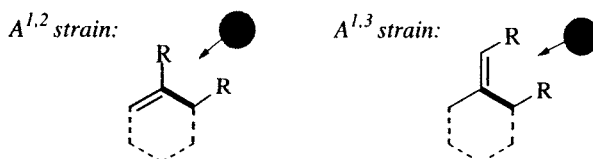
Absolute asymmetric synthesis: A synthesis in which *achiral* reactants are converted to *nonracemic*, *chiral* products, and where the *enantioselectivity* is induced only by an external force such as circularly polarized light in a photochemical reaction [65].

Absolute configuration: The arrangement in space of the ligands of a *stereogenic unit*, which may be specified by a stereochemical descriptor such as *R* or *S*, *D* or *L*, *P* or *M*. See also *chirality sense*, *chirality element*, *stereogenic element*

Achiral: See *chiral*.

Achirotopic: See *chirotopic*.

Allylic strain: The destabilization of a molecule, or an individual conformation, by *van der Waals* repulsion between substituents on a double bond and those in an allylic position [66]. Two types have been identified (see bold bond in figure): A^{1,2} strain occurs between substituents on an allylic carbon and the adjacent sp² carbon. A^{1,3} strain occurs between substituents on an allylic carbon and the distal sp² carbon. The latter effect can be quite strong [67]. Originally [66], the terms were defined in the context of cyclohexane derivatives, but more recently the effects have been recognized as important factors in conformational dynamics of acyclic systems [67].



Alternating symmetry axis (S_n): An axis about which a rotation by an angle of $360/n$, followed by a reflection across a plane perpendicular to the axis results in an entity that is indistinguishable from (superimposable on) the original. Also called a rotation-reflection axis. See also *symmetry axis*.

Alpha (α), beta (β): Stereodescriptors used commonly in carbohydrate [68] and steroid [69] nomenclature to describe *relative configuration*. In steroids, “any [substituent] that lies on the same side of the ring plane as the C₃-hydroxyl group of cholesterol [see illustration] is described as β -oriented, and the carbon to which the group is joined has the β -configuration. The opposite orientations and configurations are designated α ” [69]. The α , β nomenclature is often extended to other ring systems, but a reference stereocenter must be

¹⁴ Note that other terms defined in this glossary are italicized.

specified, either explicitly or by convention (see for example ref. [70]). Often, reference is made to a 2-dimensional drawing in which a reference plane is specified. If the reference plane is horizontal, β is above and α is below the plane, as illustrated below. If the plane is vertical, β is toward the viewer.

In carbohydrates, the β -anomer has the C1-hydroxyl or alkoxy group on the

Antarafacial, suprafacial: In a reaction where a molecule undergoes two changes in bonding (either making or breaking), the relative spatial arrangement is suprafacial if the changes occur on the same face of the molecular fragment and antarafacial if on opposite faces [73].

Anti: See *torsion angle*; *syn*, *anti*. Also used to describe *antarafacial* addition or elimination reactions [74]. Formerly used to describe the configuration of azomethines such as oximes and hydrazones (See *E*, *Z*).

Anticlinal: See *torsion angle*.

Antiperiplanar: See *torsion angle*.

Aracemic: Synonym for *nonracemic* [75]. See also *scalemic*.

Asymmetric: Lacking all symmetry elements, *i.e.*, belonging to symmetry point group C_1 .

Asymmetric carbon atom: van't Hoff's definition for a carbon atom having four different ligands (*i.e.* Cabcd). See also *stereogenic center*, *stereogenic element*.

Asymmetric center: See *stereogenic center*.

Asymmetric destruction: See *kinetic resolution*.

Asymmetric induction: The preferential formation of one *enantiomer* or *diastereomer* over another, due to the influence of a *stereogenic element* in the substrate, reagent, catalyst, or environment (such as solvent). Also, the preferential formation of one configuration of a stereogenic element under similar circumstances. 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 [58,59] as double asymmetric induction, or double diastereoselection. See Section 1.5.

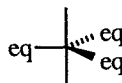
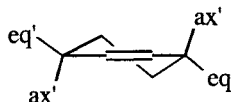
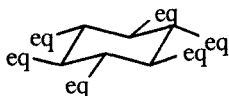
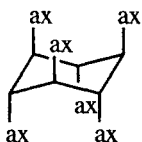
Asymmetric synthesis: A reaction or reaction sequence that *selectively* creates one configuration of one or more new *stereogenic elements* by the action of a chiral reagent or auxiliary, acting on *heterotopic* faces, atoms, or groups of a substrate. The stereoselectivity is primarily influenced by the chiral catalyst, reagent, or auxiliary, despite any stereogenic elements that may be present in the substrate. See Section 1.2.

Asymmetric transformation: The conversion of a mixture (usually 1:1) 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. An "*asymmetric transformation of the second kind*" also involves separation, such as an equilibration accompanied by selective crystallization of one stereoisomer [76]. The terms "first- and second-order asymmetric transformations" to describe these processes are inappropriate. See also *stereoconvergent*.

Atropisomers: Stereoisomers arising from *restricted rotation* around a single bond (*i.e.*, *conformers*), with a high enough rotational barrier that the isomers can be isolated (16 - 20 kcal/mole at room temperature), such as *ortho*-

disubstituted biaryls [77]. The chirality sense of a conformation may be described using the *P*, *M* system.

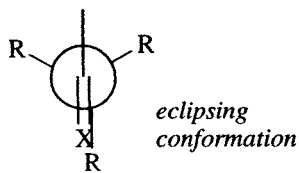
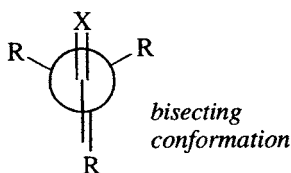
Axial, equatorial: Bonds or ligands of a cyclohexane (or saturated 6-membered heterocycle) chair conformation. The axial bonds are parallel to the C_3 (S_6) axis of cyclohexane (or the corresponding position of a heterocycle), and each equatorial bond is parallel to two of the ring bonds. In a cyclohexene, the corresponding allylic bonds or ligands are called pseudoaxial (ax') and pseudo-equatorial (eq'). In a trigonal bipyramidal structure, the three ligands in a plane with the central atom are also known as equatorial.



Axis of chirality: See *chirality element*, *stereogenic axis*, *stereogenic element*.

Baeyer strain: See *angle strain*.

Bisecting and eclipsing conformations: In a structure with the grouping $R_3C-C=X$, the conformation in which a torsion angle $R-C-C=X$ is *antiperiplanar*, and the torsion angles to the other two *R* groups is equal or nearly so is the *bisecting* conformation. The conformation in which a torsion angle $R-C-C=X$ is *synperiplanar* is called *eclipsing*.



Boat: See *chair*, *boat*, *twist*; and *half-chair*, *half-boat*.

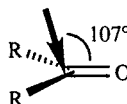
Bond opposition strain: See *eclipsing strain*.

Bowsprit, Flagpole: In the cyclohexane boat conformation the ligands on the two carbons that are out of the plane of the other four. Endocyclic ligands are *flagpole*, exocyclic ligands are *bowsprit*.



Bürgi-Dunitz trajectory: The angle of approach of a nucleophile toward a carbonyl carbon, 107° (probably more accurately $105 \pm 5^\circ$) [78-80]. See Section 4.1.

The Bürgi-Dunitz trajectory

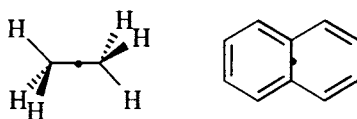


Cahn-Ingold-Prelog method: See *CIP method*.

CDA, chiral derivatizing agent: A reagent of known enantiomeric purity that is used for derivatization and analysis of enantiomer mixtures by spectroscopic or chromatographic means. See Section 2.3.1.

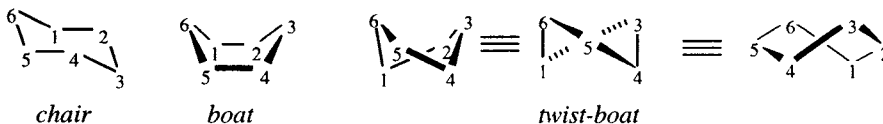
Center of chirality: See *stereogenic center*.

Center of symmetry, center of inversion (*i*): A point in an object that is the origin of a set of Cartesian axes, such that when all coordinates describing the object (x, y, z) are converted to $(-x, -y, -z)$, an identical entity is obtained. Equivalent to a two-fold *alternating axis* (S_2).



Centers of inversion (•)

Chair, boat, twist-boat: The cyclohexane *conformation* (point group D_{3d}) in which carbons 1, 2, 4, and 5 are coplanar and atoms 3 and 6 are on opposite sides of the plane is the *chair*. When atoms 3 and 6 are on the same side of the '1-2-4-5' plane, and also lie in a mirror plane, the conformation (point group C_{2v}) is called a *boat*. If atoms 3 and 6 are moved to either side of the boat's '3-6' mirror plane, the conformation (point group D_2) is the *twist-boat*. The chair and twist-boat conformations are at energy minima ($\Delta G = 5.6 - 8.5$ kcal/mole for cyclohexane [81]) while the boat is at a higher energy saddle-point. The *twist-boat* is sometimes called the *skew* conformation (however, see *torsion angle*). These terms are also applied to similar conformations of substituted cyclohexanes and to heterocyclic analogs. See also *axial, equatorial*.



Chair-chair inversion: See *ring reversal*

Chiral: A geometric figure, or group of points is chiral if it is nonsuperimposable on its mirror image [82]. A *chiral* object lacks all of the second order (improper) symmetry elements, σ (*mirror plane*), i (*center of symmetry*), and S (*rotation-reflection axis*). In chemistry, the term is (properly) only applied to entire molecules, not to parts of molecules. A chiral compound may be either *racemic* or *nonracemic*. An object that has any of the second order symmetry elements (*i.e.*, that is superimposable on its mirror image) is *achiral*. It is inappropriate to use the adjective *chiral* to modify an abstract noun: one cannot have a chiral opinion and one cannot execute a chiral resolution or synthesis.

Chiral auxiliary: A chiral molecule that is covalently attached to a substrate so as to render enantiotopic faces or groups in the substrate diastereotopic. After the

diastereoselective reaction, the auxiliary should be removable and recoverable intact. See Section 1.2.

Chirality: The property that is responsible for the nonsuperimposability of an object, or a group of points, with its mirror image.

Chirality axis: See *chirality element*.

Chirality center: See *chirality element*.

Chirality element, element of chirality: A *stereogenic axis, center, or plane* that is *reflection variant*. See also *stereogenic element*.

Chirality plane: See *chirality element*.

Chirality sense: The property that distinguishes enantiomorphs such as a right or left threaded screw. For molecules, the chirality sense may be described by *R*, *S*; or *P*, *M*. See also *absolute configuration*.

Chirality transfer: Asymmetric induction in which one stereogenic element is sacrificed as another is created.

Chiroptic: Referring to the optical properties of chiral substances, such as optical rotation, circular dichroism, and optical rotatory dispersion.

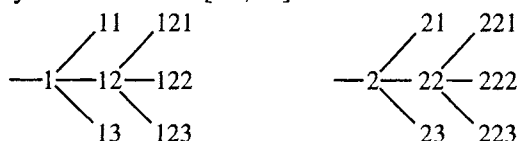
Chirotopic: The property of "any atom, and, by extension, any point or segment of the molecular model, whether occupied by an atomic nucleus or not, that resides in a chiral environment" [83]. *Achirotopic* is the property of any atom or point that does not reside in a chiral environment (see also [84]). "Chirotopic atoms located in chiral molecules are enantiotopic by external comparison between enantiomers. Chirotopic atoms located in achiral molecules are enantiotopic by internal and therefore also by external comparison.... All enantiotopic atoms are chirotopic" [83].

CIP (Cahn, Ingold, Prelog) method, CIP system: The CIP sequencing rules establish the conventional ordering of ligands for the unambiguous description of absolute configuration by descriptors such as *R*, *S*; *P*, *M*; *E*, *Z*.

There are several steps in the method, which is abbreviated as follows (for the

0. Nearer end of axis or side of plane precedes further.
1. Higher atomic number precedes lower.
2. Higher atomic mass precedes lower.
3. Cis (*Z*) precedes trans (*E*). Some special cases require the following qualification [86]: when two ligands (indistinguishable by rules 1 and 2) differ by one having the ligand of higher rank in a cis position (*Z*) to the core of the stereogenic unit, and the other in a trans position (*E*), the former takes precedence.
4. Like pair precedes unlike pair. (For a listing of like and unlike pairs, see *l,u* in this glossary).
5. *R* precedes *S*; and *M* precedes *P*

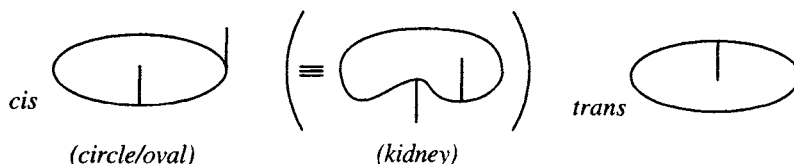
To implement the sequence rules, it is useful to construct a digraph of the ligands to be compared, as shown below. The ligands of the proximal atoms (1 and 2) are placed in the digraph such that 11 has precedence over 12, 12 over 13, 21 over 22, etc. Another layer of ligands, labeled 111, 112, ... 233, could be constructed if necessary (only one such set is shown below). In implementing the sequence rules, 1 is first compared with 2. If there is no difference, 11 is compared with 21, then 12 with 22, etc., until a decision is reached. If comparison of ligands in the next sphere is necessary, the branches of highest priority are followed [85,86].



For the vast majority of cases, *CIP* rank can be determined using only ligancy complementation and sequence rule 1. The rules result in the following (descending) sequence of *CIP* rank for several common functional groups [87]: COOCH_3 , COOH , COPh , CHO , CH(OH)_2 , *o*-tolyl, *m*-tolyl, *p*-tolyl, Ph, $\text{C}\equiv\text{CH}$, *t*-Bu, cyclohexyl, vinyl, isopropyl, benzyl, allyl, *n*-pentyl, ethyl, methyl, D, H.

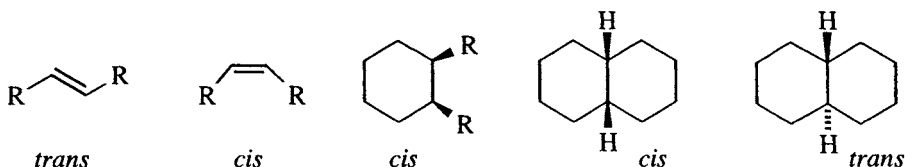
For the assignment of *CIP* descriptors, see *R*, *S*; *P*, *M*; and *E*, *Z*.

cis, trans: A stereochemical prefix to describe the relationship between two ligands on a double bond or a ring: *cis* if on the same side, *trans* if on opposite sides. For alkenes, the *cis-trans* nomenclature can be ambiguous and the *E, Z* descriptor is preferred. In a ring, the reference conformation (real or hypothetical) is planar, and approximates a circle or an oval, not a kidney. See *cis-trans isomers*.



cisoid conformation (usage discouraged): See *s-cis*, *s-trans*.

cis-trans isomers: Stereoisomeric alkenes or cycloalkanes (or heterocyclic analogs), that differ in the position of ligands relative to a reference plane: *cis* if on the same side, *trans* if on opposite sides.



Clinal: See *torsion angle*.

Configuration: The arrangement of atoms in space that distinguishes *stereoisomers*, excluding *conformational isomers*. *Atropisomers* are a special case of conformational isomers that, because they are isolable at room temperature, may have an absolute configuration descriptor assigned to the *stereogenic axis*. See also *absolute configuration*, *chirality sense*, *relative configuration*.

Conformation: In a molecule of a given *constitution* and *configuration*, the spatial array of atoms affording distinction between *stereoisomers* that can be interconverted by rotation around single bonds. The *chirality sense* of conformations may be specified using the *P*, *M* nomenclature.

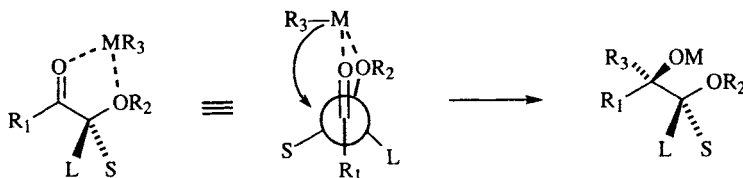
Conformational analysis: The analysis of the chemical and physical properties of different conformations of a molecule.

Conformational isomers (conformers): Stereoisomers at potential energy minima (local or global) having identical *constitution* and *configuration*, which differ only in *torsion angles*.

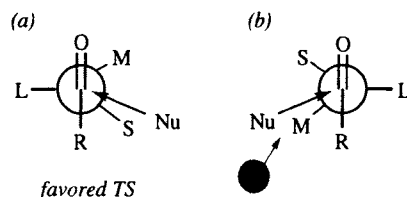
Constitution: The description of the number and kind of atoms in a molecule and their bonding (including bond multiplicities, but not *relative* or *absolute configuration*, or *conformation*).

Constitutional isomers: Isomers that differ in connectivity, such as $\text{CH}_3\text{CH}_2\text{OH}$ and CH_3OCH_3 .

Cram's rule (cyclic model): A model for predicting the major stereoisomer resulting from nucleophilic addition to an aldehyde or a ketone having an adjacent stereocenter that is capable of chelation (especially 5-membered ring chelation). After chelate formation, the nucleophile adds from the side opposite the larger of the remaining substituents on the α -stereocenter [48]. See Section 4.2.



Cram's rule (open chain model): A model to predict the major stereoisomer resulting from nucleophilic addition to a ketone or aldehyde having an adjacent *stereocenter*. The rule originally formulated by Cram in 1952 [47] has evolved into the current Felkin-Anh formulation [79,88,89], illustrated below. In the transition structure, the largest substituent of the stereocenter, or the substituent having the lowest-lying σ^* orbital (L) is perpendicular to the carbonyl, and the nucleophile attacks from the opposite side, on a trajectory that places it approximately 107° away from the carbonyl (the *Bürgi-Dunitz trajectory*). The favored transition structure (a), has this trajectory nearly eclipsing the site of the smaller of the two remaining substituents. See Section 4.1.



CSA (Chiral solvating agent): A diamagnetic additive of known enantiomeric purity used to induce anisochrony in *enantiomers* of a *racemate* for NMR analysis. See Section 2.3.4.

CSP (Chiral stationary phase): A *nonracemic* chiral stationary phase for the chromatographic separation of *enantiomers*. See Section 2.4.

CSR (Chiral shift reagent): A paramagnetic lanthanide complex of known enantiomeric purity used to induce anisochrony in *enantiomers* of a *racemate* for NMR analysis. See Section 2.3.3.

D, L: See *Fischer-Rosanoff convention*

d, l, dl: Obsolete alternatives for (+)- and (-)- used to designate the sign of rotation of *enantiomers* at 589 nm (the sodium D line), and (±)- for a *racemate*. Sometimes used as arbitrary descriptors for a single enantiomorph.

Diastereoisomers: See *diastereomers*.

Diastereomer excess (percent diastereomer excess, % de): In a reaction in which two (and only two) diastereomeric products are possible, the percent diastereomeric excess, % de is given by:

$$\% \text{ de} = \frac{|D_1 - D_2|}{D_1 + D_2} \cdot 100 = |\%D_1 - \%D_2|$$

where D_1 and D_2 are the mole fractions of the two diastereomeric products. If a reaction can produce more than two diastereomers the ratio should itself be

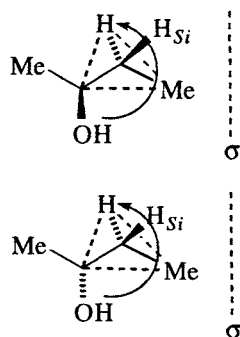
Diastereoselectivity (percent diastereoselectivity, % ds): In a reaction in which more than one diastereomer may be formed (with mole fractions D_1 , D_2 , ... D_n produced) the diastereoselectivity is the mole fraction formed of the major product (or the desired product), expressed as a percent:

$$\% \text{ ds} = \frac{D^*}{D_1 + D_2 + \dots + D_n} \cdot 100 \quad ,$$

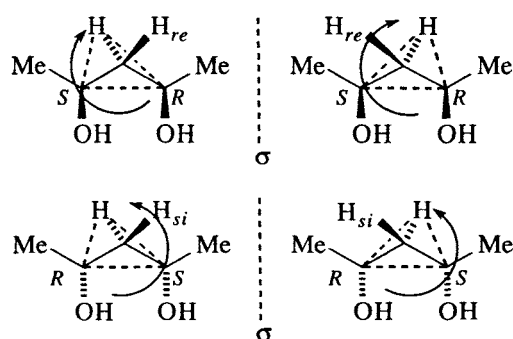
where D^* is the mole fraction of the desired isomer [90]. See Section 1.4. See also *enantioselectivity*.

Diastereotopic: The relationship of two ligands of an atom that are constitutionally equivalent, but in positions that are not symmetry related. Replacement of either ligand yields a pair of diastereomers. Also, faces of a trigonal atom that are not symmetry related, such that addition to either face gives a pair of diastereomers. Reflection variant faces may be specified as *Re* or *Si*, and ligands, *L*, may be specified as L_{Re} or L_{Si} , by noting on which face of a triangle the ligand in question sits (see *heterotopic*). Note that addition of a ligand to the *Re* face of a trigonal atom affords a tetrahedral array with the new ligand in the L_{Re} position. Reflection invariant descriptors are *re*, *si*, as illustrated below [91,92]. See also *Re*, *Si*, *homotopic*, and *enantiotopic*.

Reflection variant

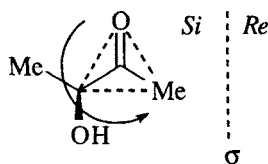


Reflection invariant

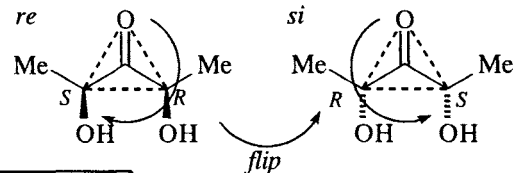


DIASTEREOTOPIC LIGANDS

Reflection variant



Reflection invariant



DIASTEREOTOPIC FACES

Dihedral angle: The angle between two defined planes. The term is most commonly applied to vicinal bonds on a *Newman projection*. See also *torsion angle*.

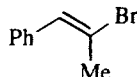
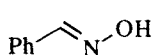
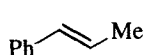
Dissymmetric: Obsolete synonym for *chiral*. Not equivalent to *asymmetric*, since chiral substances may have symmetry. See also *asymmetric*.

Double asymmetric induction: See *asymmetric induction*.

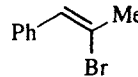
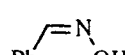
Dunitz angle: See *Bürgi-Dunitz trajectory*.

E, Z: Descriptors for the arrangement of ligands around double bonds. On either end of the double bond, the group of highest *CIP* rank is identified. If the two higher-ranking groups are on the same side of the double bond, the descriptor of the stereoisomer is *Z* (zusammen = together); if on opposite sides, *E* (entgegen = apart). See also *cis*, *trans* isomers. For enolates, some authors modify this rule such that the OM ligand (anionic oxygen with its metal) takes the highest priority. See *E(O)*, *Z(O)*.

E isomers:

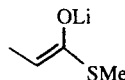
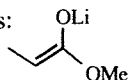


Z isomers:



***E(O)*, *Z(O)*:** Descriptors for the arrangement of ligands around enolate double bonds. The standard *E/Z* stereochemical descriptor is modified such that the OM group is given priority over the carbonyl substituent, independent of the metal and the other substituent [93]. The priority descriptors for the α -carbon are maintained, as illustrated by the following examples:

Z(O)-enolates:



***Eclipsed*, *Eclipsing*:** Two ligands on adjacent atoms are *eclipsed* if their torsion angle is near 0° (i.e., *synperiplanar*). See also *bisecting conformation*, *eclipsing strain*, *torsion angle*.

***Eclipsing conformation*:** See *bisecting conformation*.

***Eclipsing strain*:** See *torsional strain*.

***Element of chirality*:** See *chirality element*

***Enantioconvergent*:** See *stereoconvergent*

***Enantiomer*:** A *stereoisomer* that is not superimposable on its mirror image. See also *enantiomorphous*.

***Enantiomer excess*, *ee* (percent enantiomer excess, % *ee*):** For a mixture of a pure *enantiomer* and its *racemate*, the percent excess of the pure enantiomer over the racemate. % *ee* is given by:

$$\% ee = \frac{|E_1 - E_2|}{E_1 + E_2} \cdot 100 = | \% E_1 - \% E_2 | ,$$

where E_1 and E_2 are the mole fractions of the two enantiomers. See *enantiomer purity*.

***Enantiomer purity*:** A description of the enantiomer composition of a sample, historically expressed as % *ee*. Because this term implies that the impurity is the racemate (not the minor enantiomer), many authors prefer to use *enantiomer ratio*, *er*, normalized to 100%.

Enantiomer ratio, *er*: The ratio of two *enantiomers*. When used as an expression of enantiomer purity, this ratio is often normalized to 100% (i.e., 99:1, 80:20).

Enantiomerically enriched (*enantioenriched*): A sample that has one *enantiomer* in excess.

Enantiomerically pure, *enantiopure*: A sample which contains (within the limits of detection) only one *enantiomer*. Note that this is not synonymous with *homochiral* [94].

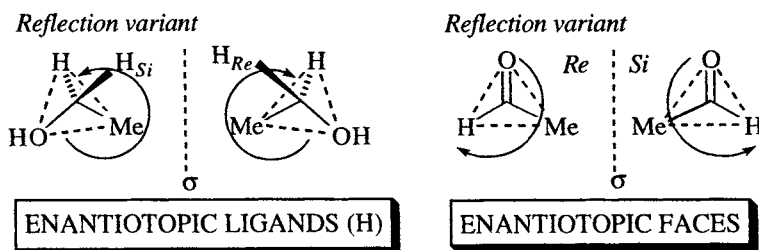
Enantiomorphous: Not superimposable on its mirror image.

Enantioselectivity (*percent enantioselectivity*, % *es*): In a reaction or reaction sequence in which one *enantiomer* (*E*₁) is produced in excess, the enantioselectivity is the mole fraction formed of the major *enantiomer*, expressed as a percent:

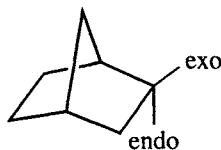
$$\% \text{ es} = \frac{E_1}{E_1 + E_2} \cdot 100 \quad .$$

See also *diastereoselectivity*.

Enantiotopic: The relationship of two ligands of an atom that are related by a *mirror plane*, *center of symmetry*, or *alternating axis*, but not by a simple (proper) *symmetry axis*. Replacement of either ligand yields a pair of *enantiomers*. Also, faces of a trigonal atom that are not symmetry related, such that addition to either face gives a pair of *enantiomers*. Note that addition of a ligand to the *Re* face affords a tetrahedral array with the new ligand in the *L_{Re}* position. The faces may be specified as *Re* or *Si*, and reflection variant ligands are best specified as *L_{Re}* or *L_{Si}*, as illustrated below [91,92]. See also *Re*, *Si*, *homotopic*, *heterotopic*, and *diastereotopic*.



***endo*, *exo*:** The stereochemical prefix that describes the relative configuration of a substituent on a bridge (not a bridgehead) of a bicyclic system. If the substituent is oriented toward the larger of the other bridges, it is *endo*; if it is oriented toward the smaller bridge, it is *exo*.



***ent*:** A prefix to the name of a chiral molecule to indicate its *enantiomer*.

Envelope: The conformation of a five-membered ring in which four atoms are coplanar, and the fifth (the flap) is out of the plane.

Epimerization: The interconversion of *epimers*.

Epimers: *Diastereomers* that differ in *configuration* at one of two or more *stereogenic units*.

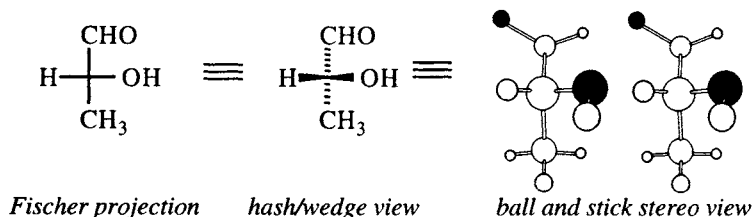
Equatorial: See *axial, equatorial*.

erythro, threo: Terms used to describe relative configuration at adjacent stereocenters. Originally, the term was derived from carbohydrate nomenclature (*cf.* erythrose, threose). In this sense, if the molecule is drawn in a *Fischer projection*, the *erythro* isomer has identical or similar substituents on the same side of the vertical chain and the *threo* isomer has them on opposite sides. In the early 1980s, proposals appeared to redefine these terms based on *zig-zag projections* [95] and *CIP priority* [96], but the latter usages are now discouraged [97]. See *l, u; pref, parf; syn, anti*.

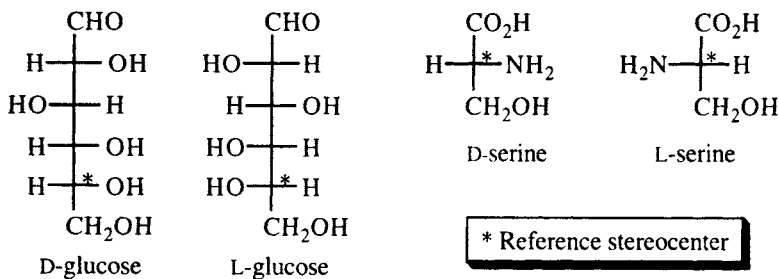
exo: See *endo, exo*.

Felkin-Anh model: See *Cram's rule (open chain model)*.

Fischer Projection (or Fischer-Tollens projection): A planar projection formula in which the vertical bonds lie behind the plane of the paper and the horizontal bonds lie above the plane. Used commonly in carbohydrate structures, where each carbon in turn is placed in the proper orientation for planar projection.



Fischer-Rosanoff convention: A method for the specification of absolute configuration, still in common use for amino acids and sugars. When drawn in a *Fischer projection* with C_1 at the top, if the functional group of the specified stereocenter is on the right, the absolute configuration is D, if on the left, it is L. For amino acids, the reference stereocenter is C_2 ; for sugars it is the highest numbered stereocenter [98].



Flagpole: See *bowsprit, flagpole*

Free rotation, restricted rotation: In the context of an experimental observation, *free rotation* is sufficiently fast (*i.e.*, the rotational barrier is sufficiently low) that different *conformations* are not observable. Conversely, *restricted rotation* is sufficiently slow (the barrier is sufficiently high) that conformational isomers can be observed.

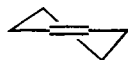
Gauche: Synonymous with a *synclinal* alignment of groups attached to adjacent atoms (*i.e.*, a torsion angle of near $+60^\circ$ or -60°). See *torsion angle*.

Geometric isomers: Synonym for *cis-trans* double bond isomers.

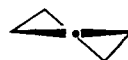
Half-boat: See *half-chair*, *half-boat*.

Half-chair, half-boat: Terms used most commonly to describe conformations of cyclohexenes in which four contiguous carbon atoms lie in a plane. If the other two atoms lie on opposite sides of the plane, the conformation is a half-chair; if they are on the same side, it is a half-boat, as shown below. Also used for 5-membered rings, where three adjacent atoms define the plane.

cyclohexene
half-chair



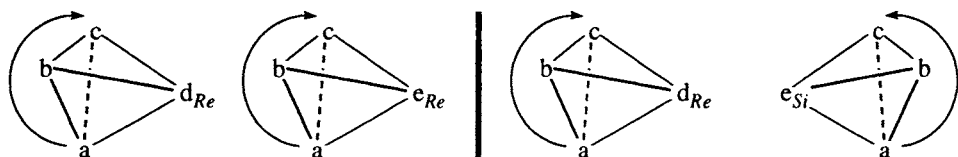
cyclopentane
half-chair



Helicity: The chirality sense of a helix. May be specified by *P*, *M*.

Heterochiral: See *homochiral*.

Heterotopic: Either *diastereotopic* or *enantiotopic*. Refers to either the *Re* or *Si* half



homofacial: *d* and *e* both reside on the *Re* face of the *abc* triangle

heterofacial: *d* is on the *Re* side of the *abc* triangle, whereas *e* is on the *Si* face.

Homotopic: Ligands that are related by an *n*-fold rotation axis. Similarly, faces of a trigonal atom that are related by an *n*-fold rotation axis. Replacement of any of the ligands or addition to either of the faces gives an identical compound. See also *heterotopic*, *enantiotopic*, and *diastereotopic*.

Inversion: See *Walden inversion*, *pyramidal inversion*, and *ring inversion*.

Isomers: Compounds that have the same molecular formula but which have different *constitutions* (*constitutional isomers*), *configurations* (*enantiomers*, *diastereomers*), or *conformations* (*conformational isomers*), and therefore have different chemical and/or physical properties.

Kinetic resolution: The separation (or partial separation) of *enantiomers* due to a difference in the rate of reaction of the two enantiomers in a *racemic mixture* with an *nonracemic chiral reagent*.

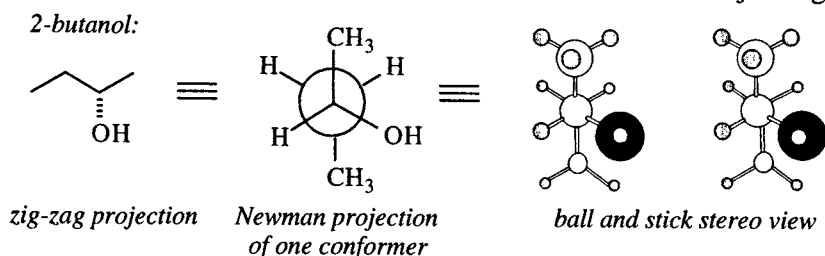
l, u: Descriptors for the specification of *relative configuration*. A pair of stereogenic units has the relative configuration *l* (for *like*) if the descriptor pairs are *RR*, *SS*, *RRe*, *SSi*, *ReRe*, *SiSi*, *MM*, *PP*, *RM*, *SP*, *ReM*, or *SiP*. The pair is specified as *u* (*unlike*) if they have descriptor pairs *RS*, *RSi*, *ReS*, *ReSi*, *MP*, *RP*, *SM*, *ReP*, and *SiM* [86]. Reflection invariant descriptors (*r*, *s*, *re*, *si*, *p*, and *m*) may be substituted in place of the reflection variant descriptors above. Note the use of lower case *l* and *u* letters, implying a *reflection invariant* relationship.

lk, ul: An extension of the *l, u* nomenclature to describe *topicity*. If a reagent of configuration *R* (or the *Re* face of a trigonal atom) preferentially approaches the *Re* face of a trigonal atom, the topicity is *lk* (*like*); it is *ul* (*unlike*) if it approaches the *Si* face. Similarly, the approach of an achiral reagent to diastereotopic faces of a trigonal atom is *lk* if the *Re* face is preferred in the *R* enantiomer, and vice versa; the topicity is *ul* if the *Si* face is preferred in the *R* enantiomer, and vice versa. In short, if the first letters of the two *stereochemical descriptors* are the same, the topicity is *lk*. If they are different, it is *ul* [102]. See the more complete listing of like and unlike pairs under *l, u*. Note the use of lower case *l* and *u* letters, implying a *reflection invariant* relationship. *Lk* and *Ul* would be used if the topicity were *reflection variant*, which would occur if one of the components was reflection invariant.

M, P: See *P, M*.

meso: A stereoisomer that has two or more *stereogenic units*, but which is *achiral* because of a *symmetry plane*. The plane reflects *enantiomorph*ic groups.

Newman projection: A projection formula that represents the spatial arrangement of the ligands on two adjacent atoms as viewed down the bond joining them.



Nonbonded interactions: Attractive or repulsive “through space” forces between atoms or groups in a molecule (intermolecular or intramolecular) that are not directly bonded to each other.

Nonracemic: Not *racemic*.

Optical activity: The property of a substance to rotate plane polarized light. See Section 2.2

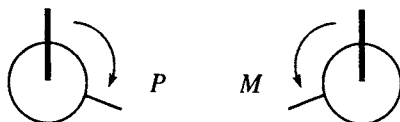
Optical purity (*op*, % *op*): The ratio of the observed *specific rotation* of a substance to the maximum possible rotation of the substance, expressed as a percent:

$$\% \text{ op} = \frac{[\alpha]}{[\alpha]_{\text{max}}} \cdot 100 \text{ .}$$

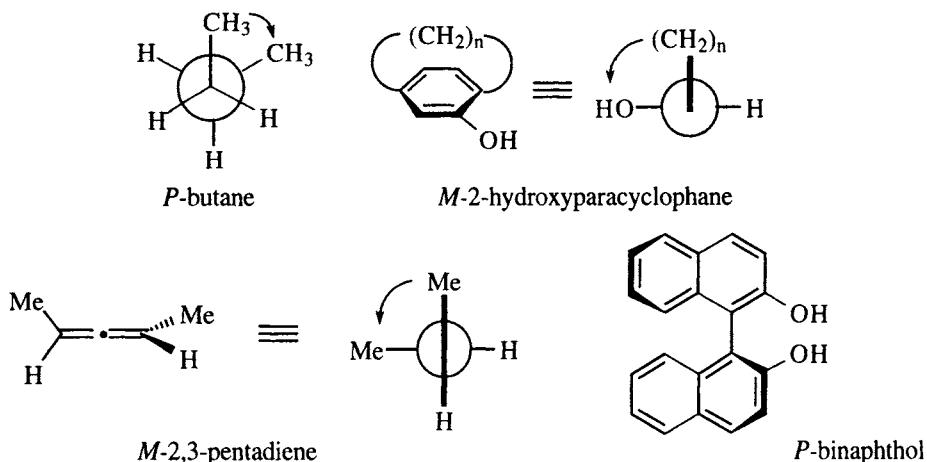
Usually (but not always) it is equal to *enantiomer excess*, or % *ee*. This term is less frequently used now, as enantiomer ratios are often determined by non-polarimetric methods. See Section 2.2.

Optical yield: For a chemical reaction, the *enantiomer excess* of the products relative to that of the starting material, expressed as a percent. In asymmetric synthesis, the denominator may be the *ee* of the chiral reagent or catalyst.

***P*, *M*:** Descriptors of chirality sense of a helix. Once the axis of the helix is identified, one chooses the ligands of the highest *CIP rank*. If the smallest angle between the ligands (*i.e.*, $\leq 180^\circ$) in a projection is clockwise going from front to rear, the chirality sense is *P* (plus), if counterclockwise, it is *M* (minus) [85,103]. Additionally, *P*, *M* may be used to describe the chirality sense of a helix of any sequence of atoms as long as they are explicitly identified. Note that it does not matter which end of the helix is viewed.



These descriptors can be used to specify enantiomeric *conformers*, such as *gauche* butane, and the *absolute configuration* of *stereogenic axes* and *planes*. Prelog and Helmchen have recommended the use of *P*, *M* instead of *R*, *S* for specifying the absolute configuration of planes and axes of chirality [86]. See also ref. [101], Ch. 14.

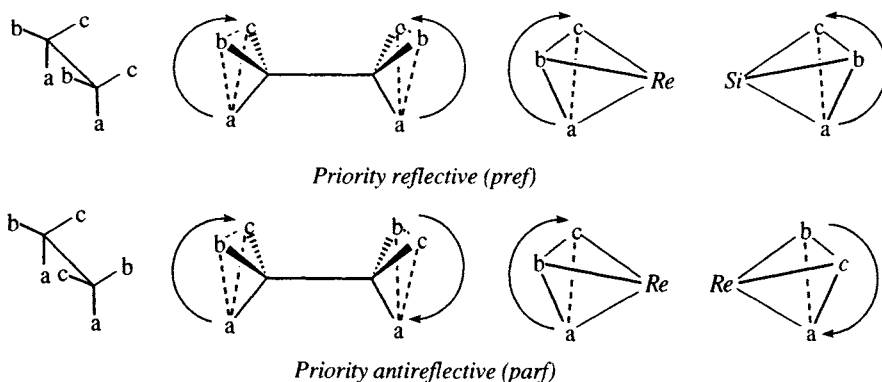


Pitzer strain: See *torsional strain*.

Planar chirality: See *stereogenic element*.

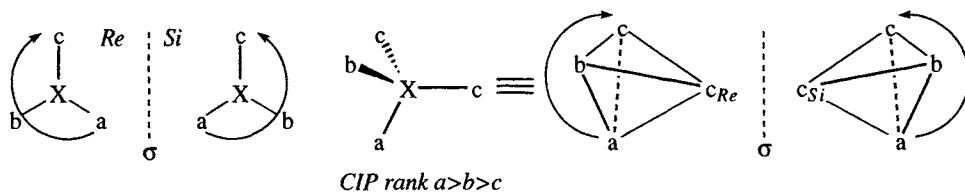
Point group (symmetry point group): The symmetry classification of a molecule based on its symmetry elements (axes, planes, etc.).

Pref, parf: Descriptors of relative configuration based on *CIP priority*. The relationship between two chirality centers is *pref* (priority reflective) if the order of decreasing priority of the three remaining groups at one chirality center is a reflection of the order of decreasing priority of the groups at the other center. When the orders of decreasing priority are not reflective of each other, the relative configuration is *parf* (priority antireflective). If the chirality centers are not adjacent, the intervening bonds are neglected and the two centers are treated as if they were directly linked. If the two centers are part of a ring, they are treated as if connected by a bond that replaces the shorter path [104].



Prochiral: Tetrahedral atoms having *heterotopic* ligands, or heterotopic faces of trigonal atoms, may be described as being prochiral. Note that it is inappropriate to describe an entire molecule as being prochiral [105]. Heterotopic faces are described using *Re*, *Si* if *reflection variant*, and *re*, *si* if reflection invariant [91]. If the *CIP priority* of the three ligands is clockwise, the face

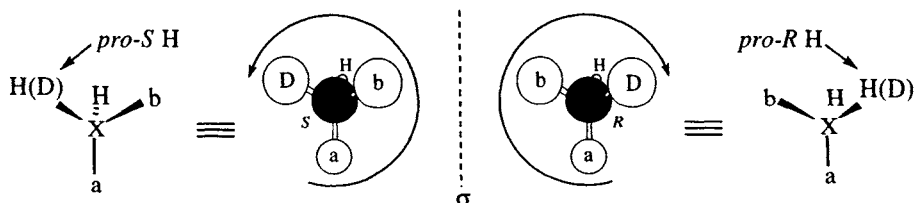
(toward the observer) is *Re*; if counterclockwise, it is *Si* [105]. For heterotopic ligands, two conventions have been used to describe prochirality. Both use the CIP rank of the ligands to specify the “prochirality sense” of each ligand. The broader rule is that of Prelog and Helmchen [91,92]. In this method, a tetrahedron is constructed of the four ligands around the prochiral center. If the ligand ‘L’ is sitting on the *Re* face of the triangle formed by the other three ligands, it is specified L_{Re} (or L_{re} if *reflection invariant*); similarly, the ligand would be specified L_{Si} or L_{si} if on the *Si* face. See also *enantiotopic*, *diastereotopic*, *heterotopic*, and *relative configuration*.



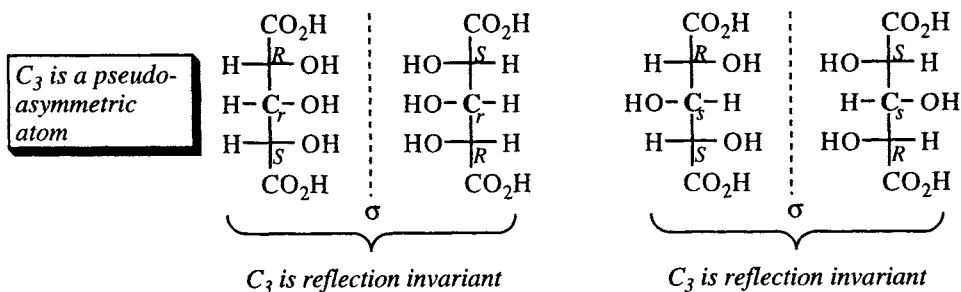
PROCHIRAL FACES

PROCHIRAL ATOMS (X), and LIGAND LABELS

Another convention, used in biochemistry to specify the hydrogen atoms of a prochiral methylene, replaces a hydrogen with a deuterium. If such replacement results in the *R* configuration, the ligand position is *pro-R*. If the *S* configuration is obtained, it is *pro-S* [105]. If *reflection invariant*, the descriptors are *pro-r* and *pro-s*.



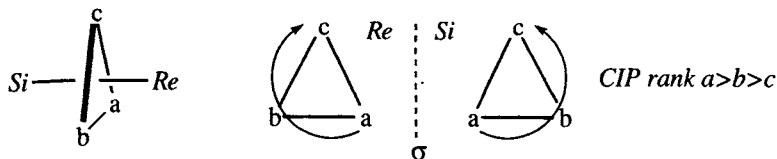
Pseudoasymmetric atom: A *stereogenic* atom of a stereoisomer that has two *enantiomorphic* ligands (reflection invariant), and two other different ligands. Exchange of any two ligands generates a *diastereomeric* compound. The CIP descriptors for pseudoasymmetric atoms are *r*, *s*. Use of this term is discouraged in favor of *stereogenic center*.



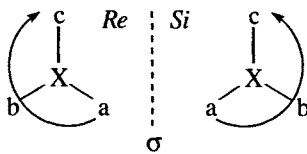
Pseudoaxial, pseudoequatorial: See *axial*, *equatorial*.

Pseudorotation: Term used by some authors to describe the out of plane motion of the ring atoms in cyclopentane during fast conformational interchange of the

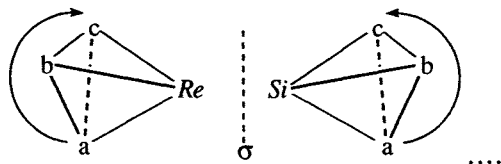
Re, *Si* (*re*, *si*): Stereochemical descriptors for *heterotopic* faces. If the *CIP* priority of the three ligands is clockwise, the face (toward the observer) is *Re* (latin *rectus*, right); if counterclockwise, it is *Si* (latin *sinister*, left) [105].



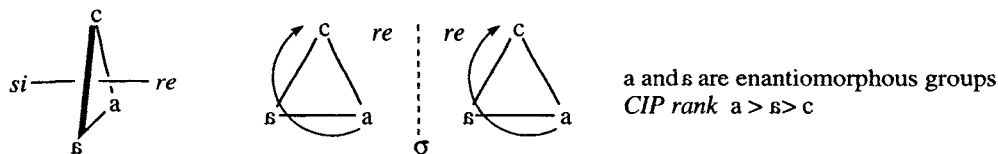
The descriptors may be used to describe the faces of trigonal atoms,



or the ligand position of a tetrahedral stereogenic unit,



Lower case descriptors (*re*, *si*) are used for the rare cases that are *reflection invariant* [91]:

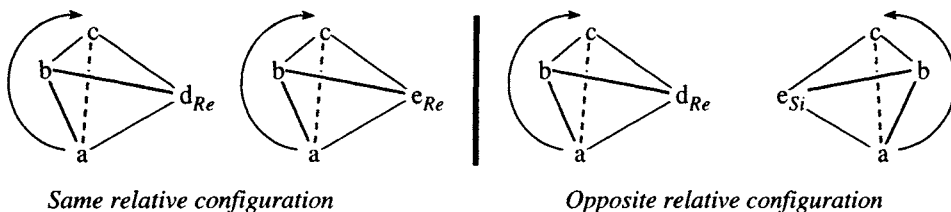


For examples of reflection invariant stereogenic centers and faces, see *diastereotopic*, and *pseudoasymmetric atom*.

Reflection variant, reflection invariant: The terms used to describe an object and its relationship with its mirror image. If the two are identical, the object is reflection invariant. If the object is *enantiomorphous* to its mirror image, it is reflection variant.

Relative configuration: The *configuration* of any *stereogenic* element with respect to another. Relative configuration is *reflection invariant*. The relative configuration of pairs of *stereogenic* units in the same molecule may be described as *R**, *R** or *l* if they have the same *CIP* descriptor, and *R**, *S** or *u* if they are different. (See *l*, *u* for a complete list of like and unlike descriptors.) The term can also be used in an intermolecular sense as follows: if the two molecules contain stereogenic units *abcd* and *abce*, and if *e* and *d* both sit on the same *heterotopic face*, the two stereogenic units have the same relative configuration. If not, they have the opposite relative configuration. The term

may be applied to starting material and products of a reaction sequence. See also *homofacial*, *heterofacial*.



Resolution: The separation of a *racemic mixture* into (at least one of) its component enantiomers. See also *kinetic resolution*.

Restricted rotation: See *free rotation*.

Retention of configuration: The product of a chemical reaction has retained its configuration if the product has the same *relative configuration* as the starting material. See also *Walden inversion*, *relative configuration*.

Ring inversion (ring reversal): The interconversion of cyclohexane *conformations* having similar shapes (chair - chair), accompanied by interchange of the *equatorial* and *axial* substituents. Similarly, the interchange of any such similarly shaped conformations in a cyclic molecule.

Rotamers: Stereoisomers of the same constitution and configuration, that differ only by torsion angles.

Rotation angle (α): The rotation of the plane of polarized light after passing through an *optically active* sample. If the angle of rotation is clockwise, the sample is *dextrorotatory* and the sign of rotation is positive (+). If the angle is counterclockwise, the sample is *levorotatory*, and the sign of rotation is (-). See also *optical activity*, *specific rotation*, and Section 2.2.

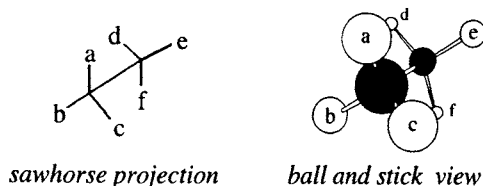
Rotation-reflection axis: See *alternating symmetry axis*.

Rotational barrier: The energy barrier between two *conformers*.

***s-cis*, *s-trans*:** Conformational descriptors for the single bond linking two double bonds (darkened below). The *synperiplanar* conformation is *s-cis*, and the *antiperiplanar* conformation is *s-trans*. See *torsion angle*.



Sawhorse formula: A perspective drawing that indicates the spatial arrangements of the ligands on two adjacent tetrahedral atoms. The bond between the two atoms is a diagonal line, with the nearer atom at the bottom.



Scalemic: Not *racemic* [106,107]. Synonymous with *aracemic*, *nonracemic*.

Sense of chirality: See *chirality sense*.

Sequence rules: See *CIP method*.

Si, si: See *Re, Si*.

Skew: See *chair*, *boat*, *twist-boat*.

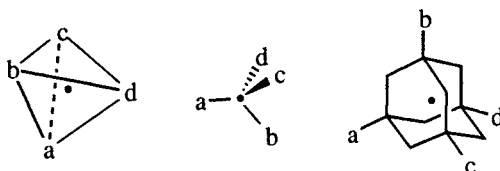
Specific rotation: The specific rotation of a sample, $[\alpha]$, is defined as:

$$[\alpha]_{\lambda}^t = \frac{100\alpha}{l \cdot c},$$

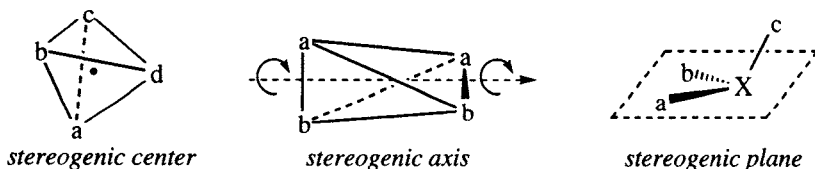
where t is temperature, λ is wavelength of the light, α is the observed rotation, l is the sample path length (in dm), and c is the concentration (in g/100 mL). $[\alpha]$ is normally reported without units, but the concentration and the solvent are usually specified in parentheses after the value of $[\alpha]$. See Section 2.2.

Staggered conformation: The *conformation* of two tetrahedral carbons is staggered

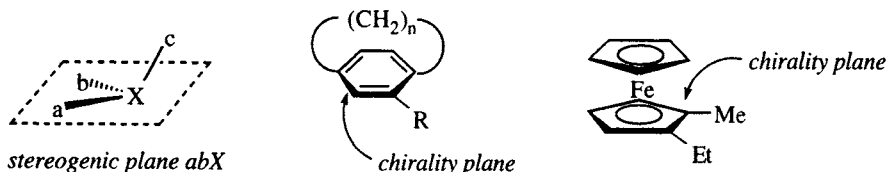
absolute configuration. If the center is reflection variant, it may be called a *chirality center*. If it is reflection invariant, it is sometimes called a *pseudoasymmetric atom*, although usage of this term is discouraged. **Stereogenic center** is thus an extension of the 'asymmetric carbon atom' of van't Hoff and LeBel, and now includes species such as N^+abcd and the sulfur atom of unsymmetric sulfoxides (where the fourth 'ligand' is a lone pair), as well as tetrahedral arrays of ligands with T_d symmetry. The *absolute configuration* may be described by the *CIP method*. See *R,S*.



Stereogenic element, stereogenic unit: A center, axis, or plane in a molecule in which exchange of two ligands leads to a new *stereoisomer*. If the stereogenic element is reflection variant, the elements are *chirality center*, *chirality axis*, and *chirality plane*. The bonding positions of stereogenic centers have point symmetry T_d ; the bonding positions of stereogenic axes have point symmetry D_2 or C_{2v} ; the bonding positions of stereogenic planes have point symmetry C_s . As a result, there must be four different ligands (abcd) on a T_d bonding center to create stereogenicity. On an axis, only the two ligands of each pair need be different (ab/ab), the two pairs may be the same. In a stereogenic plane, only one of the ligands in the plane need be different. See also *stereogenic axis*, *stereogenic center*, *stereogenic plane*.



Stereogenic plane: A planar structural fragment that, because of *restricted rotation* or structural requirements, cannot lie in a symmetry plane. If the stereogenic plane is reflection variant, the element may be called a *chirality plane*. For example with a monosubstituted paracyclophane, the stereogenic plane includes the plane of the benzene ring. For a 1,2-disubstituted ferrocene, the disubstituted cyclopentadiene lies in a chirality plane. The *absolute configuration* may be specified by either *R, S* or *P, M*. See also *stereogenic element*.



Stereoheterotopic: Either *enantiotopic* or *diastereotopic*.

Stereoisomers: Isomers of the same *constitution* that differ only in the position of atoms and ligands in space (i.e., *enantiomers* and *diastereomers*).

Stereoselectivity: In a reaction, the preferential formation of one *stereoisomer* over another (or others). See also *diastereoselectivity*, *enantioselectivity*.

Stereospecific: A pair of reactions are stereospecific if *stereoisomeric* educts afford stereoisomeric products. A stereospecific process is necessarily 100% *stereoselective*, but the converse is not necessarily true, even if the stereoselectivity is 100%. Use of the term to describe a reaction that is merely highly stereoselective is discouraged.

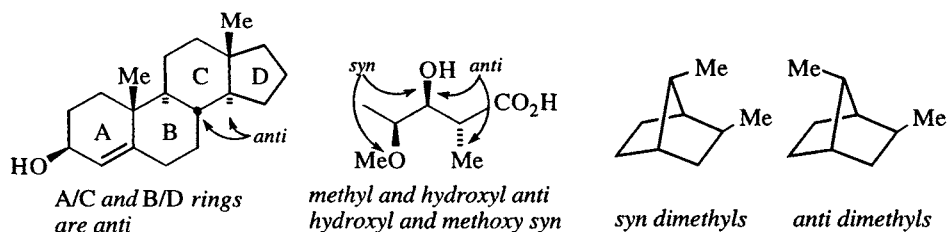
Structure: The *constitution*, *configuration*, and *conformation* of a molecule. Formerly, the term was used as a synonym for *constitution* alone.

Structural isomers: Obsolete term for *constitutional isomers*.

Superimposable, superposable: Two objects are superimposable if they can be brought into coincidence by translation and rotation. For chemical structures, *free rotation* around single bonds is permissible. Thus, two molecules of *R*-2-butanol are considered superimposable independent of their conformations.

Suprafacial: See *antarafacial*, *suprafacial*.

syn, anti: Prefixes that describe the relative configuration of two substituents with respect to a defined plane or ring (syn if on the same side, anti if opposite). Such planes may be defined arbitrarily, but some that are in common usage are illustrated below. Formerly, these terms were used to describe the configuration of oximes, hydrazones, etc. (see *E, Z*). See also *torsion angle*.



Synclinal: See *torsion angle*.

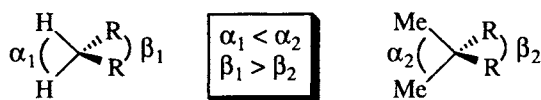
Symmetry axis (C_n): An axis of an object, about which a rotation by an angle of $360/n$ gives an entity that is superimposable on the original. See also *alternating symmetry axis*.

Symmetry elements: Axes, centers, or planes of symmetry.

Symmetry plane (σ): A mirror plane which bisects an object, such that reflection of one half produces a fragment that is superimposable on the other half.

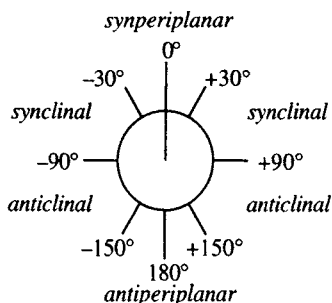
Thorpe-Ingold effect: The original phenomenon observed by Thorpe and Ingold was an accelerating effect on cyclizations [109,110]. They attributed the effect to a bond angle compression, as shown below, whereby geminal substituents enlarge bond angle α by *van der Waals* repulsion, and thereby compress bond

angle β . (It is likely that this explanation is an oversimplification. For a recent study on geminal effects on ring closure rates, see ref. [111]).



Threo: See *erythro*, *threo*.

Torsion angle: The angle, in a molecular fragment A–B–C–D (having ABC and BCD bond angles $\leq 180^\circ$), between the planes ABC and BCD (see the *Newman projection*, below), always defined such that the absolute value is less than 180° . If (looking from either direction) the turn from A to D or D to A is clockwise, the torsion angle is positive; if it counterclockwise, it is negative (see also *P*, *M*). If the torsion angle is 0° to $\pm 90^\circ$, the angle is *syn*; if between $\pm 90^\circ$ and 180° , it is *anti*. Similarly, angles from 30 to 150° and -30 to -150° are *clinal*. Combination gives *synperiplanar* for angles between 0° and $\pm 30^\circ$; 30° to 90° and -30° to -90° are *synclinal*; 90° to 150° and -90° to -150° are *anticlinal*; and $\pm 150^\circ$ to 180° are *antiperiplanar* [103]. Often the *synperiplanar* conformation is called eclipsed, the *antiperiplanar* conformation *anti*, and the *synclinal* conformation *gauche* or *skew*.



Torsional strain: Destabilization of a molecule due to a variation of a *torsional angle* from an optimal value (e. g., 60° in a saturated molecule). Also called *Pitzer strain*, *eclipsing strain*.

Torsional isomers: See conformational isomers.

trans: See *cis*, *trans isomers*.

Transannular interaction: Literally: cross-ring interactions. Non-bonded interaction between ligands attached to nonadjacent atoms in a ring, for example in a cyclohexane *boat* or in medium-sized rings.

transition state, transition structure: In a chemical reaction, the *transition state* is the ensemble of molecular structures that are at the free energy saddle point between reactants and products. The *transition structure* corresponds to the single set of atomic coordinates at the saddle point of the potential energy surface (internal, or enthalpic energy at 0° K). Thus, coordinates of the transition state vary with temperature, whereas those of the transition structure do not. In a practical sense, a structure that is drawn on a piece of paper

(whether derived from a computation or not) should be referred to as a transition structure, since it is static. The transition state is an ensemble of similar structures undergoing translational, vibrational, and rotational motion.

transoid conformation (usage discouraged): See *s-cis*, *s-trans*.

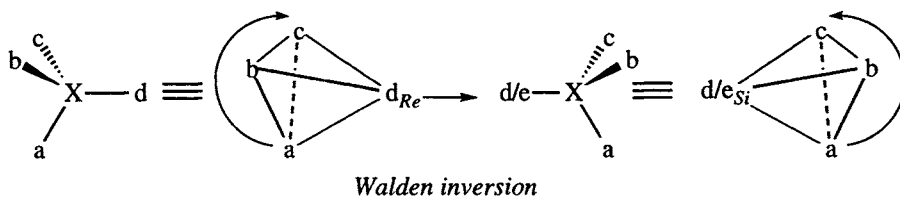
twist-boat: See *chair*, *boat*, *twist-boat*.

u: See *l*, *u*.

ul: See *lk*, *ul*.

van der Waals interactions: Attractive or repulsive interactions resulting from close approach of two molecules [112-114]. Modern usage (especially in molecular mechanics calculations) also uses the term van der Waals interactions to describe the attractive and repulsive interactions created by intramolecular approach of molecular fragments [115]. See also *nonbonded interactions*.

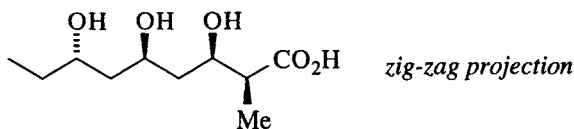
Walden inversion: Conversion of $Xabcd$ into $Xabdc$ (for an identity reaction) or $Xabce$, of opposite *configuration*. Synonymous with *inversion of configuration*.



Z: See *E*, *Z*.

Z(O): See *E(O)*, *Z(O)*.

Zig-zag projection: A stereochemical projection in which the main chain of an acyclic compound is drawn in the plane of the paper with 180° torsion angles, with substituents above the plane drawn with bold or solid wedges, and hashed lines for substituents behind the plane.



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