

## Concepts and Terminology in Organic Stereochemistry 2

Selectivity in Junctive/Disjunctive and Ligogenic/Ligolytic Processes

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# Concepts and Terminology in Organic Stereochemistry 2

Selectivity in Junctive/Disjunctive and Ligogenic/Ligolytic Processes

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To Dad and Mom,  
for their dedication and sacrifices

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## Preface

The history of organic chemistry goes back to the days of Friedrich Wöhler, two centuries ago. The stereochemical underpinnings of organic chemistry were set by Louis Pasteur, and the concept of chirality was advanced by Lord Kelvin, nearly a century later. The first stereochemical notation - that of the asymmetric carbon atom - had to await the Cahn-Ingold-Prelog (CIP) R/S rules - a half century later; it took yet another quarter century for the E/Z configurational notation for double bonds to be formulated. Indeed, the development of organic stereochemical language has lagged, and continues to lag experimental organic chemistry. In the last quarter century or so, there have been only two seminal contributions - both by Kurt Mislow and his coworkers - ones that have clarified the basic concepts of stereotopicity and chirotopicity. Notwithstanding a few other sporadic contributions by others, to date there have been no systematic attempts to unify and develop the conceptual framework and terminology of organic stereochemistry. Existing terms are frequently misused or abused, needed terms - redundant, confusing or controversial - are invented randomly, and yet other needed terms have not seen the light of day. This three-part work is an attempt to present the elements of a simple, uniform and comprehensive language of organic stereochemistry.

In Volume 1, we analyze the geometric basis of metric and topic relationships (Chapters 1 and 3), and derive a novel, simple, and universal framework - the HEDAN (*homometric/homotopic, enantiometric/enantiotopic, diastereometric/diastereotopic, astereometric/astereotopic and nonequimetric/nonequitopic*) scheme - for classifying (a) relationships between molecules (morphic relationships) (Chapter 2), (b) relationships between parts of molecules (topic relationships) (Chapter 4), (c) interconversions between molecules (morphization processes) (Chapter 2), and (d) interchanges between parts of molecules (topizations) (Chapter 4). We then establish heretofore-unknown stereochemical correlations between overall molecular structure (morphicity) and molecular sites (topicity), on the one hand, and between molecular transformations (morphizations) and molecular site interchanges (topizations), on the other (Chapter 5).

The geometric *segmentation* of a molecular state (ground state, excited state, transition state) into geometric simplexes (*geoplexes*) (Chapter 6) enables us (a) to identify the *stereogeoplex* (or *stereoplex*) as the smallest geometric element of stereogenicity (segmental stereogenicity), (b) to provide the geometric basis for defining molecular *astereogens* and *stereogens*, and (c) to prove that the concept of stereogenicity inherently encompasses the concept of chirality (enantiogenicity). The method of segmentation provides a rationale of stereoisomerism different from that based on elements of stereoisomerism (Hirschmann and Hanson) and/or elements of chirality (Prelog).

Finally, we examine the geometric segmentation of carbogenic molecules with angular (non-perpendicular and/or noncoplanar) joins (Chapter 7), and discover that the *angular join* is a fundamental geometric

element of stereogenicity (angular stereogenicity) - complementary to the *stereoplex* (shown earlier to be the fundamental unit of *segmental* stereogenicity). The method of geometric segmentation provides the common geometric basis for both configurational and conformational stereogenicity.

At the end of Volume 1, we present a very useful and also heretofore-unavailable method of describing the compositions of two-, three- and four-component mixtures (Addendum A), and define a novel logarithmic scale for denoting their compositions (Addendum B).

In Volume 2, we identify the basic reactant molecular fragments - *fundamental junctive simplexes* - and utilize them in a novel notational description of fundamental junctive/disjunctive processes (Chapter 8). We also define *topological junctive simplexes* for a parallel notation of topological junctive/disjunctive processes. The two notations are jointly used in describing composite junctive/disjunctive processes. The concepts of *site junctivity* (for an atomic site), *fundamental simplex junctivity*, *topological simplex junctivity*, *molecular junctivity*, and *process junctivity* are also defined. The terminology advanced here (a) provides a simple, generalized and useful way of describing the progressive bonding in elementary mechanistic steps, (b) specifies incipient connectivity in transition states, (c) denotes connectivity in ground-state aggregated/associated supramolecular entities, and (d) presents the framework for specifying the regioselectivity, vectoselectivity, and facioselectivity in junctive/disjunctive processes. The concept of junctivity/disjunctivity is subsequently extended to ligogenic/ligolytic processes, thereby enabling a simple and universal notation for denoting such processes, and for providing the framework for specifying the regioselectivity, vectoselectivity, and facioselectivity in each process (Chapter 9).

Having set the framework for molecular connectivity, we proceed to discuss the concept of selectivity in all its facets. We start with *morphoselectivity* (Chapter 10), and draw a clear distinction between morpholytic selectivity (selective consumption of substrate  $S_1$  over substrate  $S_2$ ) and morphogenetic selectivity (selective formation of product  $P_1$  over product  $P_2$ ). Each of these two types of morphoselectivity is classified further on the basis of the morphic relationship between reacting substances  $S_1$  and  $S_2$ , and of products  $P_1$  and  $P_2$ .

We then broach *situselectivity* (selective reaction at molecular site  $t_1$  over molecular site  $t_2$ ) and classify it on the basis of the topic relationships of reacting sites (Chapter 11). Where the focus of attention is on *site* selectivity, we emphasize that the correct term should be *situselectivity* and *not* oft-misused and -abused term *regioselectivity*. We also discuss *bisituselectivity* for transformations involving two reactant molecules/moieties each with its own preferred site of attack.

To clarify selectivity at faces of planar molecular fragments, or *facioselectivity*, we present a complete classification of all eleven types of stereotopic molecular faces (Chapter 12). We define the different modes of facioselectivity *viz.* facioaselectivity, faciononselectivity and stereofacioselectivity at each type of molecular face. We also discuss *difacioselectivity* for conjunctive processes involving the interactions of two molecular faces.

We then proceed to define *vectoplexes* and *avectoplexes* (vectogenic and avectogenic junctive simplexes, respectively), in order to introduce the novel concept of *vectoselectivity* *viz.* junctive selectivity resulting from orientational preferences of reactants (Chapter 13). We examine the interactions of two and three junctive vectoplexes/avectoplexes and derive therefrom the five modes of vectoselectivity - vectoaselectivity, vectononselectivity, stereovectoselectivity, astereovectoselectivity and nonequivvectoselectivity. We demonstrate that Hassner's original definition of regioselectivity, and the subsequent IUPAC endorsement of that term, encompass two conceptually distinct ideas. Where the focus of attention is on site selectivity, *regioselectivity* is inapplicable and should be abandoned; the correct term should be situselectivity/toposelectivity. The term *regioselectivity* denotes selectivity due to parallel/antiparallel "Markovnikov-sense" alignment/bonding/association of "unsymmetrical" reactants with "unsymmetrical" reagents. Further, we demonstrate that the broader concept of *vectoselectivity* (a) encompasses Hassner-regioselectivity for two reactants, (b) applies to junctive processes involving three or more reactants, and (c) covers a wider range of orientational possibilities of all reactants/reagents. We examine conjunctive states in vectoselective processes, and determine vectoselectivity at all eleven types of stereotopic molecular faces. In transformations involving

additions to planar molecular moieties, we consider facioselectivity and vectoselectivity jointly, and uncover twelve subclasses of facioselectivity-vectoselectivity, each with unique characteristics. Finally, the joint consideration of difacioselectivity-vectoselectivity in various processes leads to eighteen subclasses of difacioselectivity-vectoselectivity, each also with characteristic attributes.

In the last chapter of Volume 2, we introduce and discuss the novel concept of *anguloselectivity* (Chapter 14). In a ligogenic process, each sigma bond is formed by the approach of the reacting moieties along specific trajectories and through vectospecific or nonvectospecific alignments. For a given vectospecific or nonvectospecific alignment, the exact alignment of the two moieties with respect to each other, at a given point in time, represents an angulospecific alignment. Anguloselectivity refers to the preference for one angulospecific alignment over another (or others). We demonstrate that anguloselectivity complements elegantly the concept of vectoselectivity.

At the end of Volume 2, we append a generalized system for assigning specific stereodescriptors to stereotopic/paired polycentric planar molecular faces (half-spaces) (Addendum C), and a designation of paired stereotopic molecular faces and stereotopic ligands (at tetrahedral and trigonal carbon atoms) (Addendum D).

Volume 3 starts with the definition of the prostereogenicity and prochirotopicity of atoms (Chapter 15). Since stereotopicity and chirotopicity are *independent* attributes of ligand atoms, we derive *four* composite designations of an atom - achiroastereogenic (achirotopic/astereogenic, type o), chiroastereogenic (chirotopic/astereogenic, type o\*), achirostereogenic (achirotopic/stereogenic, type s), and chirostereogenic (chirotopic/stereogenic, type s\*) – and provide a subclassification of achirostereogenic (type o) and chirostereogenic (type o\*) atoms. We then proceed to define and illustrate stereogenization/destereogenization (generation/loss of a stereogenic atom), chirogenization/dechirogenization (generation/loss of a chirotopic atom), and chirostereogenization/dechirostereogenization (generation/loss of a chirostereogenic atom) in organic reactions (Chapter 16).

In Chapter 17, we develop a universal, systematic stereochemical classification of chemical transformations based on the overall changes in stereogenicity of the atoms involved during a given transformation. Three types of stereotopoprocesses are discerned – *viz.* those that are accompanied by (a) overall loss, (b) no gain/loss, and (c) overall gain of *stereogenic* atoms; we label these transformations as stereopolysis, stereopomutation, and stereopogenesis, respectively. Further subclassification is effected using the joint criteria of rotativity (expected optical activity) and stereoselectivity (preferential formation of one stereoisomers over another). Lastly, we provide a novel definition of stereospecificity. The merits of the classification of stereotopoprocesses are examined in relation to asymmetric synthesis, chiral synthesis, asymmetric induction, asymmetric destruction, kinetic resolution, and asymmetric desymmetrization.

Finally, in Chapter 18 we present an alternative, universal stereochemical classification of chemical transformations based on (a) overall loss, (b) no loss/gain, and (c) overall gain of *chirotopic* atoms; we label these chirotopoprocesses as chirotopolysis, chirotopomutation and chirotopogenesis, respectively. Further subclassification is carried out using the dual criteria of rotativity (expected optical activity) and stereoselectivity (preferential formation of one stereoisomer over another). We also introduce and define the novel concepts of chiroselectivity and chirospecificity. Finally, the merits of the classification of chirotopoprocesses are discussed, and the stereotopoprocesses and chirotopoprocesses are correlated in relation to the stereotopic molecular faces.

Moses K. Kaloustian

December , 2001  
Tarrytown, New York

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"Language... is something arising out of the work, needs, ties, joys, affections, tastes, of long generations of humanity."

Walt Whitman, *North American Review*, 1885.

# 8

## Junctive/Disjunctive Processes in Organic Chemistry

Chemical associative/dissociative processes including complexation, molecular recognition, and molecular assembly, are governed by changes in bonding due to the formation/severance of  $\sigma$  bonds,  $\pi$  bonds, hydrogen bonds, and by alterations in bonding due to dipole-dipole, ion-dipole and ion-ion interactions. The current language describing associative/dissociative processes<sup>1</sup> in organic chemistry is sometimes imprecise or inadequate. Herein we refine and define the portion of that language pertaining to processes that lead to the generation/breakdown of high-energy intermediates/transition states, or association/dissociation of ground-state aggregates.

### I. Junctive/Disjunctive Processes

A *junctive* process is one in which partial *or* complete  $\sigma$  and/or  $\pi$  bonding takes place between two unbonded atoms.<sup>2</sup> A *disjunctive* process is the exact reverse of a junctive process, i.e., it is one in which partial *or* complete  $\sigma$  and/or  $\pi$  bonding is severed between two atoms. In a junctive process, the bond order between two reactive atoms starts at 0 and increases to any value - fractional or integral - greater than 0. In a disjunctive process, for two linked atoms, one starts at any value of the bond order greater than 0 - fractional or integral - and ends up being 0. Figure 8.1 depicts the change in bond order that accompanies each junctive and disjunctive process.

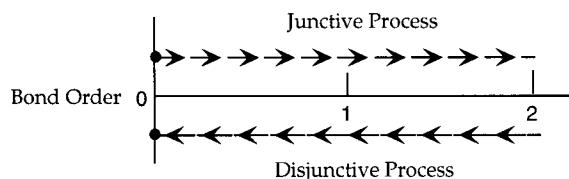


Figure 8.1. Change in Bond Order in Junctive and Disjunctive Processes

The formation of a directed bond<sup>3</sup> between two (or more) reactive atomic sites (belonging to one, two or more reactants/reactant moieties) en route to *transition state, intermediate or product(s)* (Figure 8.2) is, *ipso facto*, a junctive process. Such a process manifests itself in the formation of (a) incipient  $\sigma$  bonds ( $1+2\rightarrow[3]^\neq$ ,  $5+6\rightarrow[7]$ ), (b) full-fledged  $\sigma$  bonds ( $1+2\rightarrow 4$ ,  $5+6\rightarrow 8$ ,  $9+10\rightarrow 11$ ,  $12+13\rightarrow 14$ ), (c) partial bonds due to dipole-dipole, dipole-ion (in forming host-guest complexes; e.g.  $15+16\rightarrow 17$ ), pairwise ion-ion interactions, (d)  $\sigma/\pi$ -bonds ( $18a+18b\rightarrow[19]^\neq$ ), (e)  $\pi$ -bonds (e.g.  $21+22\rightarrow 23$ ), and (e) H-bonded aggregates (e.g.  $24a+24b\rightarrow 25$ ).

A disjunctive process is accompanied by the severance of a directed bond between one (or more) pair(s) of bonded atoms within a molecule/molecular species representing a *transition state, intermediate or reactant*. Such a process manifests itself in the cleavage of (a) incipient  $\sigma$  bonds ( $[3]^\neq\rightarrow 1+2$ ,  $[7]\rightarrow 5+6$ ), (b) full-fledged  $\sigma$  bonds ( $4\rightarrow 1+2$ ,  $11\rightarrow 9+10$ ,  $14\rightarrow 12+13$ ), (c) dipole-dipole, dipole-ion, pairwise ion-ion interactions (in dissociation of host-guest complexes; e.g.  $17\rightarrow 15+16$ ), (d)  $\sigma+\pi$  bonds ( $[19]^\neq\rightarrow 18a+18b$ ), (e)  $\pi$  bonds (e.g.  $23\rightarrow 21+22$ ), and (f) H-bonds (e.g.  $25\rightarrow 24a+24b$ ).

Note that following the definitions given above, the transformation  $[3]^\neq\rightarrow 4$ ,  $[19]^\neq\rightarrow 20$  are *not* considered junctive because they are not accompanied by *ab origine* (*ab initio*) bonding between relevant nonbonded pairs of atoms, despite the fact they are accompanied by *increased* bonding between the already-bonded pairs of atoms. That is to say, in these transformations no unlinked atoms become newly linked (therefore, they are not junctive); there is, however, *enhanced* bonding between already-linked atoms. Similarly, the  $4\rightarrow[3]^\neq$  and  $20\rightarrow[19]^\neq$  transformations are *not* disjunctive because there is only *diminished* bonding; there is *no* severance (total disconnection) between pairs of bonded atoms.

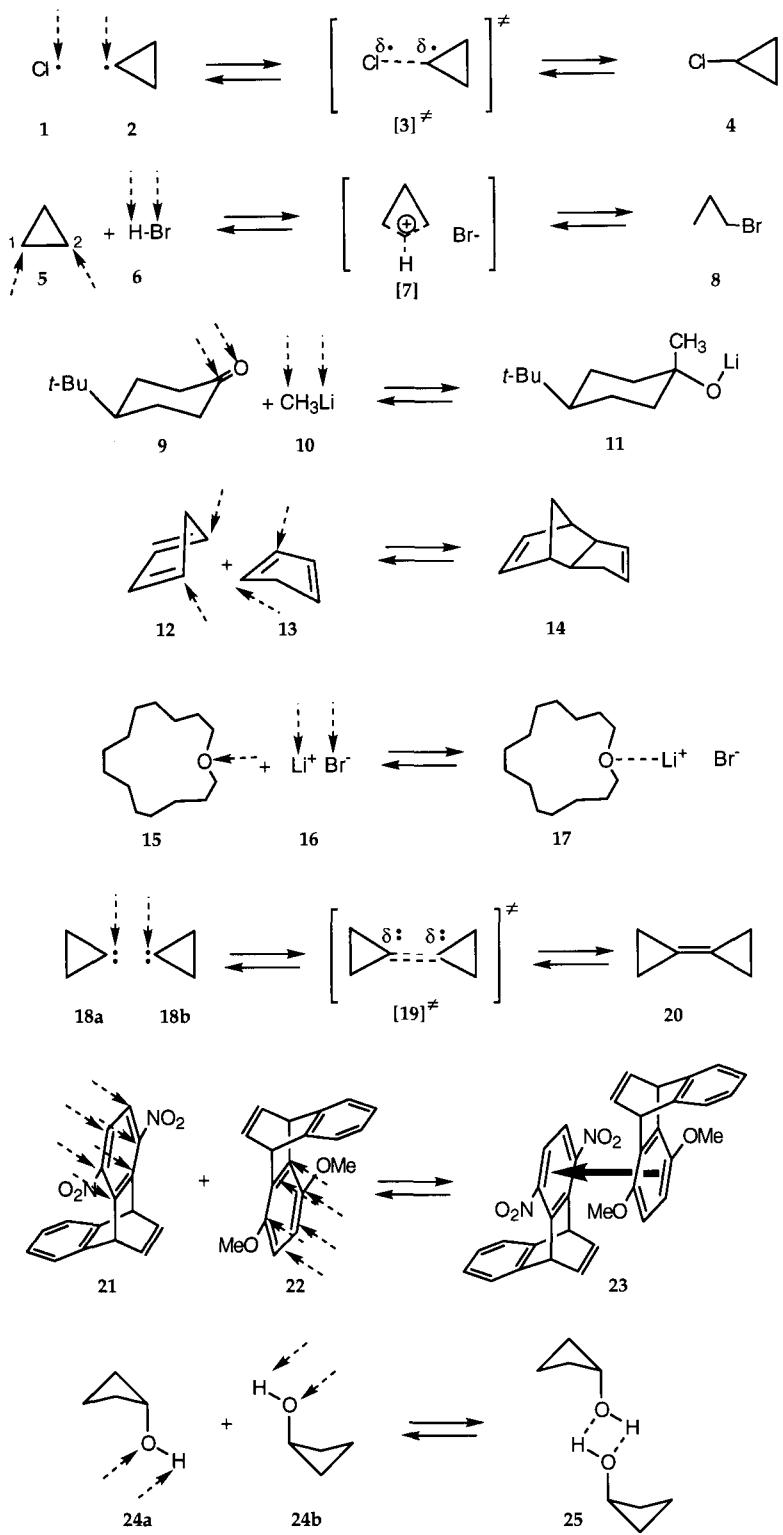
## II. Junctive Sites

A *junctive site* is a reacting atom at which a change in directed bonding occurs. In Figure 8.2 (p. 3), all junctive sites are marked with arrows. A *junctive simplex* is the smallest portion of a molecule/molecular species that encompasses the reacting atomic sites involved in a junctive process. Junctive simplexes are of two types - *fundamental* and *topological*. Processes are derived from fundamental simplexes, or topological ones, or both (*vide infra*).

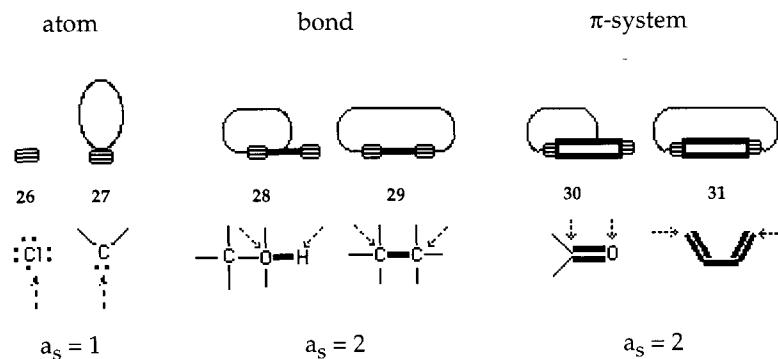
## III. Fundamental Junctive Simplexes

In carbogenic systems, a fundamental junctive simplex is, generally, an atom (type 26,27),<sup>4</sup> a  $\sigma$ -bond (type 28,29), or, a  $\pi$ -system (type 30,31), as represented in Figure 8.3 (p. 4).<sup>5</sup> The *atomicity* of a simplex ( $a_s$ ) is the number of junctive atoms of the simplex taking part in a given junctive process.

Chlorine atom 1 (in  $1+2\rightarrow[3]^\neq$ ) and the carbenic carbon in 18a ( $18a+18b\rightarrow[19]^\neq$ ) are *atomic junctive simplexes* (type 26 and 27 (Figure 8.3), respectively); for each of them,  $a_s=1$ . In the latter case, it is solely the central carbon that constitutes the junctive atom; the rest of the molecule is not part of the simplex. *Bond junctive simplexes* are exemplified by the O-H bond (type 28) in 24a for the transformation  $24a+24b\rightarrow 25$ , and the C-C bond of 5 (type 29) in transformation  $5+6\rightarrow 7$ . In these cases, the junctive sites are the terminal atoms of the  $\sigma$ -bond; thus,  $a_s=2$ . Lastly,  *$\pi$ -junctive simplexes* are typified by ketone 9 (type 30, Figure 8.3) during the course of its reactions with an alkyl lithium reagent ( $9+10\rightarrow 11$ ), and 12 (type 31, Figure 8.3;  $a_s=2$ ), in its Diels-Alder reactions ( $12+13\rightarrow 14$ ); in the latter, the junctive sites are the terminal carbons of the  $\pi$ -system. Hence, for each of 30 and 31,  $a_s=2$ .



**Figure 8.2.** Examples of Junctive/Disjunctive Transformations



**Figure 8.3.** Fundamental Junctive Simplexes and their Atomicities

#### IV. Fundamental Junctive/Disjunctive Processes

Fundamental junctive/disjunctive processes involving interactions between two or three fundamental simplexes (*vide infra*) are described as binary and ternary processes, respectively. A given process - be it binary or ternary- is either *simple* or *complex*. The junctive process is *simple*, if only junctive *or* disjunctive components are present; it is *complex*, if junctive *and* disjunctive components are both present (*vide infra*).

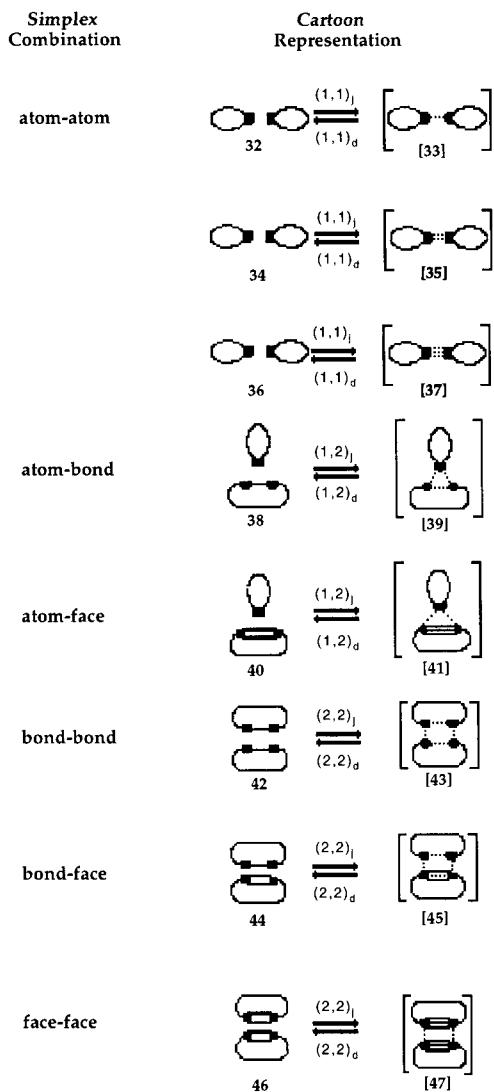
Simple binary and ternary junctive processes are denoted as  $(m,n)_j$ ,  $(m,n,p)_j$ , respectively ( $m, n, p$  are the atomicities  $a_s$  of the participating simplexes; i.e.  $m,n,p=1,2,\dots$ ). The corresponding reverse processes are denoted as  $(m,n)_d$ ,  $(m,n,p)_d$  and they constitute simple disjunctive processes (subscripted suffixes  $j$  and  $d$  mean junctive and disjunctive, respectively). Figure 8.4 depicts cartoon representations and notational designations of simple binary and ternary junctive processes (the square bracketed entity, in each case, represents a *conjunctive state*).<sup>6</sup>

The simplest binary junctive process  $(1,1)_j$  results from atom-atom combination e.g.  $32 \rightarrow [33]$ ,  $34 \rightarrow [35]$ ,  $36 \rightarrow [37]$ . The  $(1,2)_j$  atom-bond, atom-face junctive processes are exemplified by transformations  $38 \rightarrow [39]$  and  $40 \rightarrow [41]$ , respectively. The  $(2,2)_j$  junctive processes resulting from bond-bond, bond-face, and face-face associations are represented by  $42 \rightarrow [43]$ ,  $44 \rightarrow [45]$  and  $46 \rightarrow [47]$ , respectively.

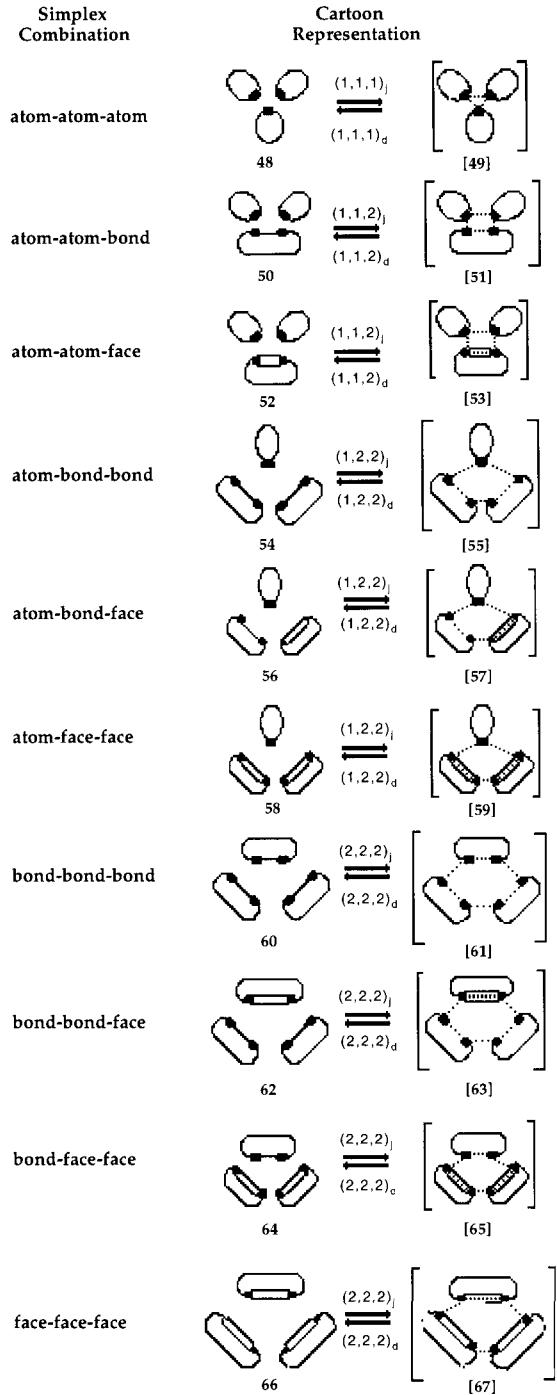
The ternary  $(1,1,1)_j$  junctive process resulting from atom-atom-atom associations is given by  $48 \rightarrow [49]$ . Similarly,  $(1,1,2)_j$  processes arise from atom-atom-bond, atom-atom-face interactions (e.g.  $50 \rightarrow [51]$ ,  $52 \rightarrow [53]$ ), whereas  $(1,2,2)_j$  processes stem from atom-bond-bond, atom-bond-face and atom-face-face interactions (e.g.  $54 \rightarrow [55]$ ,  $56 \rightarrow [57]$ ,  $58 \rightarrow [59]$ ). Finally, the ternary bond-bond-bond, bond-bond-face, bond-face-face, and face-face-face associations are designated  $(2,2,2)_j$  as in  $60 \rightarrow [61]$ ,  $62 \rightarrow [63]$ ,  $64 \rightarrow [65]$ , and  $66 \rightarrow [67]$ , respectively.

The notation for a reverse (disjunctive) process is identical with that for the corresponding junctive processes except for the subscript  $j$  (for junctive); the latter is modified to  $d$  (for disjunctive). For example, the reverse of the  $(1,2)_j$  process  $38 \rightarrow [39]$  is  $(1,2)_d$  process  $[39] \rightarrow 38$ . Figure 8.4 includes the notational designations of all the pure reverse/disjunctive processes.

### Binary Processes

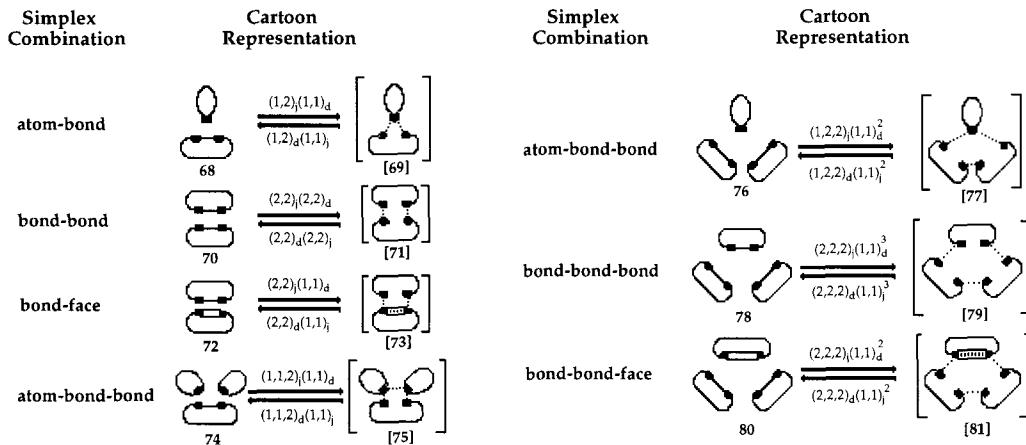


### Ternary Processes



**Figure 8.4.** Cartoon Representations of Fundamental Simple Junctive and Disjunctive Processes

We now turn to complex processes which, by definition, incorporate junctive as well disjunctive components e.g.  $(m,n)_j(m,n)_d$ ,  $(m,n,p)_j(m,n)_d$ ,  $(m,n)_j(m,n,p)_j(m,n)_d$ , etc.<sup>7</sup> Figure 8.5 portrays representative idealized cases e.g.  $68 \rightarrow [69]$  -  $(1,2)_j(1,1)_d$ ,  $70 \rightarrow [71]$  -  $(2,2)_j(2,2)_d$ ,  $72 \rightarrow [73]$  -  $(2,2)_d(1,1)_j$ ,



**Figure 8.5.** Cartoon Representations of Complex Junctive/Disjunctive Processes

$74 \rightarrow [75]$  -  $(1,1,2)_j(1,1)_d$ ,  $76 \rightarrow [77]$  -  $(1,2,2)_j(1,1)_d^2$ ,  $78 \rightarrow [79]$  -  $(2,2,2)_j(1,1)_d^3$ ,  $80 \rightarrow [81]$  -  $(2,2,2)_j(1,1)_d^2$ . The reverse processes would be  $[69] \rightarrow 68$  -  $(1,2)_d(1,1)_j$ ,  $[71] \rightarrow 70$  -  $(2,2)_d(2,2)_j$ ,  $[73] \rightarrow 72$  -  $(2,2)_d(1,1)_j$ ,  $[75] \rightarrow 74$  -  $(1,1,2)_d(1,1)_j$ ,  $[77] \rightarrow 76$  -  $(1,2,2)_d(1,1)_j^2$ ,  $[79] \rightarrow 78$  -  $(2,2,2)_d(1,1)_j^3$ , and  $[81] \rightarrow 80$  -  $(2,2,2)_d(1,1)_j^2$ .

Figure 8.6 illustrates the above designations of chemical transformations, mechanistic steps of various chemical transformations, and formation of H-bonded aggregates.

Thus, the coupling of carbenes  $82\text{a}+82\text{b} \rightarrow 83$  is a  $(1,1)_j$  process; the reverse would be a  $(1,1)_d$  process. The addition of cyclopropylidene to cyclohexene  $84+85 \rightarrow 86$  is a  $(1,2)_j$  process, while the reverse is a  $(1,2)_d$  disjunctive process. The Diels-Alder dimerization  $87\text{a}+87\text{b} \rightarrow 88$  is  $(2,2)_j$ , and the reverse is  $(2,2)_d$ . The trimerization of water  $89\text{a}+89\text{b}+89\text{c} \rightarrow 90^8$  is  $(2,2,2)_j$  and the reverse dissociative process is  $(2,2,2)_d$ . The free-radical chlorination of cyclopropane can be visualized to proceed through two different mechanisms. In the first of these, the attack of a chlorine atom on a H of a C-H bond of cyclopropane  $(91+92) \rightarrow [93]$  (step a) proceeds to yield HCl and cyclopropyl radical  $[93] \rightarrow 94+95$  (step b); the two steps are described as  $(1,1)_j$  and  $(1,1)_d$  respectively; the reverse steps c and d are  $(1,1)_j$  and  $(1,1)_d$ . In the alternative mechanism, attack of the chlorine atom is on the C-H bond  $(91+92) \rightarrow [96]$  (step a') continues on to give 97 and 98 (step b'). These two steps are described as  $(1,2)_j$  and  $(1,2)_d$ ; the corresponding reverse processes are  $(1,2)_j$  and  $(1,2)_d$ . The examples until here were of the simple type; the last two examples are complex. In the nucleophilic addition of methylolithium to 4-t-butylcyclohexanone  $(99+100 \rightarrow 101)$  is  $(2,2)_j(1,1)_d$  process and the reverse is  $(1,1)_j(2,2)_d$ . Finally, in the case of acid-base reaction between cyclopentanol and lithium hydride  $(102+103 \rightarrow 104+105)$ , the process is  $(2,2)_j(2,2)_d$ , and so is the reverse.

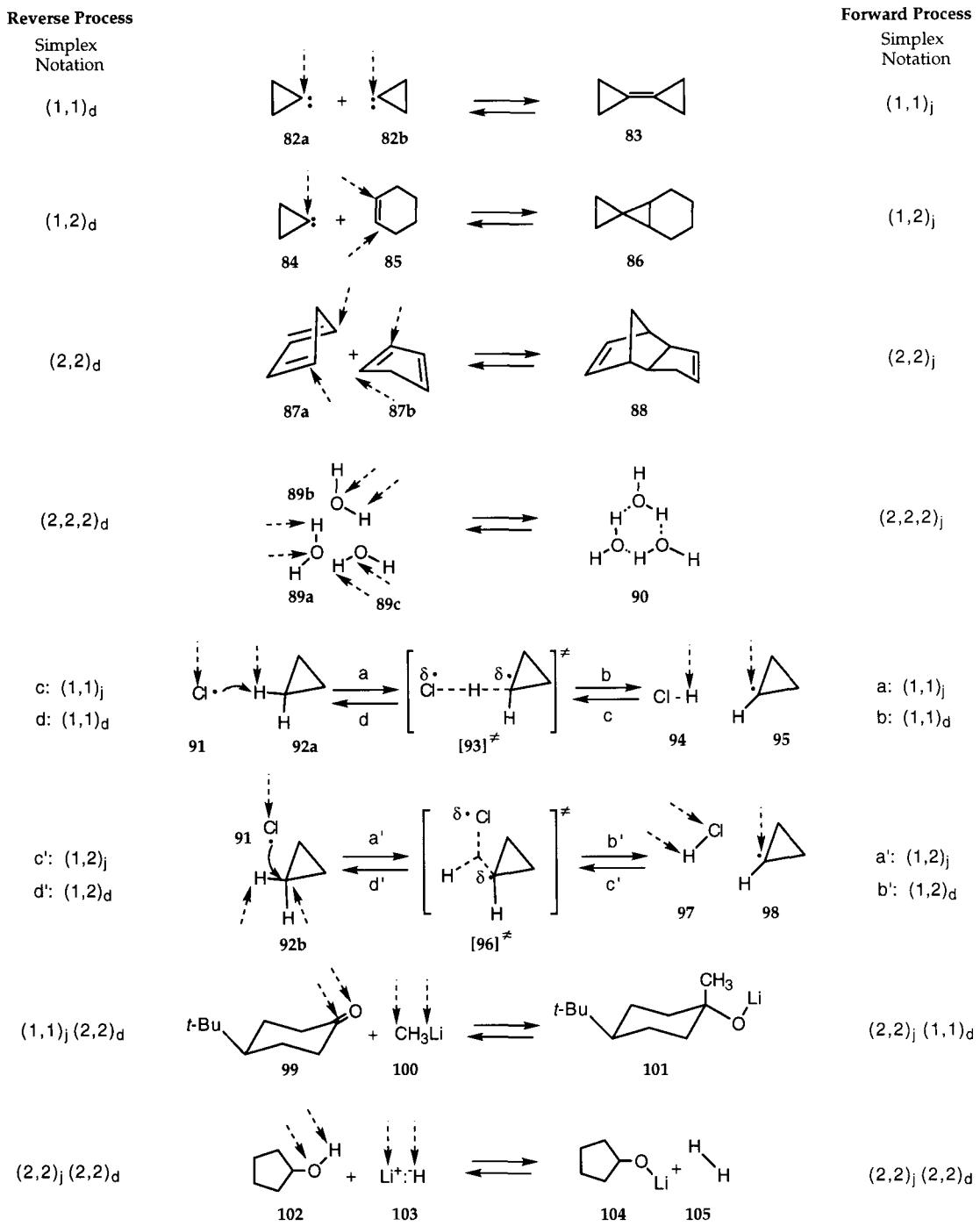


Figure 8.6. Simplex Notation for Junctive/Disjunctive Processes

In these examples, the simplex notation for the forward process is the exact opposite of the reverse process e.g.  $(1,1)_j$  for  $91+92 \rightarrow [93]$  and  $(1,1)_d$  for  $[93] \rightarrow 91+92$ , respectively. It should be noted further that the simplex notation for an overall transformations is equal to the sum of its parts e.g.  $(1,1)_j$  for  $91+92 \rightarrow [93]$  plus  $(1,1)_d$  for  $[93] \rightarrow 94+95$  equals  $(1,1)_j(1,1)_d$  for  $91+92 \rightarrow 94+95$ .

## V. Topological Junctive/Disjunctive Processes

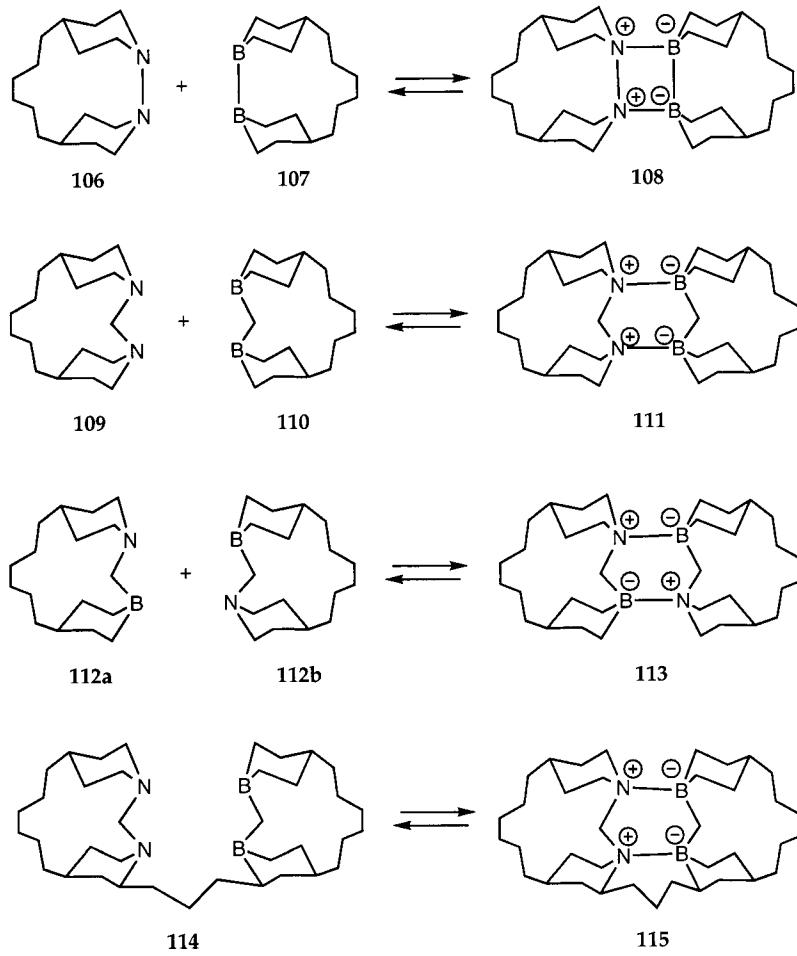
Using the notations for fundamental junctive simplexes given above, each of the hypothetical transformations in Figure 8.7, *viz.*  $106+107 \rightarrow 108$ ,  $109+110 \rightarrow 111$ ,  $112a+112b \rightarrow 113$ , and  $114 \rightarrow 115$ , involves two separate  $(1,1)_j$  processes, and could be described as a  $(1,1)_j(1,1)_j$  or  $(1,1)_j^2$  process. However, it should be noted that the two junctive N atoms, in each of **106** and **109**, constitute a *single topological bijunctive moiety*; so do the two junctive boron sites in each of **107**, and **110**. In the case of **112a** (**112b**), the N and B atoms in the *same* molecule also represent a single topological bijunctive simplex. It is clear that these transformations represent a common topological  $(2_t,2_t)_j$  process (where  $2_t$  designates a *topological bijunctive simplex*, or *topological biplex*). These examples demonstrate convincingly that the concept of junctivity can be extended to complex molecular systems with multijunctive sites. The said extension lays the basis for *topological junctivity*, with the fundamental units being termed *topological simplexes*.

A *topological simplex* is a minimum set of junctive atoms (in a molecule *or* part of molecule) that take part in a junctive process involving another minimum set of junctive atoms in the same or different molecule. The *atomicity* of a *topological simplex* ( $a_t$ ) is the sum of junctive atoms in the minimum set defined above. Thus, each of molecules **106**, **107**, **109**, **110**, and **112a** (**112b**) possesses a topological bijunctive simplex; molecule **114** possesses *two* such simplexes. These examples demonstrate that (a) a single molecule may have one (or more) topological simplex(es), and (b) a given topological simplex must be embedded in one and the same molecule i.e. parts of a topological simplex cannot be in different molecules/molecular fragments.

The associative interaction of two and three topological simplexes (*vide infra*) leads to *simple* topological junctive processes (Figure 8.8, p. 10); these are denoted as  $(m_t,n_t)_j$ ,  $(m_t,n_t,p_t)_j$  for bimolecular and termolecular associations,<sup>9</sup> respectively ( $m_t$ ,  $n_t$ ,  $p_t$  are the atomicities of the participating topological simplexes *i.e.*  $m,n,p=1,2$ ; subscripted suffixes  $j$  and  $d$ , mean junctive and disjunctive, respectively;  $t$  stands for topological). The corresponding reverse (disjunctive) processes are denoted as  $(m_t,n_t)_d$ ,  $(m_t,n_t,p_t)_d$ . Cartoon representations of a few such processes are depicted in Figure 8.8 , along with the abbreviated designations.

Examples of binary associations are exemplified by atom/biplex  $(1,2_t)$  -  $116 \rightarrow [117]$ , and biplex/biplex  $(2_t,2_t)$  -  $118 \rightarrow [119]$ . Similarly, ternary associations atom/atom/biplex  $(1,1,2_t)$ , atom/biplex/biplex  $(1,2_t,2_t)$ , and biplex/biplex/biplex  $(2_t,2_t,2_t)$  are represented by  $120 \rightarrow [121]$ ,  $122 \rightarrow [123]$ , and  $124 \rightarrow [125]$ , respectively. Molecular examples of topological junctive processes are given Figure 8.9 (p. 11).

The minimal β-hairpin of **127** is generated by a  $(2_t,2_t)_j$  junctive process of **126**;<sup>10</sup> the complexation of  $\text{Li}^+$  by 15-crown-5, on the other hand, is a  $(1,5)_j(1,1)_d$  process. The adenine-thymine pairing  $(131+132 \rightarrow 133)^{11}$  is a  $(2_t,2_t)_j$  process, while  $134+135 \rightarrow 136^{12}$  is a  $(3_t,3_t)_j$  process. Rebek's dimerization  $137a+137b \rightarrow 138^{13}$  is a  $(2_t,2_t)_j^2$  process, whereas the association of diamine dioxide **140** with hydrogen peroxide<sup>14</sup> is a  $(1,2_t,1)_j$  process. The aggregation of  $142+143a+143b^{10}$  is a  $(2_t,2_t)_j(3_t,3_t)_j$  process, and the tetramerization of  $145a-d \rightarrow 146^{15}$  is a  $(2_t,2_t)_j^4$  process. Figure 8.9 (p. 11) also gives the designation of the corresponding reverse processes.



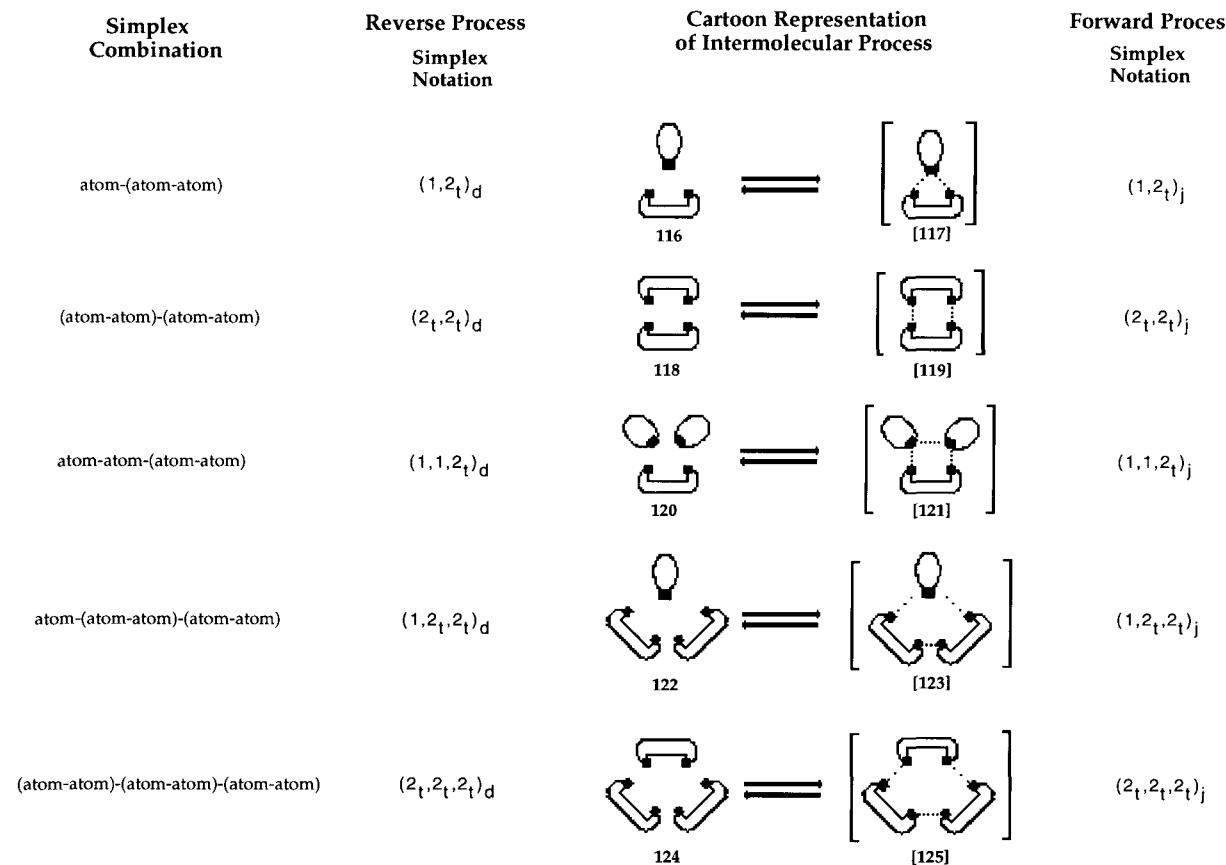
**Figure 8.7.** Hypothetical Examples of Intermolecular and Intramolecular Examples of Topologically Junctive Processes

## VI. Generalized Junctive/Disjunctive Processes

A junctive/disjunctive process may be a composite of both types of simplexes - fundamental and topological. Such a process can be represented by a generalized notation, similar to the ones described above. Figure 8.10 (p. 12) illustrates four representative cases.

The association of a simple biplex with a topological biplex  $(2,2_t)_j$  is represented by  $147 \rightarrow [148]$ . A variant of the latter, with associative interaction between the two atomic sites of the topological biplex  $(2,2_t)_j(1,1)_j$ , is exemplified by  $149 \rightarrow [150]$ . Ternary associations of the type  $(2,2_t)_j(1,1)_j^2$  include termolecular and bimolecular cases  $151 \rightarrow [152]$  and  $153 \rightarrow [154]$ , respectively.

Figure 8.11 portrays the application of the generalized notation to four cases taken from the chemical literature.



**Figure 8.8.** Cartoon Representations of Topological Intermolecular and Intramolecular Junctive/Disjunctive Processes

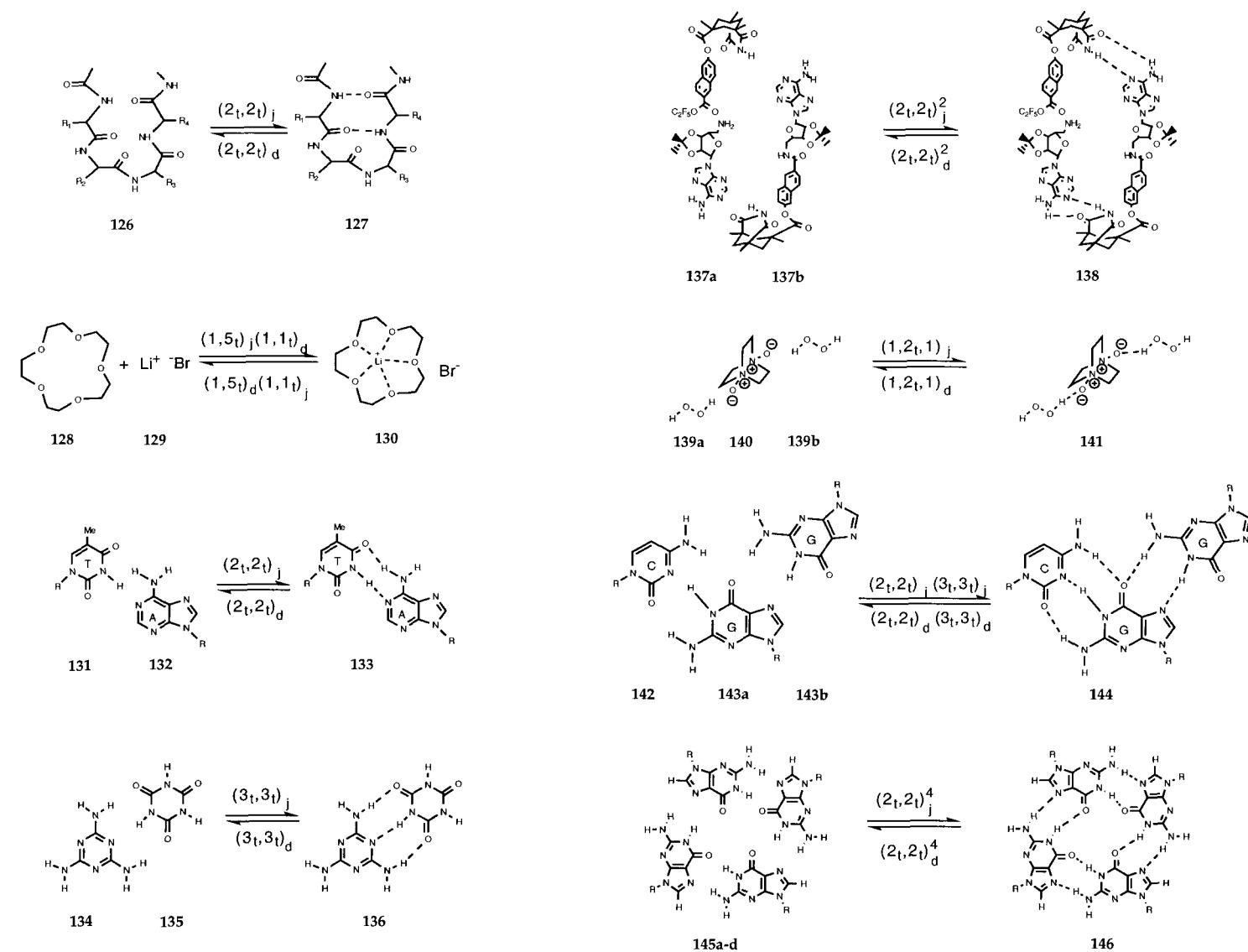
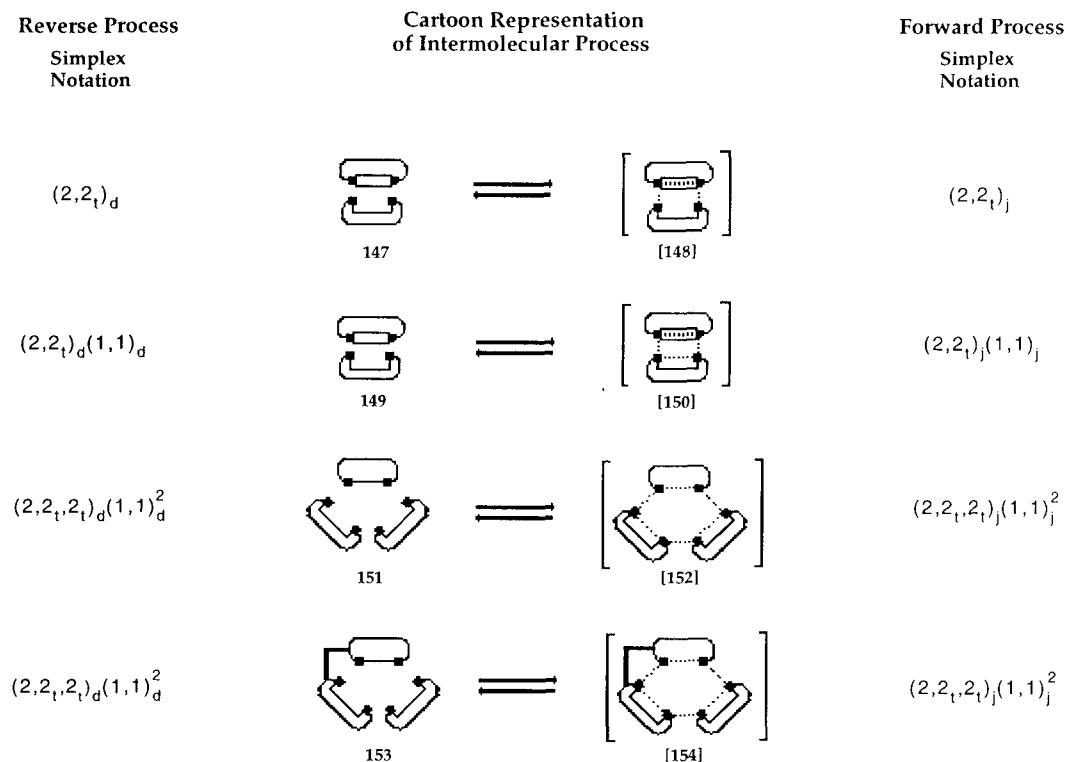
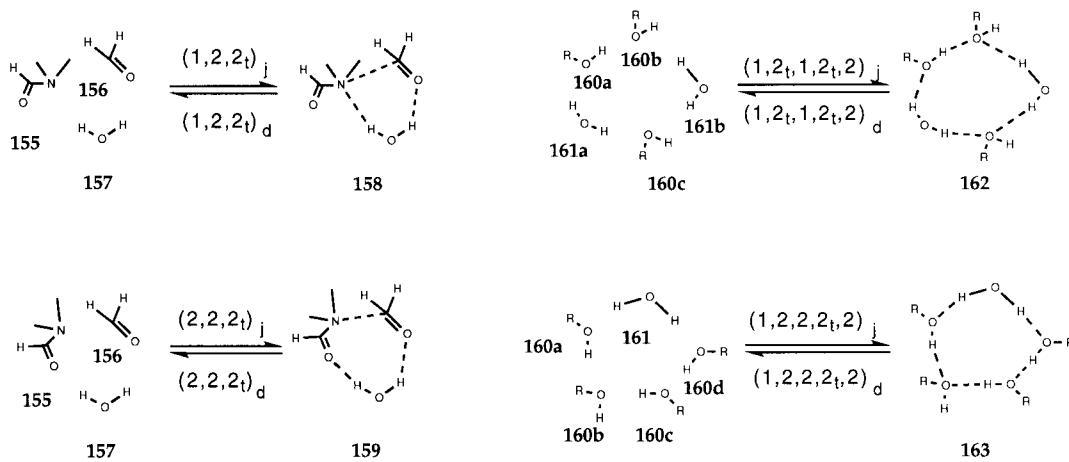


Figure 8.9. Examples of Topological Junctive/Disjunctive Processes



**Figure 8.10.** Cartoon Representation of Composite (Fundamental and Topological) Junctive/Disjunctive Processes



**Figure 8.11.** Examples of Composite Junctive/Disjunctive Processes

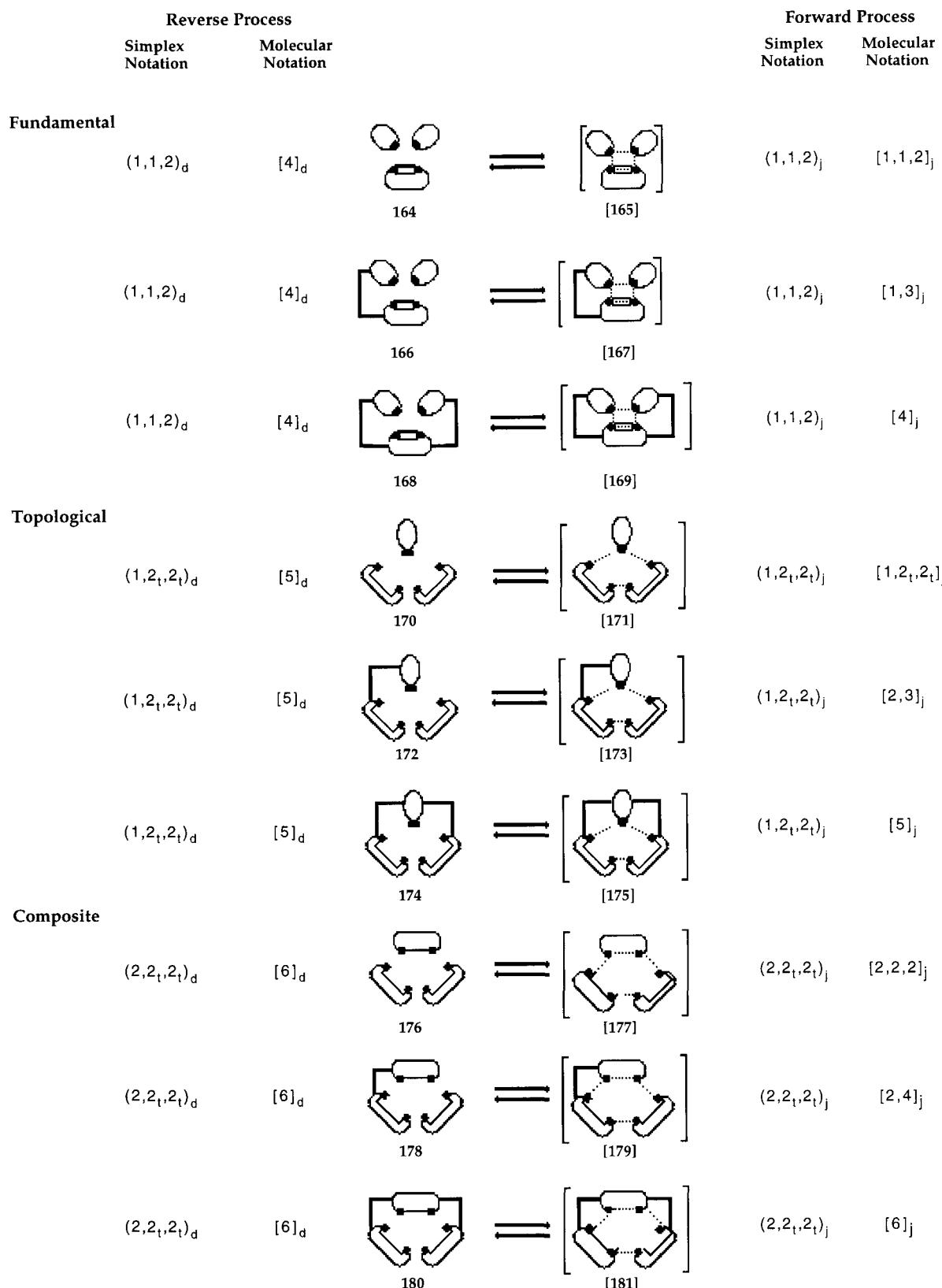
The ternary association of dimethylformamide, formaldehyde and water may occur as a  $(1,2,2_t)_j$  process ( $155+156+157 \rightarrow 158$ ) or a  $(2,2,2_t)_j$  process ( $155+156+157 \rightarrow 159$ ). The pentamolecular association  $160a/b/c+161b/c \rightarrow 165$  is a  $(1,2_t,1,2_t,2)_j$  process, whereas  $160a/b/c/d + 161 \rightarrow 163$  is a  $(1,2,2,2_t,2)_j$  process.<sup>16</sup>

## VII. Molecularity of Junctive/Disjunctive Processes

### Molecular Notation $[m,n,p]_j$ , $[m,n]_j$ and $[m]_j$

The simplex notation for junctive/disjunctive processes - fundamental/topological/composite - is independent of the molecularity of the process; the *simplex* notation of an *intramolecular* process remains *unchanged* in relation to the corresponding intermolecular case. This is a consequence of the fact that junctivity is defined in terms of atomicity of the reacting *simplexes*, and not of *molecules* (*vide infra*). Figure 8.12 depicts three fundamental  $(1,1,2)_{j/d}$  processes -  $164=[165]$ ,  $166=[167]$ ,  $168=[169]$ , three topological  $(1,2_t,2)_{j/d}$  processes -  $170=[171]$ ,  $172=[173]$ ,  $174=[175]$ , and three composite  $(2,2_t,2)_{j/d}(1,1)_{j/d}^2$  processes -  $176=[177]$ ,  $178=[179]$ ,  $180=[181]$ , along with their simplex notations. Figure 8.12 also lists an alternative notation - the molecular notation, that takes into account the molecularity of each forward and reverse process. The latter notation utilizes *square brackets* (instead of parentheses).<sup>17</sup>

Using the molecular notation, the three  $(1,1,2)_j$  forward processes in Figure 8.12 are described as  $[1,1,2]_j$ ,  $[1,3]_j$  and  $[4]_j$ , respectively. For  $164 \rightarrow [165]$ , there are three molecular components, the first component utilizes 1 atom in the junctive process, the second one also utilizes one atom, and the third, two atoms; thus the transformation constitutes a  $[1,1,2]_j$  process. Transformation  $166 \rightarrow [167]$  is a  $[1,3]_j$  process, since there are two molecular components, the first one involving one reacting atom, and the second one, three reacting atoms; in the case of  $[4]_j$  process  $168 \rightarrow [169]$ , there is only one molecule, and that one has four reacting atoms. The reverse processes of the three examples just cited are all unimolecular (each associated form is considered a single molecular entity) and described as  $[4]_{d_j}$ . Similarly, the three  $(1,2_t,2)_{j/d}$  processes of Figure 8.12 are designated as  $[1,2,2]_j$ ,  $[2,3]_j$  and  $[5]_j$ , respectively. The first one,  $170 \rightarrow [171]$ , involves three molecular components - one



**Figure 8.12.** Molecular Notations for Intermolecular and Intramolecular Junctive/Disjunctive Processes

with one atom, and two atoms for each of the other two; process 172 $\rightarrow$ [173] involves two molecules - one with two atomic sites, and the other one with three; lastly, process 174 $\rightarrow$ [175] has one molecule with five reactive atomic sites. The reverse (1,2,<sub>t</sub>2)<sub>d</sub> processes are all unimolecular, and all three are described as [5]<sub>d</sub>, since in each there is one molecule with five atomic sites. Finally, the three (2,2,<sub>t</sub>2)<sub>j</sub>(1,1)<sub>j</sub> processes are designated by molecular notations [2,2,2]<sub>j</sub>, [2,4]<sub>j</sub>, and [6]<sub>j</sub>, respectively, whereas each of the three reverse (2,2,<sub>t</sub>2)<sub>d</sub>(1,1)<sub>d</sub> processes is [6]<sub>d</sub> since each has a single molecule with six atomic sites.

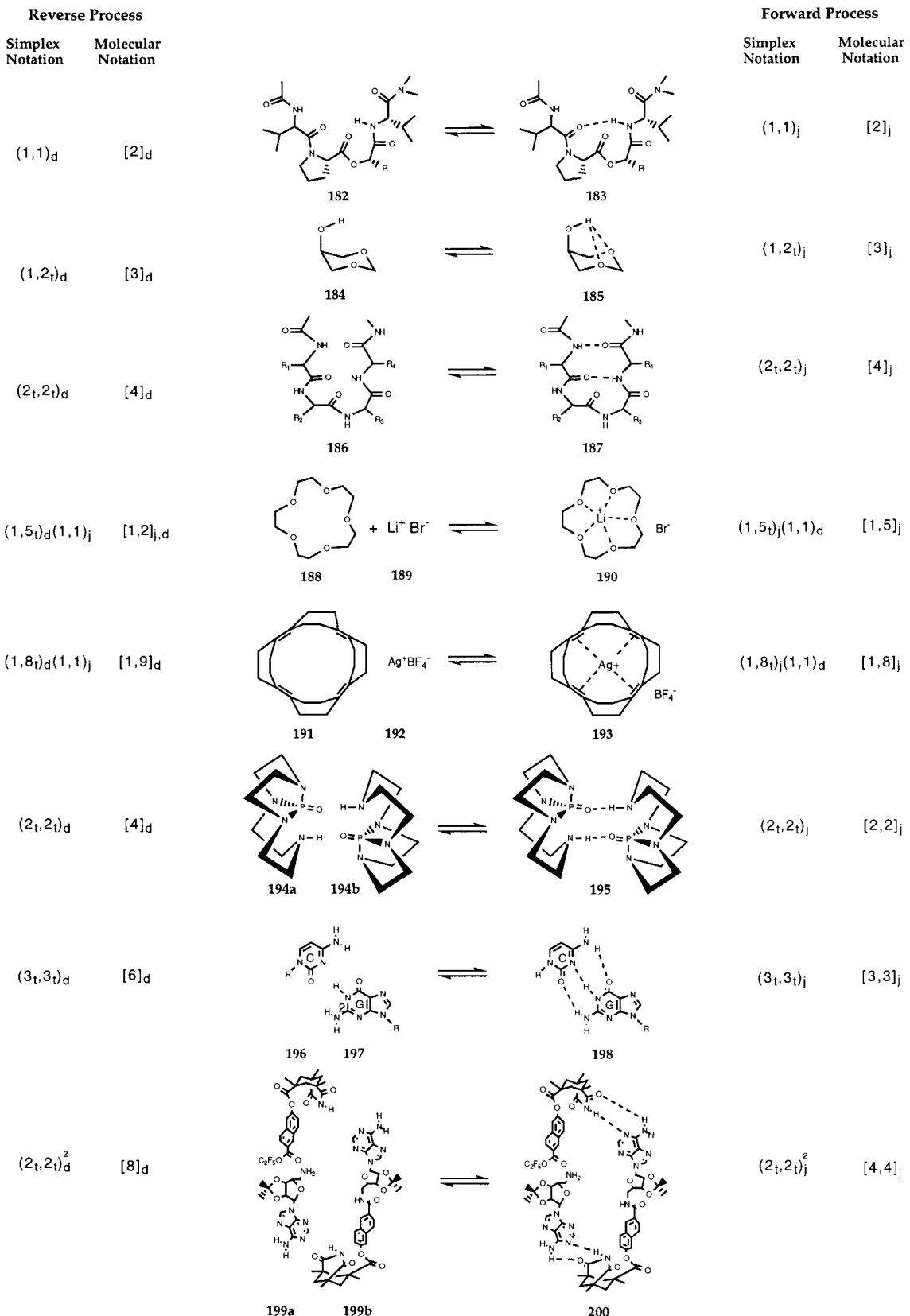
It is clear from these examples that the usefulness of the molecular notation lies in its ability to differentiate between processes of common simplex notation; for example, the three (1,1,2)<sub>j</sub> processes in Figure 8.12 are [1,1,2]<sub>j</sub>, [1,3]<sub>j</sub> and [4]<sub>j</sub>, respectively. The limitation of the molecular notation is seen in dissociative processes; the three (1,1,2)<sub>j</sub> processes are uniformly described as [4]<sub>d</sub>, and thus no differentiation among the three is possible.

Figure 8.13 illustrates the simplex and molecular notations for a number of unimolecular and bimolecular junctive/disjunctive processes taken from the chemical literature. The peptide loop of 183 is (1,1)<sub>j</sub>, the bifurcated H-bond in 185 is (1,2<sub>t</sub>)<sub>j</sub>, and the peptide loop in 187 is (2,<sub>t</sub>2)<sub>j</sub>. The complexation of Li<sup>+</sup> with 15-crown-5, and of Ag<sup>+</sup> with tetraene 191 are described as (1,5<sub>t</sub>)<sub>j</sub>(1,1)<sub>d</sub> and (1,8<sub>t</sub>)<sub>j</sub>(1,1)<sub>d</sub> processes, respectively; the (1,1)<sub>d</sub> components refer to the severance of the ionic "bond". The dimerization of cyclenphosphine oxide 194<sup>18</sup> is a (2,<sub>t</sub>2)<sub>j</sub> process, the C-G pairing in 196+197 $\rightarrow$ 198 is a (3,<sub>t</sub>3<sub>t</sub>)<sub>j</sub> process, while the dimerization of 199 is a (2,<sub>t</sub>2)<sub>j</sub><sup>2</sup> junctive process.

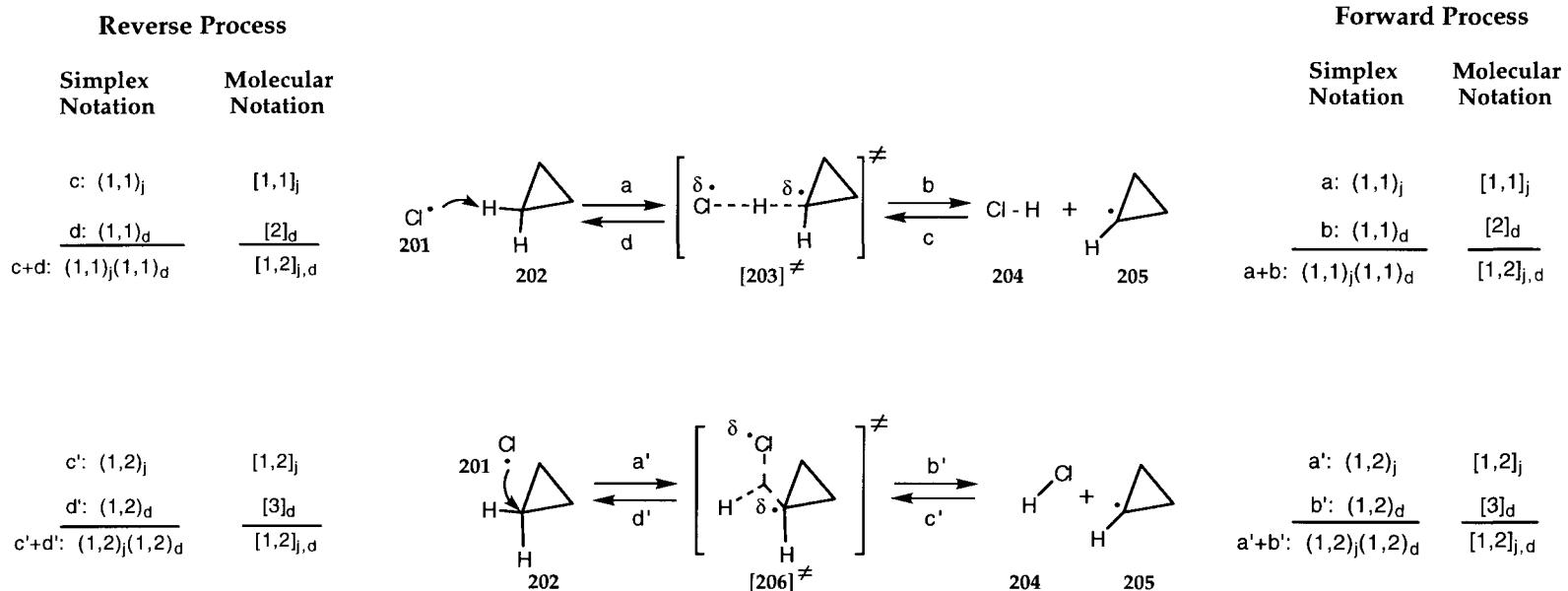
The notation for junctive processes is applicable to mechanisms of organic reactions as well. In the two alternative mechanisms for the free-radical chlorination of cyclopropane, the reaction pathway proceeds towards the transition state through either (1,1)<sub>j</sub>- (201+202 $\rightarrow$ [203] $\neq$ ) or (1,2)<sub>j</sub>- (201+202 $\rightarrow$ [206] $\neq$ ), whereas the transition state transforms into products through either (1,1)<sub>d</sub>- ([203] $\neq$  $\rightarrow$ 204+205) or (1,2)<sub>d</sub>- ([206] $\neq$  $\rightarrow$ 204+205).

Junctive processes of higher order are shown in Figure 8.15 (p. 18). The association of two hydrogen peroxide molecules with diamine dioxide 208 is specified as (1,2,<sub>t</sub>1)<sub>j</sub>; the transformation 210+211+212 $\rightarrow$ 213 is either (1,2,2<sub>t</sub>)<sub>d</sub> (210+211+212 $\rightarrow$ 213) or (2,2,2<sub>t</sub>)<sub>d</sub> (210+211+212 $\rightarrow$ 214), and the hypothetical termolecular C-G-G association 215+216a+216b $\rightarrow$ 217 is a (2,<sub>t</sub>2<sub>t</sub>)(3,<sub>t</sub>3<sub>t</sub>)<sub>j</sub> process. The tetramerization 225a,b,c,d $\rightarrow$ 223 is a (2,<sub>t</sub>2<sub>t</sub>)<sup>4</sup> process, whereas the pentamolecular association of water and alcohols may be described as the result of either (1,2,<sub>t</sub>1,2,<sub>t</sub>2)<sub>j</sub> (220a,b+221a,b,c $\rightarrow$ 222) or (1,2,<sub>t</sub>1,2,<sub>t</sub>2)<sub>j</sub> (220+221a,b,c,d $\rightarrow$ 223) processes.<sup>19</sup>

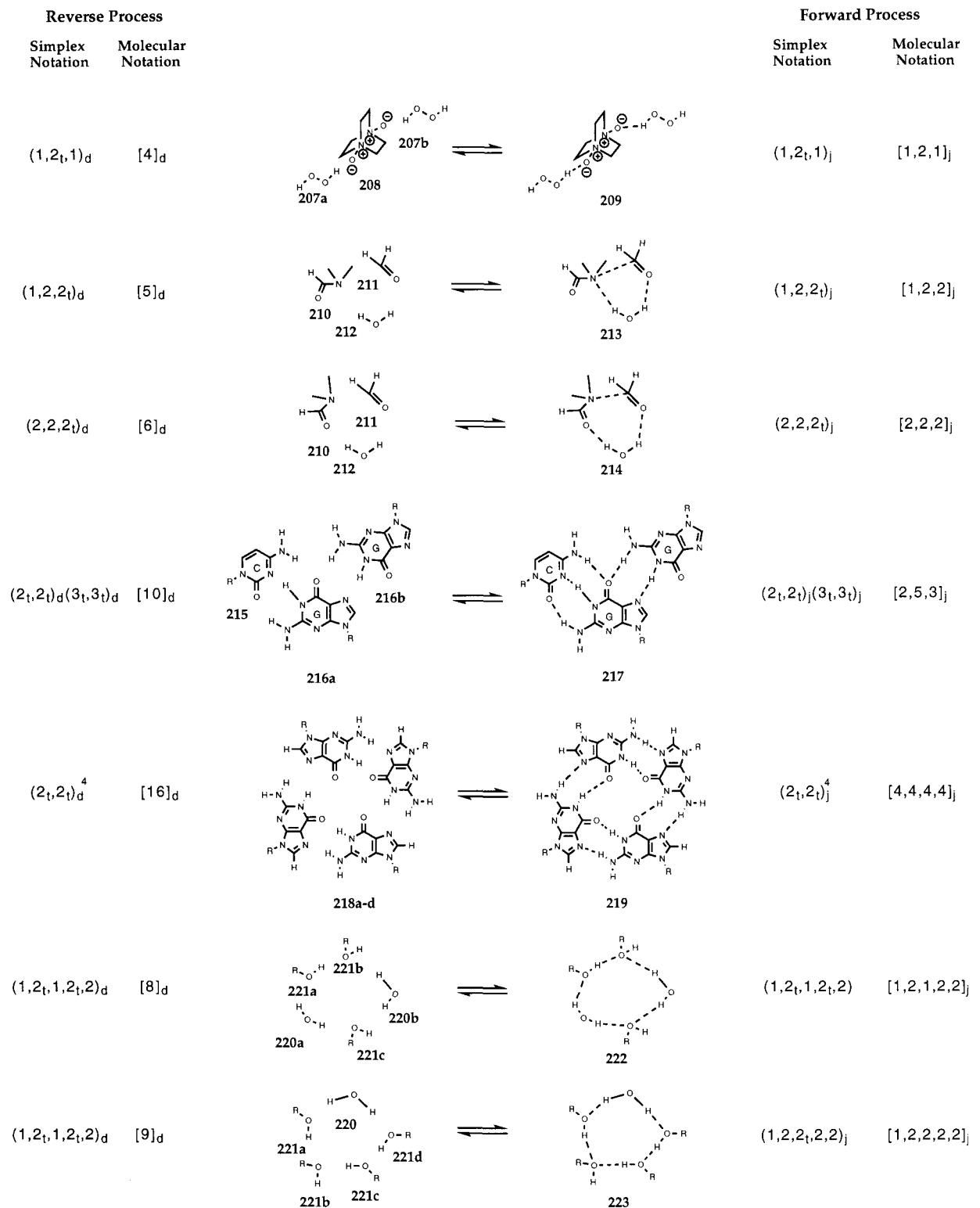
The examples given above show that (a) the simplex notation and molecular notations for a given process may be numerically similar e.g. (2,<sub>t</sub>2)<sub>j</sub> and [2,2]<sub>j</sub> for 194a,b $\rightarrow$ 195, or dissimilar e.g. (1,1)<sub>j</sub> vs. [2]<sub>j</sub> for 182 $\rightarrow$ 183, (b) the *simplex* notations for forward and reverse processes bear a symmetric relationship, e.g. (1,1)<sub>j</sub> for 182 $\rightarrow$ 183 vs. (1,1)<sub>d</sub> for 183 $\rightarrow$ 182 (only the subscripts <sub>j</sub> and <sub>d</sub> are interchanged), (c) the *molecular* notations for the forward and reverse processes are not necessarily numerically similar e.g. [2]<sub>j</sub> for 182 $\rightarrow$ 183 and [2]<sub>d</sub> for 183 $\rightarrow$ 182, respectively, but [4,4]<sub>j</sub> for 199a,b $\rightarrow$ 200 vs. [8]<sub>d</sub> for 200 $\rightarrow$ 199a,b, (d) the *simplex* notation for an overall transformation is always equal to the sum of its parts: 201+202 $\rightarrow$ [203] $\neq$  $\rightarrow$ 204+205 is (1,1)<sub>j</sub>(1,1)<sub>d</sub>, and 201+202 $\rightarrow$ [206] $\neq$  $\rightarrow$ 204+205 is (1,2)<sub>j</sub>(1,2)<sub>d</sub>; the reverse processes have similar designations (subscripts <sub>d</sub> and <sub>j</sub> are interchanged) (e) the *molecular* notation for an overall transformation is not necessarily equal to the sum of its parts, 201+202 $\rightarrow$ 204+205  $\neq$  {201+202 $\rightarrow$ [203] $\neq$ } + {[203] $\neq$  $\rightarrow$ 204+205} i.e. [1,2]<sub>j,d</sub>  $\neq$  [1,1]<sub>j</sub> + [2]<sub>d</sub>, (f) the *simplex* notation for an overall transformation is dependent on the path (mechanism), 201+202 $\rightarrow$ [203] $\neq$  $\rightarrow$ 204+205  $\neq$  201+202 $\rightarrow$ [206] $\neq$  $\rightarrow$ 204+205 i.e. (1,1)<sub>j</sub>(1,1)<sub>d</sub>  $\neq$  (1,2)<sub>j</sub>(1,2)<sub>d</sub>; (g) the molecular notation for an overall transformation is independent of the path (mechanism); [1,2]<sub>j,d</sub> stands for both mechanisms 201+202 $\rightarrow$ [203] $\neq$  $\rightarrow$ 204+205 and for 201+202 $\rightarrow$ [206] $\neq$  $\rightarrow$ 204+205.



**Figure 8.13.** Examples of Unimolecular and Bimolecular Junctive Processes



**Figure 8.14.** Examples of Unimolecular and Bimolecular Junctive Processes



**Figure 8.15.** Examples of Composite Trimolecular, Tetramolecular and Pentamolecular Junctive Processes

## VIII. Notations for Junctive/Disjunctive Processes

Figure 8.16 (p. 20) summarizes the interrelationships between junctive simplexes and processes derived from them.

A junctive simplex is either *fundamental* ( $m,n,p$ ; not subscripted) or *topological* ( $m_t,n_t,p_t$ ; subscript  $t$  means a topological simplex). Monoatomic simplexes are always fundamental and are not subscripted.

Processes may involve *junctive* and/or *disjunctive* simplexes (subscripts  $j$  and  $d$  mean junctive and disjunctive components, respectively):<sup>19</sup>

junctive:  $(m,n)_j, (m,n,p)_j, (m_t,n_t)_j, (m_t,n_t,p_t)_j$   
disjunctive:  $(m_t,n_t)_d, (m,n,p)_d$

Fundamental junctive/disjunctive processes (shown in square parentheses) are derived from fundamental simplexes, and are either *simple* or *complex*:

simple:  $(m,n)_j, (m,n,p)_j, (m_t,n_t)_d, (m,n,p)_d$  (only junctive or disjunctive components are found)  
complex:  $(m,n)_j(m,n)_d$  (both junctive and disjunctive components are present).

Topological junctive/disjunctive processes (shown in square parentheses) are derived from topological simplexes and are also either *simple* or *complex*:

simple:  $(m_t,n_t)_j, (m_t,n_t,p_t)_j, (m_t,n_t)_d, (m_t,n_t,p_t)_d$  (only junctive or disjunctive components are found)  
complex:  $(m_t,n_t)_j(m_t,n_t)_d$  (both junctive and disjunctive topological components are present).

Composite junctive/disjunctive processes (shown in square parentheses) are derived from fundamental and topological simplexes, and are either *simple* or *complex*:

simple:  $(m,n)_j, (m_t,n,p_t)_j, (m_t,n)_d, (m,n,p_t)_d$  (simplexes are junctive or disjunctive)  
complex:  $(m_t,n_t)_j(m_t,n_t)_d$  (both junctive and disjunctive topological components are included).

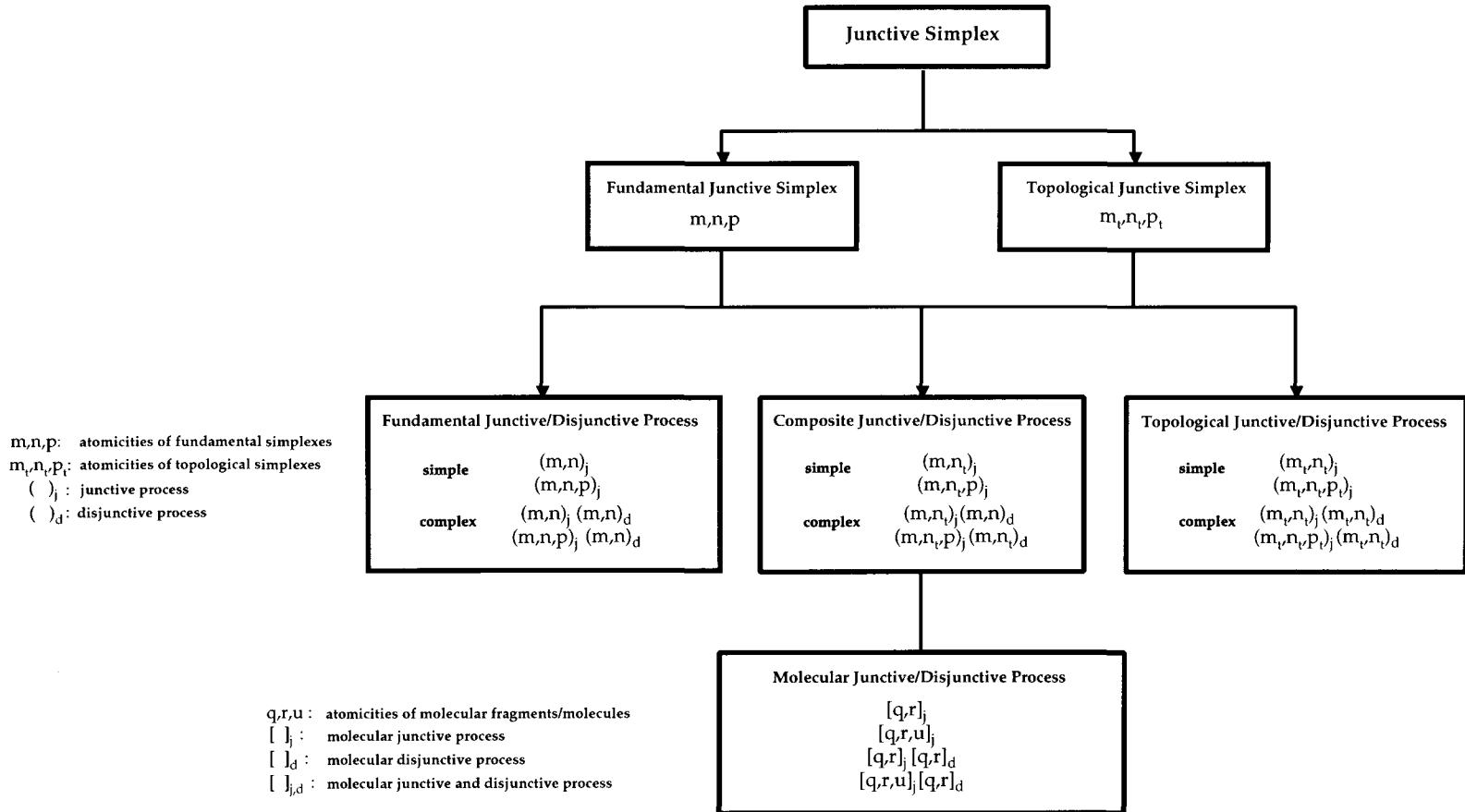
Molecular junctive/disjunctive processes (shown in square brackets) are derived from molecules with fundamental and topological simplexes, and are also either *simple* or *complex*:

simple:  $[m,n]_j, [m_t,n,p_t]_j, [m_t,n]_d, [m,n,p_t]_d$  (simplexes are junctive or disjunctive)  
complex:  $[m_t,n_t][m_t,n_t]_d$  (both junctive and disjunctive topological components are involved).

Note that (a) binary components precede ternary ones, (b) within binary sets, the numerically smaller set is specified first (the same is true of ternary ones), and (c) for numerically identical sets, the junctive precedes the disjunctive.

## IX. Junctivity Matrices

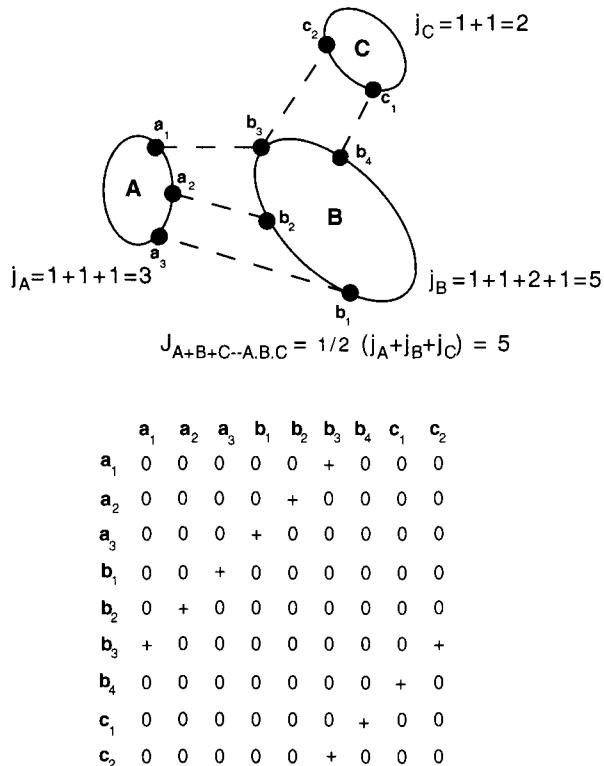
In describing junctive/disjunctive processes, with increasing numbers of interacting molecular entities, and increasing number of interactions between different reactive sites, the denotation can



**Figure 8.16.** Summary of Notations for Fundamental, Composite and Topological Simplexes and Fundamental, Composite and Topological Processes, and, Molecular Junctive/Disjunctive Processes

become cumbersome. Indeed, the exact and complete way to specify junctivity is through tables of junctivity (*vide infra*). This is similar to constructing constitution matrices.<sup>20</sup> We consider here the termolecular [3,5,2] association between 215, 216a and 216b with three, four and two junctive sites, respectively (Figure 8.15). The junctivity between A and B is (3,3)<sub>j</sub>, that between B and C is (2,2)<sub>j</sub>; hence, the complete forward process may be described as (3,3)<sub>j</sub>(2,2)<sub>j</sub>. The exact junctivities of the different sites are unclear in this denotation; hence, the need for a matrix (Figure 8.17).

In the matrix, a zero indicates no junctivity; a + sign indicates junctivity between the atoms taking part in the new bonding, e.g. those between A and B - a<sub>1</sub>/b<sub>3</sub>, a<sub>2</sub>/b<sub>2</sub> and a<sub>3</sub>/b<sub>1</sub>. The bonding between B and C is clearly given in the matrix with the + sign appearing for b<sub>3</sub>/c<sub>2</sub> and c<sub>1</sub>/b<sub>4</sub>; it so happens that b<sub>3</sub> is being linked to a<sub>1</sub> in A, and c<sub>2</sub> in C.



**Figure 8.17.** Junctivity Matrix of a Ternary System ABC

#### X. Net Atom Junctivity ( $j_a$ ), Molecular Junctivity ( $j_m$ ), Process Junctivity ( $J_{\text{for}}/J_{\text{rev}}$ )

It is possible to evaluate the junctivity of the overall forward or reverse junctive/disjunctive process numerically, by analyzing the changes in junctivity/disjunctivity at each of the participating/reacting atoms. Such an analysis requires defining *net atom junctivity* ( $j_a$ ) for a

given reacting atom, *simplex junctivity* ( $j_s$ ) for each reacting simplex, and *molecular junctivity* ( $j_m$ ) for each molecule/molecular fragment. Thence, each forward transformation is characterized by *forward process junctivity* ( $J_{\text{for}}$ ), and each reverse transformation, by *reverse process junctivity* ( $J_{\text{rev}}$ ) (*vide infra*).

*Net atom junctivity*,  $j_a$ , of atom X, is the net number of new incipient directed bonds between X and atoms it becomes bonded to. It is the number of incipient directed bonds minus the number of severed directed bonds, and is given by Equation 8.1:

$$j_a = j_j - j_d \quad (8.1)$$

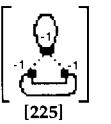
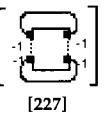
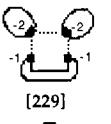
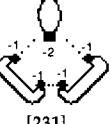
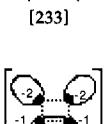
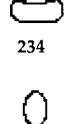
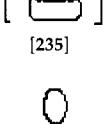
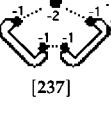
*Atom junctivity*,  $j_j$ , of a reacting atom X, is the number of incipient directed bonds it forms with other junctive sites, along the reaction path, intramolecularly or intermolecularly.<sup>21</sup> X is monojunctive, bijunctive, trijunctive,..., n-junctive an *atom*, if it forms 1,2,3,...n directed bonds ( $j_j=1,2,3,\dots,n$  respectively). The actual  $j_j$  value of X varies from one transformation to another. In Figure 8.14 (p. 17), for example, in the linear approach of Cl. to a C-H bond in cyclopropane to give an apex-chlorinated transition state ( $201+202 \rightarrow [203]^{\neq}$ ),  $j_j$  value of Cl. is 1, because it attacks a single H atom. However,  $j_j=2$  for Cl. in its perpendicular approach to a C-H bond of cyclopropane, to give an edge-chlorinated cyclopropane in the transition state ( $201+202 \rightarrow [206]^{\neq}$ ); in the latter case, both atoms of the C-H bond simplex are attacked. It should be noted, however, that the junctive *atomicity* of Cl. ( $a_s$ ) in both cases is 1 (*vide supra*). In the reaction of cyclopropylidene 82a with itself,  $82a+82b \rightarrow 83$  (Figure 8.6), the  $j_j$  value of the carbenic atom is 2; it is also 2 in the addition reaction with cyclohexene,  $84+85 \rightarrow 86$ . In the former case, the junctive atomicity of the carbenic carbon is 1, while in the latter, it is 2 (*vide supra*).

*Atom disjunctivity*,  $j_d$ , for an atom X is the number of incipient directed bonds totally being severed from X along the reaction path. In the reverse direction of the above three processes, the "bonded X atom" is transformed to its original bonding state, and  $j_d=-j_j$ . In  $[93]^{\neq} \rightarrow 91+92$ , for the Cl,  $j_j=-1$ ; in  $[96]^{\neq} \rightarrow 91+92$  for the Cl,  $j_j=-2$ ; in  $83 \rightarrow 82a+82b$ , for C,  $j_j=-1$ , and in  $86 \rightarrow 84+85$ ,  $j_j=-2$  for the C.

Note that (a)  $j_a > 0$  if  $j_j > j_d$ ;  $j_a < 0$  if  $j_j < j_d$ ;  $j_a = 0$  if  $j_j = j_d$ , and (b)  $j_a = j_j$  in purely junctive ( $j_d = 0$ ) processes, and  $j_a = j_d$  in purely disjunctive ( $j_j = 0$ ) processes. In the *overall* addition of HBr addition to cyclopropane,  $5+6 \rightarrow 8$  (Figure 8.2, p. 3),  $j_a$  of C1 (and of C2) is  $+1-1=0$ ; in contrast, the carbonyl carbon of 9 in the  $9+10 \rightarrow 11$  has a  $j_a$  value of +1. In the reverse transformation,  $11 \rightarrow 9+10$ , the  $j_a$  value of the carbinolic C is -1.<sup>22</sup>

*Molecular junctivity* ( $j_m$ )<sup>23</sup> characterizes a molecule/molecular reactant M undergoing a given transformation through its reacting simplexes - fundamental or topological. M is monojunctive, bijunctive, trijunctive,..., n-junctive a *molecule*, with  $j_m = 1,2,3,\dots,n$ , respectively.<sup>24</sup> Molecular junctivity is defined for pragmatic reasons. While the concept of topological junctivity emphasizes the similarity between the *simplexes* in an interacting set, molecular junctivity, in contradistinction, reflects the junctivity between *molecules* of an interacting set.

Finally, on the basis of  $j_m$  (*vide supra*), we define *forward process junctivity* ( $J_{\text{for}}$ ) and *reverse process junctivity* ( $J_{\text{rev}}$ ). The former term is the net gain of incipient directed bonds in the process (proceeding in the forward direction), whereas the latter term is the net gain of

Reverse	$J_{rev}$	Cartoon Representation ( $j_a$ values)	$J_{for}$	Forward Process	
$(1,2_t)_d$	-2	 [224]	 [225]	+2	$(1,2_t)_j$
$(2,2_t)_d$	-2	 [226]	 [227]	+2	$(2,2_t)_j$
$(1,1,2_t)_d$	-3	 [228]	 [229]	+3	$(1,1,2_t)_j$
$(1,2_t,2_t)_d$	-3	 [230]	 [231]	+3	$(1,2_t,2_t)_j$
$(2_t,2_t,2_t)_d$	-3	 [232]	 [233]	+3	$(2_t,2_t,2_t)_j$
$(1,1,2)_d$	-3	 [234]	 [235]	+3	$(1,1,2)_j$
$(1,2_t,2_t)_d$	-3	 [236]	 [237]	+3	$(1,2_t,2_t)_j$
$(2,2_t,2_t)_d$	-3	 [238]	 [239]	+3	$(2,2_t,2_t)_j$

**Figure 8.18.** Cartoon Representations of  $j_a$  values and  $J_{for}$  and  $J_{rev}$

incipient directed bonds for r molecular entities in the process (proceeding in the forward direction):

$$J_{\text{for}} = 1/2 \sum_r j_m \quad (8.6)^{25}$$

The *reverse process junctivity* ( $J_{\text{rev}}$ ) is the negative of the *forward process junctivity* ( $J_{\text{for}}$ ):

$$J_{\text{rev}} = -J_{\text{for}} \quad (8.8)$$

Figure 8.18 depicts cartoon representations along with the  $j_a$ ,  $J_{\text{for}}$  and  $J_{\text{rev}}$  values for representative examples.

In the first transformation of Figure 8.18,  $224 \rightarrow [225]$ ,  $J_{\text{for}} = 1/2 [(1+1) + (1+1)] = +2$ ;  $J_{\text{rev}} = 1/2 [(-1-1) + (-1-1)] = -2$ , or  $J_{\text{rev}} = -J_{\text{for}} = -(+2) = -2$ . In the case of  $228 \rightarrow [229]$ ,  $J_{\text{for}} = 1/2 [(2+1) + (2+1)] = +3$  and  $J_{\text{rev}} = -3$ . The  $j_a$  values needed to calculate  $J_{\text{for}}$  are always those for the reactant(s) e.g. 224 and 228; the  $j_a$  values needed to calculate  $J_{\text{rev}}$  are those given for the "reactant(s)" of the reverse process i.e. [225] and [229]. Similar considerations apply to the other examples in Figure 8.18.  $J_{\text{for}}$  and  $J_{\text{rev}}$  values are presented for a number of literature cases in Figure 8.19.

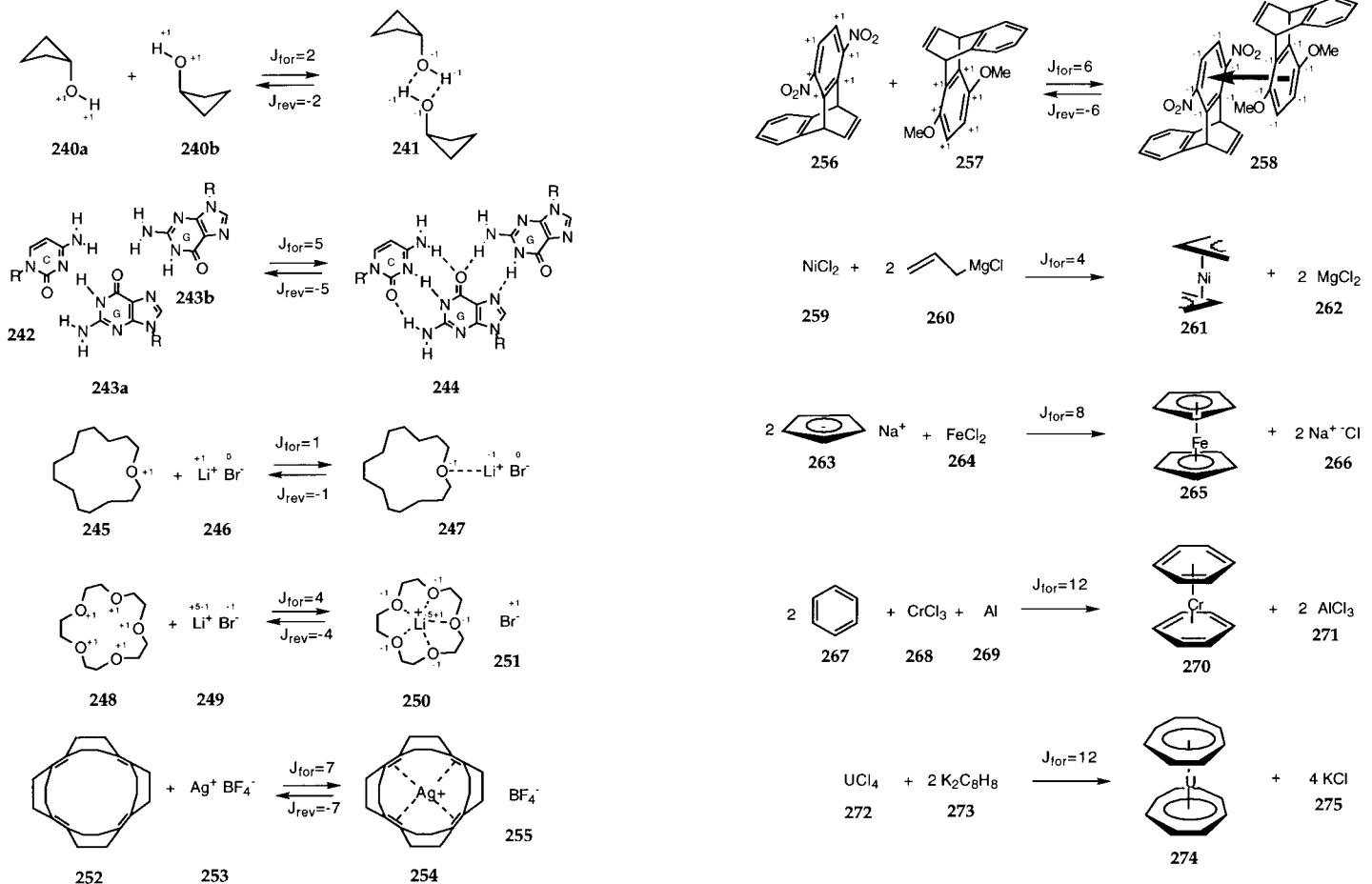
The dimerization of cyclobutanol has a  $J_{\text{for}}$  value of 2; the termolecular C-G-G association has a  $J_{\text{for}}$  value of +5. The coordination of LiBr with macrocycle 245 has a  $J_{\text{for}}$  value of +1 (assuming that Li is still in the bonding vicinity of Li; in contradistinction, the complexation of LiBr with 15-crown-5 has a  $J_{\text{for}}$  value of +4 (here, the severance of LiBr "bond" is assumed to be complete). For the complexation of  $\text{Ag}^+$  with macrocyclic tetraene 252,  $J_{\text{for}} = +7$ ; here too, the formal ionic bond with fluoroborate is considered completely severed, because of the necessary physical separation between  $\text{Ag}^+$  and  $\text{BF}_4^-$ . The  $\pi$ -complexation  $256+257 \rightarrow 258$  is characterized by  $J_{\text{for}} = +6$ ; the atomic junctivities are shown in Figure 8.19. Finally, the formation of organometallic complexes 261, 265, 270 and 274 have  $J_{\text{for}}$  values of +4, +8, +12 and +12 respectively.

$J_{\text{for}}$  and  $J_{\text{rev}}$  are useful in describing individual mechanistic steps, as in the reaction of cyclopropane with hydrogen bromide -  $276+277 \rightarrow 278 \rightarrow 279$  (Figure 8.20, p. 26).

In determining  $J_{\text{for}}$  for the first forward step ( $276+277 \rightarrow 278a$ ), we note that one must utilize the  $j_a$  values for reactants 276 and 277; for the second forward step  $278a \rightarrow 279$ , one uses the  $j_a$  values shown for "reactant" 278. In determining  $J_{\text{rev}}$  for  $279 \rightarrow 278b$  we need the  $j_a$  values shown for "reactant" 279, and in going from 278b to 276+277, we use the  $j_a$  values marked for "reactant" 278b. Note that 278a and 278b bear different sets of  $j_a$  values, since each set is for the process that follows - in the forward or reverse direction.

$J_{\text{for}}$  and  $J_{\text{rev}}$  are also useful in distinguishing between alternative mechanisms for the same overall transformation e.g.  $280+281 \rightarrow [282]^{\neq} \rightarrow 283+284$  vs.  $280+281 \rightarrow [285]^{\neq} \rightarrow 283+284$ .

For the former sequence,  $J_{\text{for}} = +1$  and  $-1$  for the forward pathways; for the latter sequence  $J_{\text{for}} = +2$  and  $-2$ . For the reverse pathways,  $J_{\text{rev}} = +1$  and  $-1$  for the first mechanism, and  $J_{\text{rev}} = +2$  and  $-2$  for the second mechanism.



**Figure 8.19.**  $J_{\text{for}}$  and  $J_{\text{rev}}$  for Various Junctive/Disjunctive Transformations

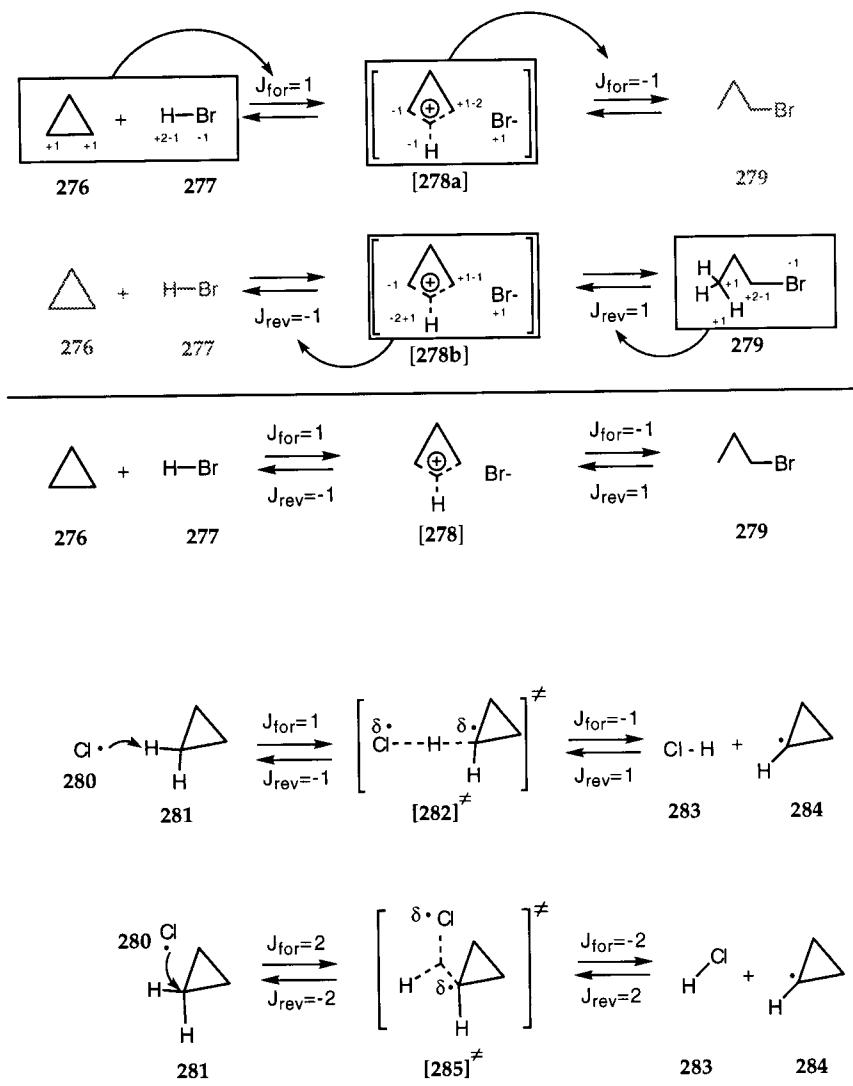


Figure 8.20.  $J_{\text{for}}$  and  $J_{\text{rev}}$  for Various Junctive/Disjunctive Transformations

In sum,  $J_{\text{for}}$  is a quantitative index of the efficacy of construction of assembled frameworks; the more positive the  $J_{\text{for}}$  value, the higher the degree of association or assembly. The efficacy of the breakdown of organic frameworks is also quantitatively assessed in terms of  $J_{\text{for}}$ ; the more negative the  $J_{\text{for}}$  value (the more positive the  $J_{\text{rev}}$ ) is, the greater the extent of disassembly would be. Examples 244, 250, 254, 258, 261, 265, 270, 274 have  $J_{\text{for}}$  values of 4-12, indicative of relatively high degrees of junctivity. The reverse processes would correspondingly exhibit high degrees of disjunctivity. If a chemical equation is balanced, one must take into account all associative and dissociative components. It is of course possible to define  $J_{\text{for}}$  and  $J_{\text{rev}}$  for unbalanced equations; here, the comparison would be between similar (and similarly unbalanced) processes.

The concept of the junctivity lays the framework for discussing the concepts of ligogenicity (Chapter 9), vectoselectivity (Chapter 13), and regioselectivity (Chapter 13).

## XI. Usefulness of the Concept of Junctivity

### A. Valency, Coordination Number and Atom Junctivity

The concept of *atom junctivity* differs from the concepts of valency and coordination number. The *valency* of atom X in a given molecule M refers to the number of *bonds* between X and all its immediate neighbors. The coordination number is the number of neighboring *atoms* bonded to X in molecule M. Thus, valency and coordination number characterize atom X in a given "static" state of molecule M. In contrast, net atom junctivity of X ( $j_j$ ) characterizes a *change in bonding* of X for a specified *process* involving molecule M (from ground state to transition state/other ground state (intermediate, or product)), or from transition state to ground state (reactant, product, or intermediate). In Figure 8.21 below, the divalent, monocoordinate oxygen of HMPA **286a** is monojunctive, whereas the corresponding divalent, monocoordinate O in **286b** is bijunctive. In the reverse processes, trivalent, dicoordinate oxygen of **289** is monodisjunctive, while the tetravalent, tricoordinate oxygen in **290** is bisdisjunctive;  $j_j$  for the oxygen in the said transformation is +2.<sup>26</sup>

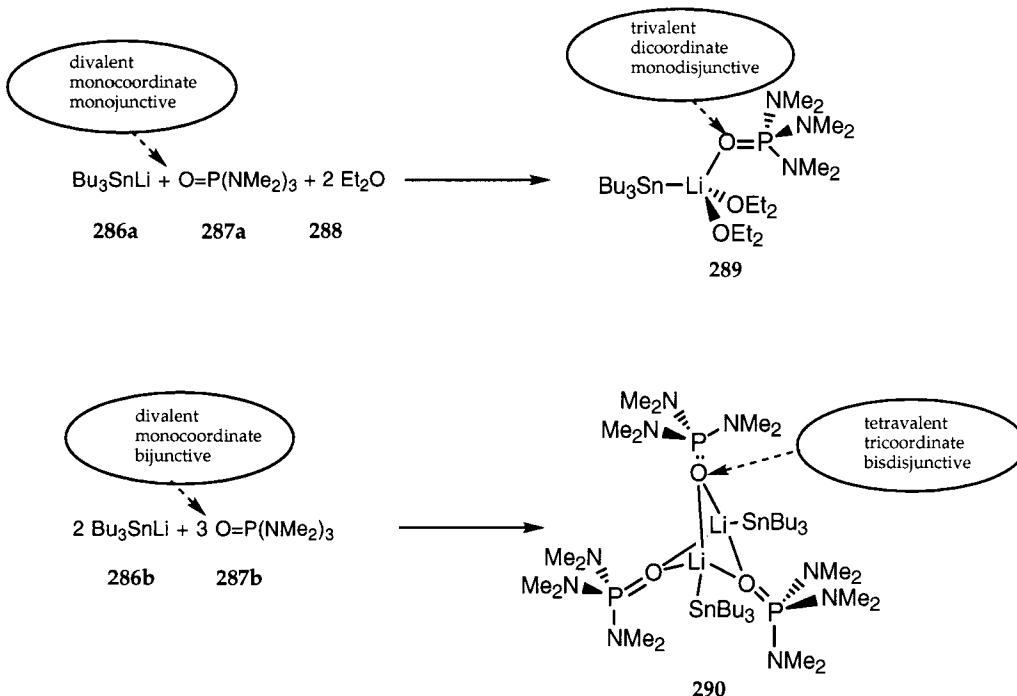


Figure 8.21. Valency, Coordination Number, and Atom Junctivity

These examples show that *atom junctivity/disjunctivity* differs from and complements the concepts of valency and coordination number.

## B. "Dentateness" and Atom Junctivity

In organometallic systems, the number of donor atoms on the ligand molecule determines the number of connections the ligand makes to the central atom. Thus, an n-dentate ligand contributes n donor atoms. For example, 15-crown-5 (248, Figure 8.19, p. 25) with five donor atoms is a pentadentate ligand. In the complexation process,  $\text{Li}^+$  is pentajunctive. Thus junctivity characterizes the bonding changes on the central  $\text{Li}^+$  ion, while "dentateness" describes the number of junctive sites of the ligand. The net atomic junctivity  $j_a$  of  $\text{Li}^+$  is +4. In the reverse (dissociation) process,  $j_a = -4$  for the complexed  $\text{Li}^+$  of 250 (there are 5 disconnections and 1 reconnection).

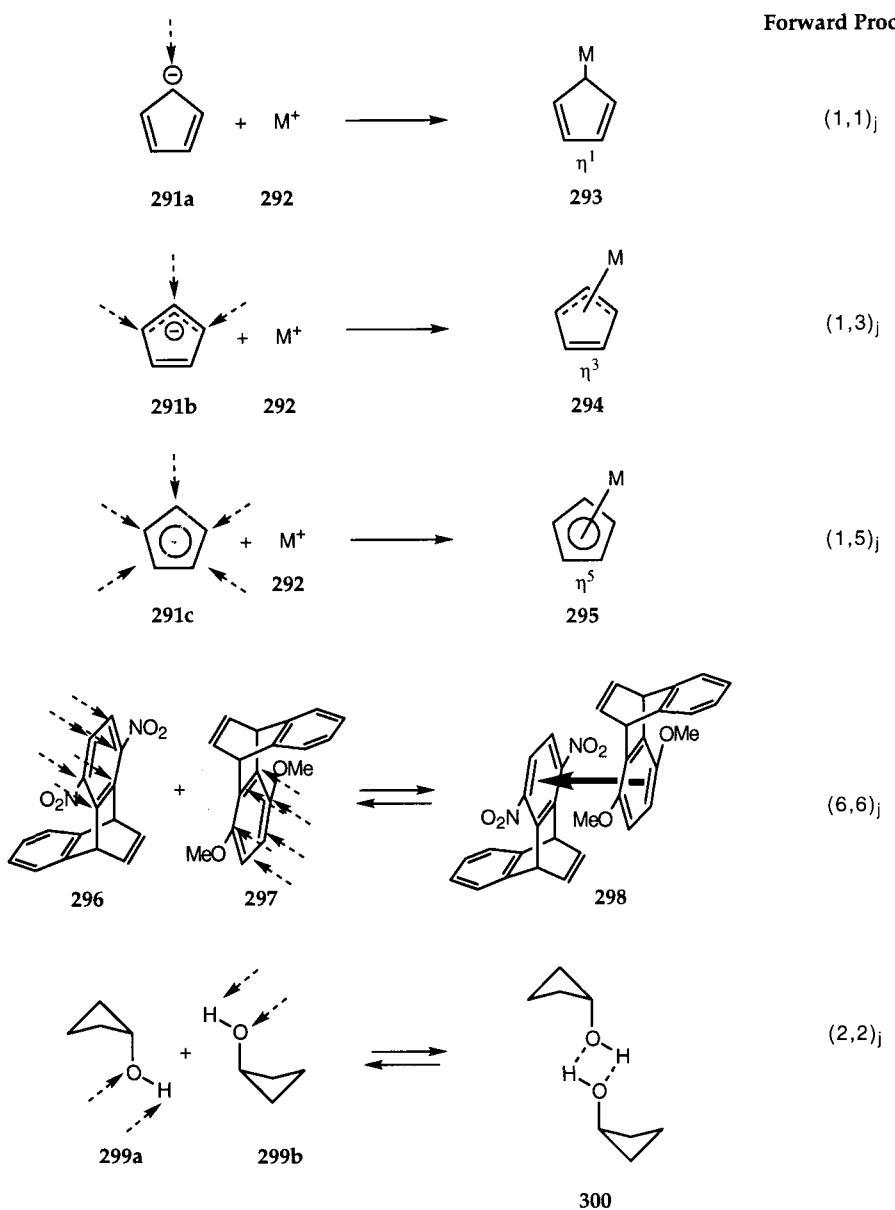


Figure 8.22.  $\eta$  and  $(m,n)_j$  Notations

## XII. Usefulness of Process Notation ( $m,n$ )<sub>j</sub>

### A. $(m,n)_j$ vs. Woodward-Hofmann's $[m,n]$ Notation

The  $(m,n)_j$  notation given here bears a certain similarity to Woodward-Hofmann's  $[m,n]$  notation for cycloaddition reactions. Nevertheless, the two are distinct. Thus the  $[\pi_2+\pi_2]$  cycloaddition  $12+13 \rightarrow 14$  (Figure 8.2, p. 3) is a  $(2,2)_j$  junctive process; the numbers are coincidentally identical. Cycloaddition reactions of the type  $[\pi_2+\pi_4]$ ,  $[\pi_4+\pi_4]$ ,  $[\pi_2+\pi_6]$  etc. are also  $(2,2)_j$  junctive processes. The  $(2,2)_j$  notation also applies to the transition states, as well as the products, in all these cycloadditions.

### B. $(m,n)_j$ vs. $\eta$

In organometallic *molecules* of the type  $M^+.L$ , the number of atoms of the ligand L bonded to the *single*, central, *metal* ion  $M^+$ ,<sup>27</sup> is designated by the  $\eta$  (eta) descriptor as in the  $\eta^1$ ,  $\eta^3$ ,  $\eta^5$  – cases 293, 294, and 295, respectively (Figure 8.22).

The *transformations* to generate 293, 294, and 295 (say by  $M^+ + L \rightarrow M^+.L$ ) may be described as  $(m,n)_j$  processes *viz.*  $(1,1)_j$ ,  $(1,3)_j$ ,  $(1,5)_j$  processes, where  $m=1$ ,  $n=1,3,5$ . Thus,  $n=\eta$  ( $m=1$ ). However, the  $\eta$  designation is inapplicable to molecules resulting from  $(m,n)_j$  processes where  $m>1$ . For example, the  $\eta$  designation is of no help in describing 298 and 300 (neither one has a metallic center, let alone single and central).

Enter our  $(m,n)_j$  designation of junctivity. This allows for the specification of the junctivity of *both* (or more) partners in the junctive process. The above two transformations  $296+297 \rightarrow 298$  and  $299a+299b \rightarrow 300$  are described as  $(6,6)_j$  and  $(2,2)_j$  processes, respectively. These examples show that the  $\eta$  descriptor and the  $(1,n)_j$  designation have a strong relationship for *single-metal complexes*, but the latter designation is of *wider and general scope* as it is extendable to binary  $(m,n)_j$ , ternary  $(m,n,p)_j$  and higher systems.

The concept of junctivity described here is, in principle, extendable to self-assembly of 2D and 3D H-bonded networks.

### Summary

We have defined junctive and disjunctive processes as those that involve the formation and breakdown of directed bonds. We have defined fundamental and topological junctive simplexes, and identified the fundamental types of junctive/disjunctive processes. For a given reacting site, site junctivity ( $j_a$ ) is defined as the number of directed bonds formed at that site and simplex junctivity ( $j_s$ ) as the sum total of all the site ligogenicities within the simplex. Molecular junctivity ( $J$ ) is defined as the sum total of all the simplex junctivities, and the net process junctivity,  $J_{\text{for}}$ , the difference of the *process junctivity* ( $J_g$ ) and *process disjunctivity* ( $J_d$ ). The junctivity of the reverse process,  $J_{\text{rev}}$ , is the negative of  $J_{\text{for}}$ . The designations presented are useful in describing (i) mechanistic steps from ground state to transition state and *vice versa*, (ii) ground state to ground state (reactant to intermediate, reactant to product). In effect, the said designations are applicable to any two points on the potential energy surface representing a junction or disjunction in a chemical process.

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"Truth has no special time of its own. Its hour is now – always."

Albert Schweitzer

# 9

## Ligogenic/Ligolytic Processes in Organic Chemistry

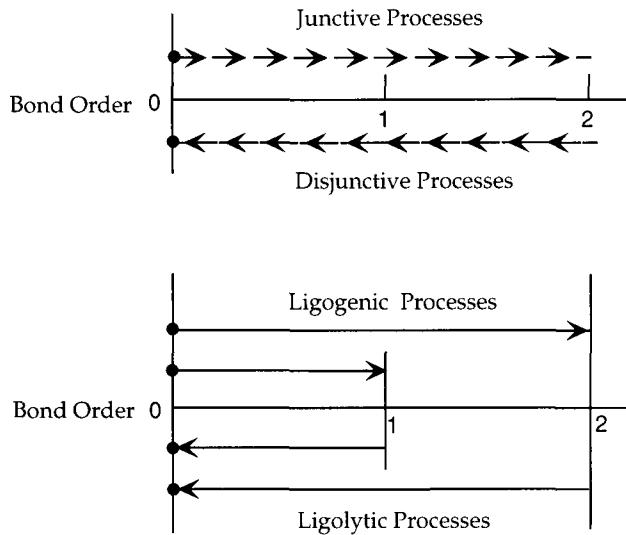
In the previous chapter, we discussed the concept of junctivity/disjunctivity in connection with associative and dissociative processes in organic chemistry. Ligogenic/ligolytic processes constitute a subgroup of junctive/disjunctive transformations; they involve *distinct*  $\sigma$  and/or  $\sigma+\pi$  bond formation and/or cleavage; associations through H-bonding, and complexation through  $\pi$ -bonding are specifically excluded. Thus, every ligogenic process is necessarily junctive; however, every junctive process is not necessarily ligogenic. Similarly, every ligolytic process is necessarily disjunctive; every disjunctive process is not necessarily ligolytic (*vide infra*).

### I. Ligogenic/Ligolytic Processes

A *ligogenic* process is one in which distinct  $\sigma$  or  $\sigma/\pi$  (but not just  $\pi$ ) bonding takes place between two unbonded atoms.<sup>28,29,30</sup> For canonical structures, one uses localized bonding models. In a ligogenic process, the bond order between two reactive atoms *starts at 0* and increases to *integral* values greater than 0 e.g. 1, 2, 3.... . An *aligogenic* process is one where junctivity might occur, but without formation of any  $\sigma$  bond e.g. in the formation of H-bonded species or  $\pi$ -complexes. A *ligolytic* process is the exact reverse of a ligogenic process (*vide infra*). In a ligolytic process, for two linked atoms, one starts at any integral value of a bond order greater than 0 and *ends up* at 0. Figure 9.1 depicts the change in bond order that accompanies each ligogenic and ligolytic process.

In Figure 9.2, guest-host complexation **1+2→3**,  $\pi$ -complexation **4+5→6**, dimerization through H-bonds **7a+7b→8** are all junctive transformations; they are *not* ligogenic transformations because in none of them is there formation of distinct  $\sigma$  or  $\sigma+\pi$  bonds. In contrast, the *overall*

transformations  $9+10 \rightarrow 11$ ,  $12a+12b \rightarrow 13$ ,  $14+15 \rightarrow 16$ ,  $17+18 \rightarrow 19$ , and  $20+21 \rightarrow 22$  are ligogenic junctive processes since each one of them involves formation of new  $\sigma$  or  $\sigma+\pi$  bonds.



**Figure 9.1.** Changes in Bond Order in Junctive/Disjunctive Processes vs. Ligogenic/Ligolytic Processes

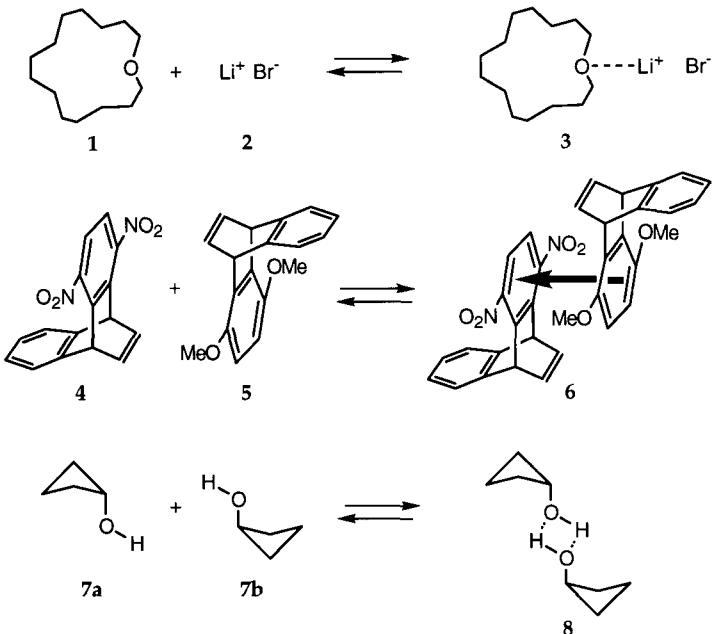
Guest-host decomplexation  $3 \rightarrow 1+2$ ,  $\pi$ -decomplexation  $6 \rightarrow 4+5$ , and dissociation of H-bonded dimers  $8 \rightarrow 7a+7b$  are disjunctive but they *not* ligolytic because no distinct  $\sigma$  bonds, or  $\sigma/\pi$ -bonds, is(are) broken in any one of them. Overall transformations  $11 \rightarrow 9+10$ ,  $13 \rightarrow 12a+12b$ ,  $16 \rightarrow 15+14$ ,  $19 \rightarrow 17+18$ , and  $22 \rightarrow 20+21$  represent typical ligolytic processes, since each one of them involves (total) cleavage of a  $\sigma$  or  $\sigma+\pi$  bond. Every ligolytic process, starts out as a dissociative process with severance of a  $\sigma$  or  $\sigma+\pi$  bond along the reaction coordinate, and terminates with the final disjunction of the molecular entities.

Clearly, junctivity/disjunctivity is universally applicable to all types of associative/dissociative processes involving directed bonding e.g. partial  $\sigma$  bonding,  $\sigma+\pi$  bonding, H-bonding, as well as bonding based on dipole-dipole, ion-dipole, pairwise ion-ion interactions. However, the domain of ligogenesis/ligolysis is limited to systems involving the formation/breaking of localized  $\sigma$  and/or  $\sigma+\pi$  bonds, and is especially pertinent to carbogenic systems; a  $\pi$  bond alone is excluded from our working definition.

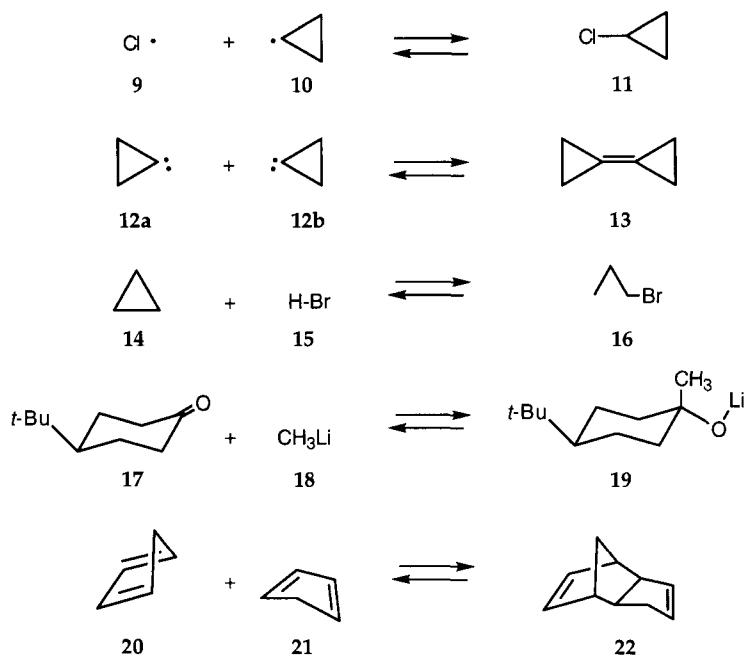
## II. Ligogenic Simplexes vs. Junctive Simplexes

There is a direct correspondence between a junctive simplex and a ligogenic simplex - be it fundamental or topological (see Chapter 8). This direct correspondence is expected since, notwithstanding difference in the *degree* of bonding, actual point(s) of connection and disconnection are identical, for junctive as well as ligogenic processes. It follows that there should be a direct correspondence between junctive processes and ligogenic processes, on the one hand, and between disjunctive processes and ligolytic processes, on the other. Figure 9.3 summarizes the direct correspondence for simplexes - fundamental and topological, and for processes - fundamental, topological, and composite.

### Junctive Processes



### Ligogenic Processes



**Figure 9.2.** Examples of Junctive vs. Ligogenic Processes

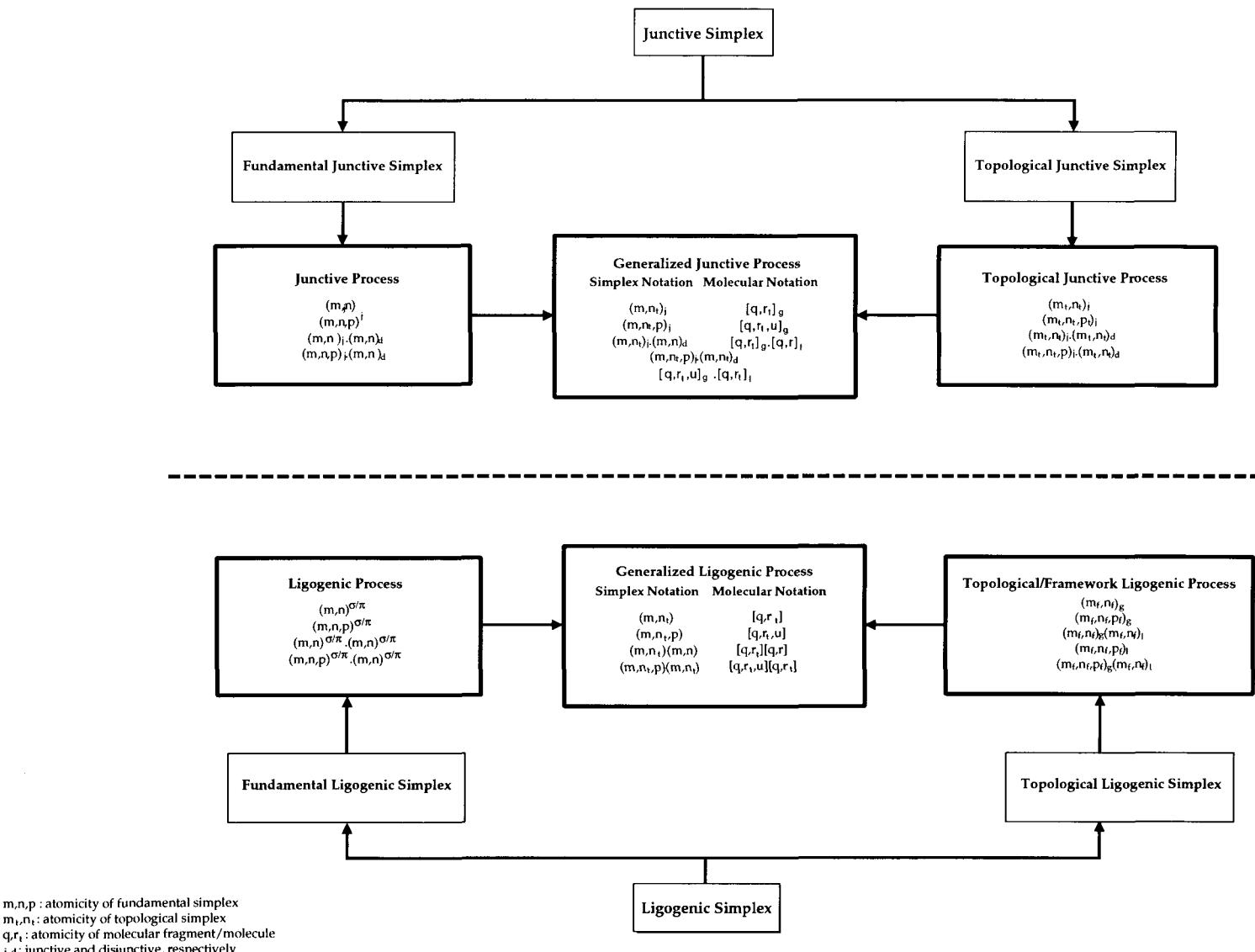


Figure 9.3. Correspondence Between Junctive/Ligogenic Simplexes and Processes

### III. Ligogenic/Ligolytic Processes - Simple vs. Complex

Fundamental ligogenic/ligolytic processes involving interactions between two or three simplexes (*vide infra*) are described as binary and ternary processes, respectively. A fundamental ligogenic/ligolytic process is deemed simple if only ligogenic or ligolytic components are present; it is complex if ligogenic and ligolytic components are both present (*vide infra*).

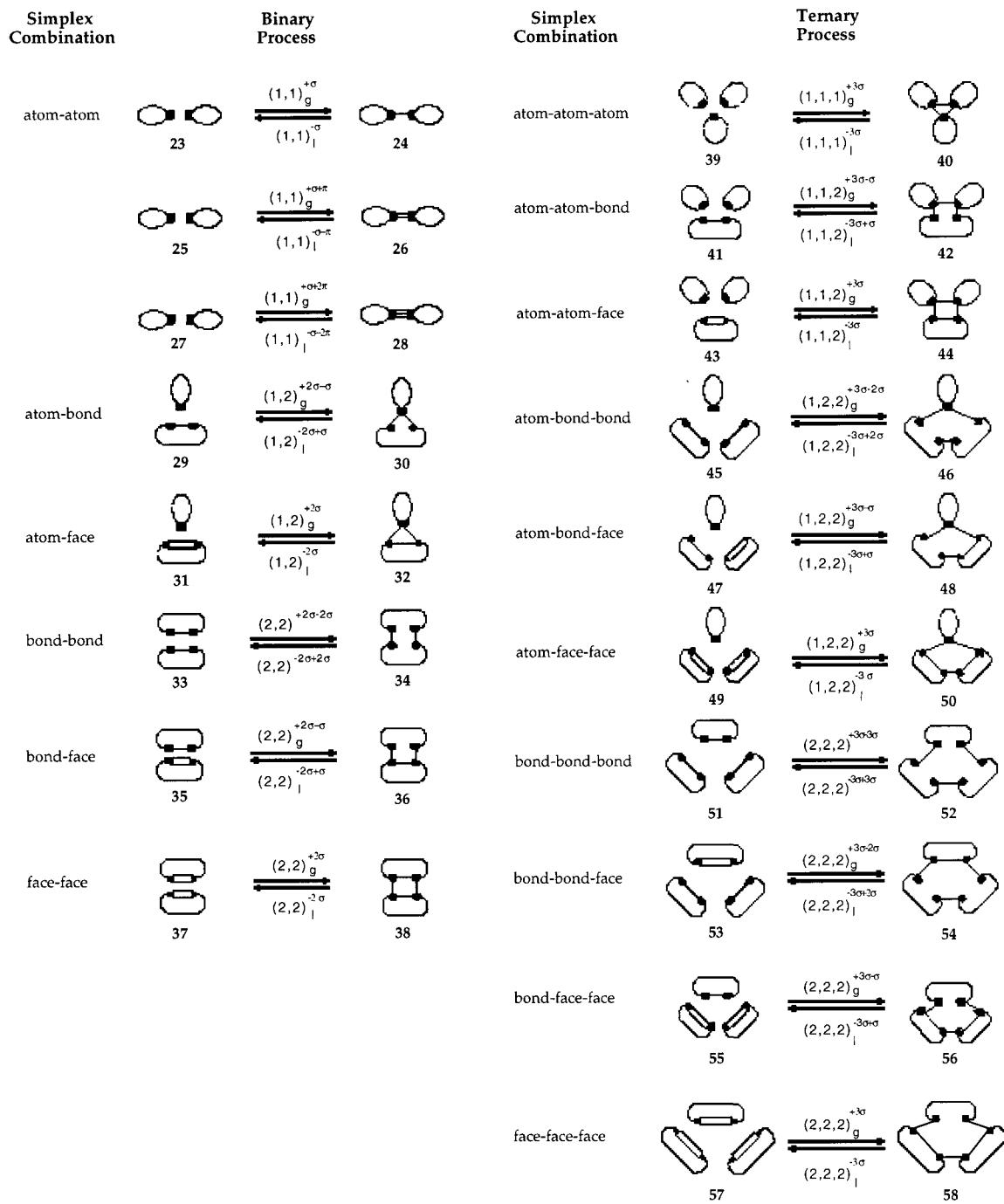
Simple binary and ternary ligogenic processes are denoted as  $(m,n)_g^{\sigma/\pi}$ ,  $(m,n,p)_g^{\sigma/\pi}$ , respectively ( $m, n, p$  are the atomicities  $a_s$  of the participating simplexes;  $m,n,p = 1,2,\dots$ );  $\sigma/\pi$  notation specifies the number of  $\sigma$  and  $\pi$  formed (+) or broken (-). The corresponding reverse processes are denoted as  $(m,n)_1^{\sigma/\pi}$ ,  $(m,n,p)_1^{\sigma/\pi}$  and they constitute pure ligolytic processes; subscripted suffixes  $_g$  and  $_1$  mean ligogenic and ligolytic, respectively. For example,  $(1,2)_g^{+2\sigma-\pi}$  represents a (1,2)-ligogenic process in which two  $\sigma$  bonds are formed, and one  $\pi$  bond is severed. In the reverse processes, subscripts  $_g$  and  $_1$  are interchanged; so are the + is and - signs for the  $\sigma$  and  $\pi$  bonds. The reverse of the aforementioned process is  $(1,2)_1^{-2\sigma+\pi}$ , that is, it is a (1,2)-ligolytic process entailing the loss of two  $\sigma$  bonds and the gain of a  $\pi$  bond.

A *complex* process incorporates ligogenic *as well as* ligolytic components. For example, in transformation  $(1,1)_1^{-\sigma}(1,2)_g^{-2\sigma}$ , there is a (1,1)-ligolytic process with a loss of a  $\sigma$  bond, and a (1,2)-ligogenic process in which two  $\sigma$  bonds are formed. The reverse process is designated as  $(1,1)_g^{+\sigma}(1,2)_1^{-2\sigma}$ , i.e. a (1,1)-ligogenic process in which a  $\sigma$  bond is formed and, simultaneously, a (1,2)-ligolytic process in which two  $\sigma$  bonds are cleaved.

An overall transformation is said to be *ligogenic* if one or more net  $\sigma$  bond(s) is(are) formed ( $+\sigma$ ); it is *ligolytic* if one or more net  $\sigma$  bond(s) is(are) broken ( $-\sigma$ ); it is *nonligogenic* if no net  $\sigma$  bond(s) is(are) formed (no  $+\sigma$  or  $-\sigma$ ) or broken. We make a distinction between *aligogenic* and *nonligogenic*. An *aligogenic* process is one where junctivity might occur but without formation of any  $\sigma$  bond. A *nonligogenic* process is one in which  $\sigma$  bonds are formed and broken but such that the net change in the number of  $\sigma$  bonds is exactly equal to zero. The subscripts  $_g$  and  $_1$  (for ligogenic and ligolytic processes) or absence of subscripts (for nonligogenic processes) indicate the net result of total of all ligogenic/ligolytic steps. Thus,  $(1,2)_g^{+2\sigma}$  is ligogenic, whereas  $(2,2,2)_g^{+3\sigma-3\sigma}$  is overall nonligogenic (no  $_g$  or  $_1$  subscript). Figure 9.4 portrays notations and cartoon representations of ligogenic, ligolytic, nonligogenic processes derived from atoms, bonds, and 2-centered  $\pi$ -molecular faces.

Among binary processes portrayed in Figure 9.4, all forward processes are ligogenic except 33 $\rightarrow$ 34, which turns out to be nonligogenic. The corresponding reverse processes (all unimolecular) are ligolytic, except 34 $\rightarrow$ 33 which is ligoneutral. Among the ternary processes, all forward processes are ligogenic except 51 $\rightarrow$ 52; among the reverse processes (all unimolecular) they are all ligolytic, except 52 $\rightarrow$ 51 which is, again, ligoneutral. In all of these transformations, the  $\sigma/\pi$  notation (a) clearly denotes the ligogenic and ligolytic *components* for the ligogenic, ligolytic, and ligoneutral *processes*, (b) enables one to differentiate between processes that have identical simplex designations e.g. the three atom-atom ligogenic combinations 23 $\rightarrow$ 24 is  $(1,1)_g^{+\sigma}$ , 25 $\rightarrow$ 26 is  $(1,1)_g^{+\sigma+\pi}$ , 27 $\rightarrow$ 28 is  $(1,1)_g^{+\sigma+2\pi}$ .

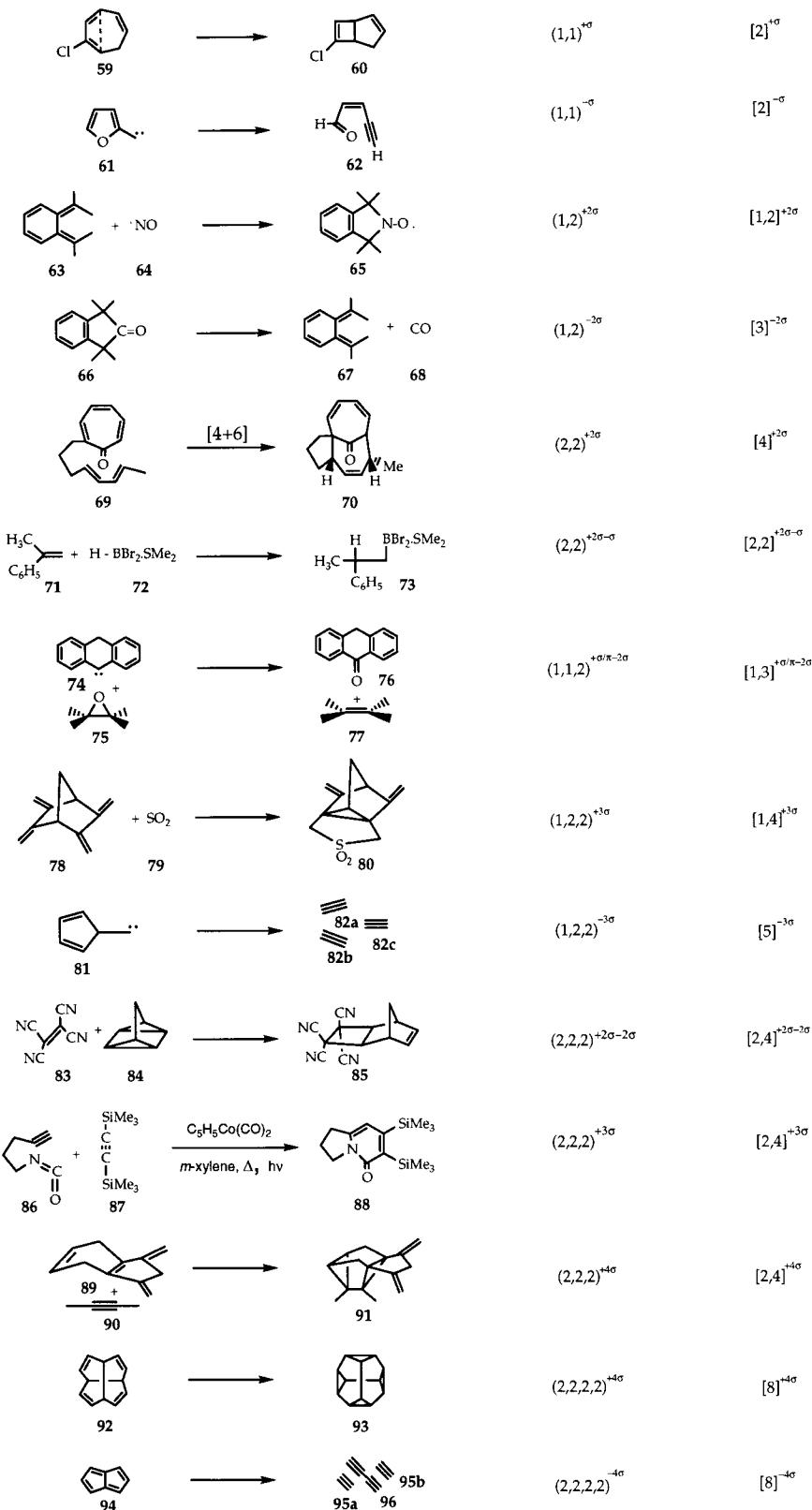
Molecular examples of ligogenic/ligolytic processes - simple and complex - with the terminology adopted above are given in Figure 9.5 (p. 37).



**Figure 9.4.** Cartoon Representations of Fundamental Simple Ligogenic and Ligolytic Processes

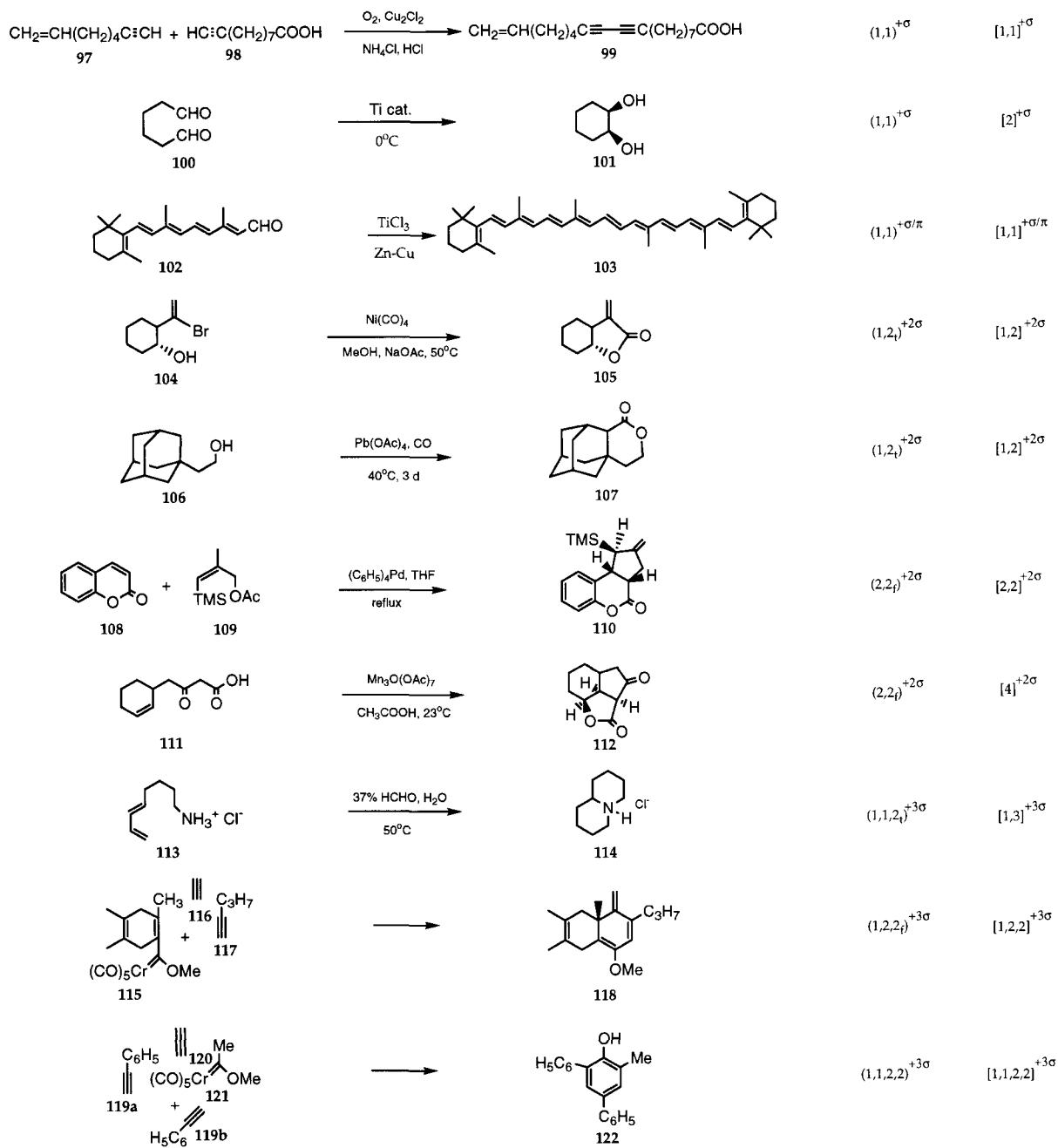
**Simplex Notation**

**Molecular Notation**



**Figure 9.5.** Simplex Notation and Molecular Notation for Ligolytic/Ligogenic Transformations

Simplex Notation Molecular Notation



**Figure 9.6.** Topological and Molecular Notations for Formal Ligogenic/Ligolytic Transformations

Electrocyclization **59**→**60** is a (1,1)<sup>+σ</sup> process, whereas ring opening **61**→**62** is a (1,1)<sup>-σ</sup> process. Similarly, **63**+**64**→**65** and **66**→**67** are considered as (1,2)<sup>+2σ</sup> and (1,2)<sup>-2σ</sup> processes, respectively. The [ $\pi^4+\pi^6$ ] cycloaddition **69**→**70** is a (2,2)<sup>+2σ</sup> process and the hydroboration **71**+**72**→**73** is (2,2)<sup>+2σ-σ</sup>.

The oxidation of carbene (**74**+**75**→**76**+**77**) is a rare (1,1,2)<sup>+σ+π-2σ</sup> process. The next two transformations - **78**+**79**→**80** and **81**→**82a**+**82b**+**82c** - exemplify (1,2,2)<sup>+3σ</sup> and (1,2,2)<sup>-3σ</sup> processes. Ternary transformations **83**+**84**→**85**, **86**+**87**→**88** and **89**+**90**→**91** constitute (2,2,2)<sup>+2σ-2σ</sup>, (2,2,2)<sup>+3σ</sup> and (2,2,2)<sup>+4σ</sup> processes, respectively, whereas **92**→**93** and **94**→**95a**+**96**+**95b** represent (2,2,2,2)<sup>+4σ</sup> and (2,2,2,2)<sup>-4σ</sup> processes.

#### IV. Simplex Notation vs. Molecular Notation

Figure 9.5 above gives also the molecular notation for the transformations just presented. As in the case of junctive processes, the molecular notation is given in square brackets (instead of parentheses) and the number of numerals, within each bracket, is the actual number of participating molecular species, the value of each numeral being the number of atomic sites in that molecular species undergoing bonding changes. For example, **59**→**60** is [2]<sup>+σ</sup> - two atomic sites are linked in a single molecule. On the other hand, **63**+**64**→**65** is a [1,2]<sup>+2σ</sup> process, since NO· (**64**), with one site, becomes bonded to two sites in **63** - with concomitant formation of 2 σ bonds. The reaction of **74** with **75** is [1,3]<sup>+σ+π-2σ</sup> process because it involves a single site of **74** and three sites in **75**. The addition of alkyne **87** to **86** is a [2,4]<sup>+3σ</sup> process since there are bonding changes at two atomic sites of **87** and four sites in **86**. It might be noted that for the sake of simplicity, the subscripts <sub>g</sub> and <sub>l</sub> are left out. They can be used, if needed, for additional clarification.

The simplex and molecular notations offer two alternatives for describing ligogenic/ligolytic processes. The former emphasizes the reacting moieties with no regard to molecular boundaries, whereas the latter stresses the bonding changes within the context of the reacting molecules. The simplex notations may be used to the desired detail e.g. (1,1)<sub>g</sub><sup>+σ+2π</sup>, (1,1)<sup>+σ+π+-2σ</sup>, or (1,1)<sub>g</sub>. Similarly, a process may be represented as [2,4]<sub>l</sub><sup>+2σ-σ-π+π</sup>, [2,4]<sup>+2σ-σ-π+π</sup>, or [2,4]<sub>l</sub>.

#### V. Formal Ligogenic Transformations

The usefulness of ligogenicity/ligolyticity can be extended to overall (multi-step) organic reactions/synthetic transformations. By focusing on the junctive skeletal elements, one can specify the overall effective, or *topological* ligogenicity/ ligolyticity of the process.

The couplings in transformations **97**+**98**→**99**, **100**→**101** and **102**→**103** are, in effect, examples of (1,1)-ligogenic processes. Transformations **104**→**105** and **106**→**107** constitute (1,2<sub>t</sub>)-ligogenic processes (each of **104** and **106** possesses a topological biligogenic moiety), whereas **108**+**109**→**110** and **111**→**112** represent (2,2<sub>t</sub>)-ligogenic processes. Finally, the condensation of formaldehyde with **113** to give **114**, and the elegant multicomponent ligogenic processes **115**+**116**+**117**→**118**, and **119a**+**119b**+**120**+**121**→**122** are examples of (1,1,2<sub>t</sub>), (1,2,2<sub>t</sub>) and (1,1,2,2) transformations, respectively.

## VI. Net Atom Ligogenicity ( $l_a$ ), Molecular Ligogenicity ( $l_m$ ) and Process Ligogenicity ( $L_{\text{for}}$ , $L_{\text{rev}}$ )

In the course of a chemical transformation, each reacting atom is characterized by *net atom ligogenicity* ( $l_a$ ), each simplex, by a *simplex ligogenicity* ( $l_s$ ), each molecule/molecular fragment, by *molecular ligogenicity* ( $l_m$ ), each forward transformation, by *forward process ligogenicity* ( $L_{\text{for}}$ ), and, each reverse transformation, by *reverse process ligogenicity* ( $L_{\text{rev}}$ ) (*vide infra*).<sup>31</sup>

*Net atom ligogenicity*,  $l_a$ , of  $X$ , in the course of a forward (or reverse) direction of a reversible transformation, characterizes a reacting atom  $X$  that undergoes ligogenic as well as ligolytic changes. It is the number of  $\sigma/\pi$  bonds formed minus the number of severed  $\sigma/\pi$  bonds, i.e. the net number of new  $\sigma/\pi$  bonds between  $X$  and atoms it becomes bonded to, and is given by Equation 9.1:

$$l_a = l_g - l_l \quad (9.1)$$

where *atom ligogenicity*,  $l_g$ , of reacting atom  $X$ , is the number of  $\sigma/\pi$  bonds it forms with other ligogenic sites, along the reaction path, intramolecularly or intermolecularly.  $X$  is said to be monoligogenic, biligogenic, triligogenic,...,  $n$ -ligogenic an *atom*, if it forms 1,2,3,... $n$   $\sigma/\pi$  bonds ( $l_g = 1,2,3,\dots,n$  respectively). The actual  $l_g$  value of  $X$  varies from one transformation to another.

*Atom ligolyticity*,  $l_l$ , for atom  $X$  is the number of  $\sigma/\pi$  bonds totally being severed from  $X$ , along the reaction path. Note that (a)  $l_a > 0$ , if  $l_g > l_l$ ;  $l_a < 0$ , if  $l_g < l_l$ ;  $l_a = 0$ , if  $l_g = l_l$ , and (b)  $l_a = l_g$  in purely ligogenic processes ( $l_l = 0$ ), and  $l_a = l_l$  in purely ligolytic processes ( $l_g = 0$ ).<sup>32</sup>

*Molecular ligogenicity* ( $l_m$ ) characterizes a molecule/molecular reactant  $M$  undergoing a given transformation, through one or more of its reacting simplexes - fundamental or formal.<sup>33</sup> Molecular ligogenicity, in addition to formal simplex ligogenicity, is defined for pragmatic reasons. While the concept of topological ligogenicity emphasizes the similarity between the *interacting set of simplexes*, molecular ligogenicity, on the other hand, reflects the ligogenicity between *interacting set of molecules*.

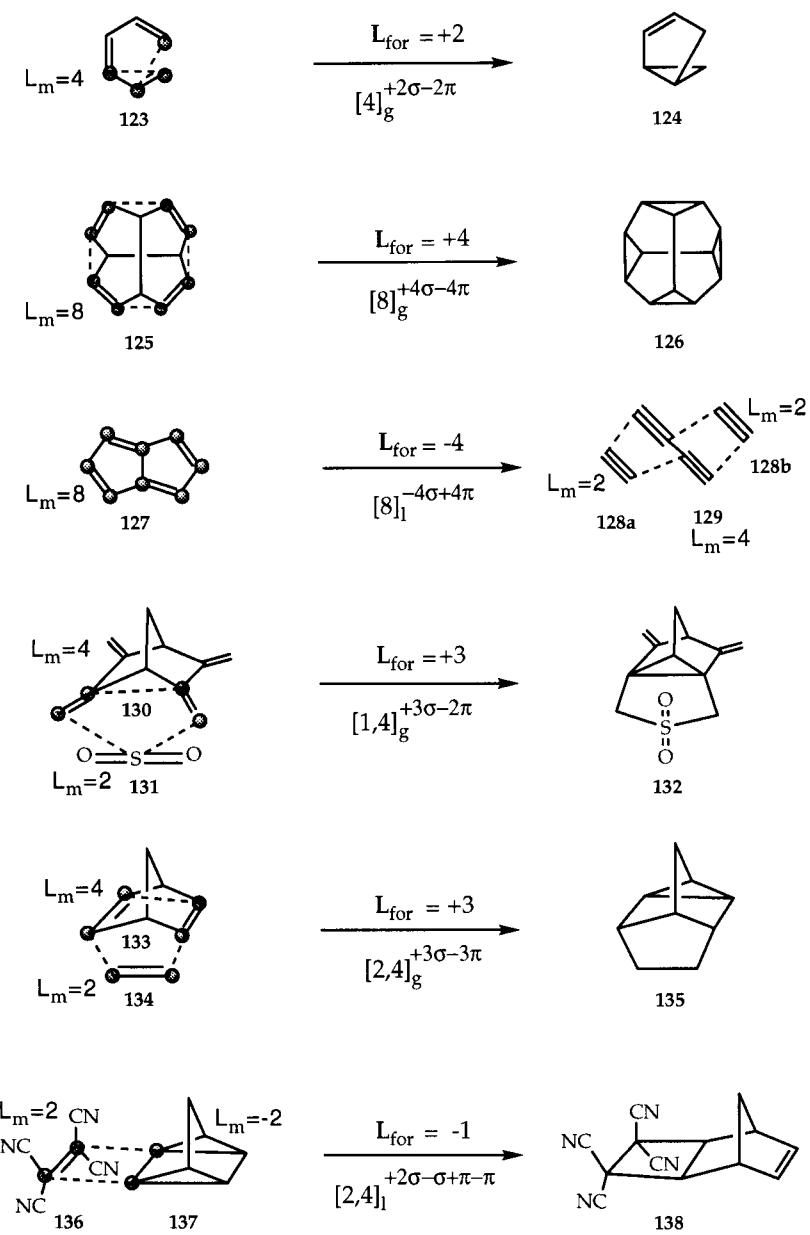
Finally, we define *forward process ligogenicity* ( $L_{\text{for}}$ ) and *reverse process ligogenicity* ( $L_{\text{rev}}$ ). The former is the net gain of incipient directed bonds in the process (proceeding in the forward direction). For a process involving  $r$  simplexes

$$L_{\text{for}} = 1/2 \sum_r l_m . \quad (9.5)^{34}$$

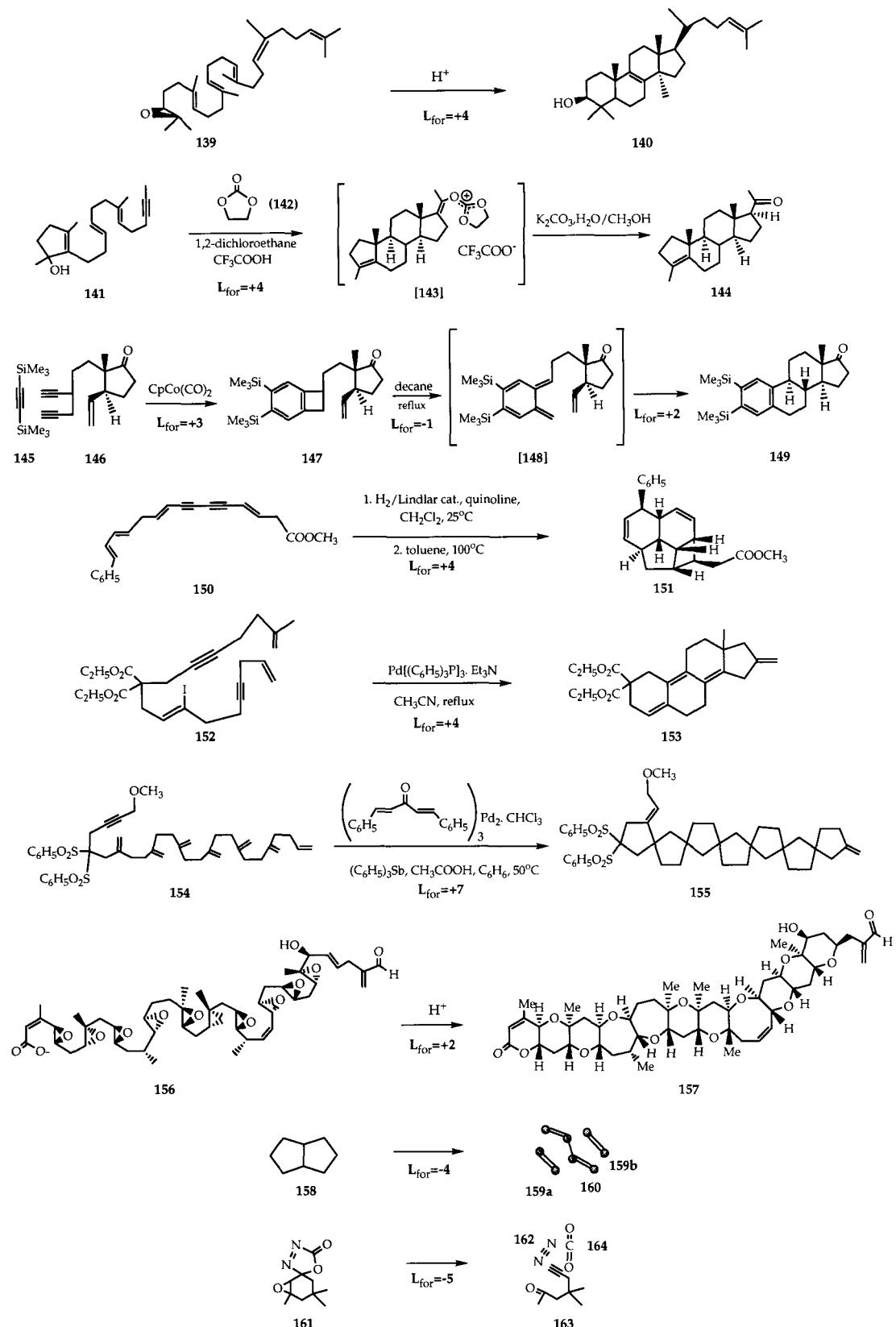
The *reverse process ligogenicity* ( $L_{\text{rev}}$ ) is the negative of the *forward process ligogenicity* ( $L_{\text{for}}$ ):

$$L_{\text{rev}} = - L_{\text{for}} \quad (9.7)$$

Figure 9.7 shows molecular ligogenicities ( $l_m$  values) and process ligogenicities ( $L_{\text{for}}$  values) for various intramolecular and intermolecular transformations. The forward direction of the first intramolecular case, **123→124**, is described as  $[4]_g^{+2\sigma-2\pi}$ ; the  $l_m$  value of **123** is 4, and  $L_{\text{for}} = L_m/2 = +2$ . For the next intramolecular cases,  $L_{\text{for}} = +4$  (**125→126**;  $[8]_g^{+4\sigma-4\pi}$ );  $L_{\text{for}} = -4$  for **127→128a+128b+129**, a  $[8]_g^{-4\sigma+4\pi}$  transformation. In a typical bimolecular case, **130+131→132** - a  $[1,4]_g^{+3\sigma-2\pi}$  process,  $L_{\text{for}} = 1/2(4+2) = +3$ . Similarly, for **133+134→135** - a  $[2,4]_g^{+3\sigma-3\pi}$  process,  $L_{\text{for}} = 1/2(2+4) = 3$ ; for **136+137→138**, a  $[2,4]_l^{+2\sigma-\sigma-\pi+\pi}$  process,  $L_{\text{for}} = 1/2(2+0) = 1$ .



**Figure 9.7.** Molecular Ligogenicity ( $L_m$  value) and Process Ligogenicity ( $L_{\text{for}}, L_{\text{rev}}$ ) for Various Intramolecular and Intermolecular Transformations



**Figure 9.8.** Examples of Higher-Order Formal Assembling and Disassembling Transformations

All  $L_{\text{for}}$  values are applicable to pure and composite transformations, and to formal overall transformations as well (*vide supra*). This is a consequence of the fact that the formal ligogenic representation ignores all the intermediate steps of a multistep process. The overall process ligogenicity is broken down into contributions from the reacting atoms, simplexes and molecular moieties. In the case of  $L_{\text{for}} = 0$ , there is no net new  $\sigma$  bonds; hence, the process is *nonligogenic*.

The efficacy of the skeletal *construction* of molecular frameworks, in organic synthesis, can be quantitatively assessed in terms of process ligogenicity ( $L_{\text{for}}$ ); the more positive the  $L_{\text{for}}$  value is, the higher the degree of associative  $\sigma$ -assembly would be. The extent of the skeletal *breakdown* of molecular frameworks, in degradative analytical work, is quantitatively assessed in terms of  $L_{\text{for}}$ ; the more negative the  $L_{\text{for}}$  value is, the higher the extent of dissociative  $\sigma$ -disassembly would be. Figure 9.8 illustrates a few exquisite literature examples of assembly and disassembly of skeletal frameworks, along with their  $L_{\text{for}}$  values.

The synthesis of lanosterol (140) from epoxide 139<sup>35</sup> has an  $L_{\text{for}} = +4$ . The key multiple ring-closure step 141+142→[143] in Johnson's synthesis of progesterone<sup>36</sup> has also an  $L_{\text{for}} = +4$  ( $L_{\text{for}}$  for [143]→144 would depend on the by-products). Next, we see the three steps 145+146→147→[148]→149 in Vollhardt's synthesis of estrone<sup>37</sup> with  $L_{\text{for}}$  is +3, -1, +2 respectively; for the overall transformation  $L_{\text{for}} = +3-1+2 = +4$ . The next two transformations, 150→151 in Nicolaou's biomimetic synthesis of endiandric acid A,<sup>38</sup> and Negishi's palladium-catalyzed tetracyclization 152→153<sup>39</sup> are also characterized by  $L_{\text{for}} = +4$ . Trost's one-step polycyclization 154→155<sup>40</sup> has an impressive  $L_{\text{for}} = +7$ , but Nicolaou's hypothetical transformation 156→157<sup>41</sup> has a surprising  $L_{\text{for}}$  value of only +2, because each epoxide must undergo  $\sigma$ -cleavage; indeed  $L_{\text{for}} = +11-9 = +2$ . In the last two examples, 158→159a+159b+160<sup>42</sup> and 161→162+163+164,<sup>43</sup>  $L_{\text{for}}$  is -4 and -5, respectively.

With the definitions of junctivity and ligogenicity given in this and the previous chapter, the stage is set for a discussion of vectoselectivity and regioselectivity (Chapter 13).

## Summary

We have defined ligogenic and ligolytic processes as those junctive and disjunctive processes, respectively, that involve the formation and breakdown of  $\sigma$  bonds, respectively. The fundamental types of ligogenic processes are simple (either ligogenic or ligolytic) or complex (ligogenic *and* ligolytic). Simple ones are designated by the notation  $(n,m,\dots)_g$  or  $(n,m,\dots)_l$  while complex ones are denoted as  $(n,m,\dots)_g(n,m,\dots)_l$ ; n and m are the simplex ligogenicities. For a given reacting site, site ligogenicity ( $l_s$ ) is defined as the number of bonds formed at that site; molecular ligogenicity ( $L_m$ ) is defined as the sum total of all the ligogenicities in a molecule/molecular species, and, for a transformation, the net process ligogenicity is given by  $L_{\text{for}}$ . The ligogenicity of the reverse process,  $L_{\text{rev}}$ , is the negative of  $L_{\text{for}}$ .  $L_{\text{for}}$  and  $L_{\text{for}}$  provide measures of the efficacy of skeletal build-up ( $L_{\text{for}} > 0$ ) and of skeletal breakdown ( $L_{\text{for}} < 0$ ) of molecular  $\sigma$ -frameworks, respectively.

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"All words are pegs to hang ideas on."

Henry Ward Beecher, *The Human Mind*,  
Proverbs from Plymouth Pulpit, 1870.

# 10

## Morphoselectivity

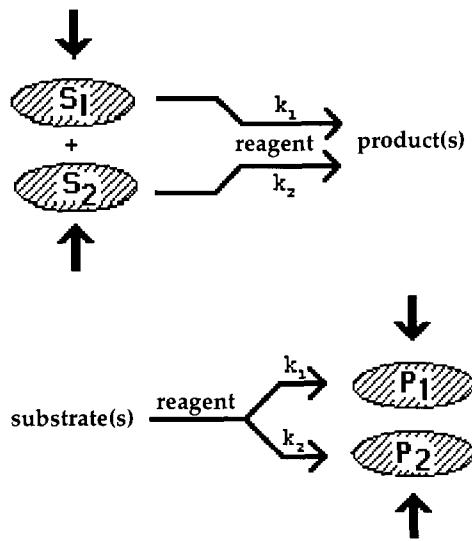
Selectivity is one of the most fundamental attributes of chemical transformations. It is a multi-faceted concept expressed through a multitude of terms that reflect differing aspects of selectivity. The variety of terms of selectivity in the chemical literature is a consequence of the multiple needs to denote (a) the extent or rate of *consumption* of one of two (or more) reactants, (b) the extent or rate of *formation* of one of two (or more) possible products (with regard to either stereochemistry or constitution), or (c) the preference of reaction site(s) (e.g. atom, bond, molecular face, functional group) in a molecule. Owing to the multiplicity of criteria utilized, it is unfortunate, but not surprising, that terms are sometimes used imprecisely or inaccurately. In this and subsequent chapters we clarify and refine the terminology for selectivity.

In determining selectivity in ligogenic processes (Chapter 9), the center of attention is usually on either whole molecules  $S_1$  vs.  $S_2$ , or, molecular sites  $t_1$  vs.  $t_2$ . In the former instance, one deals with *morphoselectivity* - selectivity based on *morphic* relationships between molecules; in contrast, in the latter instance, one invokes *situselectivity* - selectivity based on *topic* relationships between molecular sites. In this chapter we deal with morphoselectivity; situselectivity is treated in the next chapter. The concept of morphoselectivity is synonymous with substrate selectivity,<sup>44,45,46,47</sup> structural selectivity,<sup>48</sup> intermolecular selectivity,<sup>49</sup> shape selectivity,<sup>50</sup> and, enzyme substrate selectivity,<sup>51</sup> it is also implicit in intermolecular chemoselectivity. This chapter deals with the concept of morphoselectivity, and establishes the commonality of all the above literature terms.

### I. Morpholytic Selectivity vs. Morphogenic Selectivity

For a given a molecular transformation, the focus is on either the *consumption* of a reactant  $S$  ("morpholytic process," Gr. *morphe*, form, shape; *lysis*, unbinding ),<sup>52</sup> or, the *generation* of a product  $P$  ("morphogenic process," Gr. *morphe*, form, shape; *genesis*, L. generation).<sup>53</sup>

Morphoselectivity pertaining to the selective *consumption* of reactant  $S_1$  over  $S_2$  is termed *morpholytic selectivity (morpholytoselectivity)*, whereas that characterizing the selective *generation* of product  $P_1$  over  $P_2$  is designated as *morphogenic selectivity (morphogenoselectivity)*. The corresponding processes are said to be morpholytoselective and morphogenoselective, respectively. The distinction between selective morpholysis and selective morphogenesis is portrayed in Figure 10.1 below.



**Figure 10.1.** Idealized Representation of Competitive Morpholytic Processes ( $S_1$  vs.  $S_2$ ) and Morphogenic Processes ( $P_1$  vs.  $P_2$ )

### A. Morpholytic Selectivity

A given morpholytic process may be selective, nonselective, or aselective. A reaction, involving substances  $S_1$  and  $S_2$  as reactants, is said to involve *selective morpholysis*, if  $S_1$  is consumed more rapidly (or slowly) than  $S_2$  ( $S_1 \neq S_2$ ). In *nonselective morpholysis*,  $S_1$  and  $S_2$  are consumed at expectedly- or accidentally-identical rates. An *aselective morpholytic process*, on the other hand, is one in which selective consumption of reactant(s) is operationally unobservable, because there is only *one* reactant substrate  $S$  (i.e.  $S_1=S_2=S$ ), regardless of whether the reaction leads to *one or more* products. The case involving one reactant substrate transforming into more than one product may be termed *aselective divergent morpholysis*.

The particular type of morpholytic selectivity is defined by the morphic relationship between  $S_1$  and  $S_2$  (*vide infra*). If  $S_1$  and  $S_2$  are stereomeric with respect to each other, then the process is characterized by *stereomorpholytic selectivity*. More specifically, if  $S_1$  and  $S_2$  are enantiomeric, or, diastereomeric with respect to each other, the process is said to display *enantiomorpholytic selectivity* or *diastereomorpholytic selectivity*, respectively. Consumption of homomeric molecules (homomeric substances) is aselective; hence, there is no such thing as selective *homomorpholysis*. On the other hand, if  $S_1$  and  $S_2$  are nonstereomeric with respect to each other, the process is marked by *nonstereomorpholytic selectivity*. If  $S_1$  and  $S_2$  are astereomeric, or, nonequimERIC with respect to each other, the process is said to exhibit *astereomorpholytic selectivity* or *nonequimorpholytic selectivity*, respectively. For

selectivity in junctive/complexative processes, the corresponding terms are *stereomorphojunctive*, *enantiomorphojunctive*, *diastereomorphojunctive*, *nonstereomorphojunctive*, *astereomorphojunctive*, and *nonequimorphojunctive*.

There is a distinction between *nonstereomorpholytic selectivity* and *stereomorpholytic nonselectivity*. The former term refers to selectivity for two reactants that are nonstereomeric with respect to each other, whereas the latter term refers to the absence of selectivity in process where reactants are stereomeric with respect to each other. In Figure 10.2 below, we illustrate the above terms with *select* examples from the chemical literature.

Enantiomorpholytic selectivity is exemplified by the reaction of racemic ketone ( $\pm$ )-1 with horse liver alcohol dehydrogenase (HLADH),<sup>54</sup> and the lipase-catalyzed hydrolysis of ( $\pm$ )-mentyl pentanoate, ( $\pm$ )-4, with *Candida rugosa* lipase (CRL); in the latter reaction, there occurs preferential hydrolytic cleavage of the (1*R*)-enantiomer to give alcohol 5 (enantiomeric ratio = 13:1) along with unreacted ester 6.<sup>55</sup> As alcohol 5 is formed (from the corresponding ester), ester 4 becomes enriched with respect to the unreacted (1*S*)-enantiomer and this accounts for the *kinetic resolution* of ( $\pm$ )-4. A variant of enantiomorpholytic selectivity is portrayed in the selective complexation of the two enantiomers of racemic 7, using chiral podand ionophore 8 (enantioselective binding of L/D = 94.5:5.5).<sup>56</sup> Diastereomorpholytic selectivity is evident in the epoxidation of diastereomeric 2-octenes, 9/10,<sup>57</sup> with Rebek's ester-acid chloride 11 and H<sub>2</sub>O<sub>2</sub>; k<sub>cis</sub>/k<sub>trans</sub>=7.7.

An example of astereomorpholytic selectivity is provided by the reaction of difluorocarbene precursor 16 with a mixture of 2-butene (14) and 2-methylpropene (15) (k<sub>14</sub>/k<sub>15</sub>=12.8).<sup>58</sup>

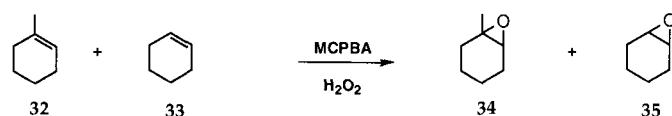
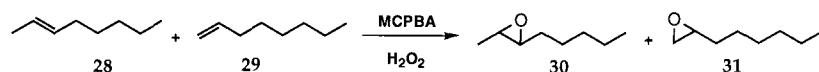
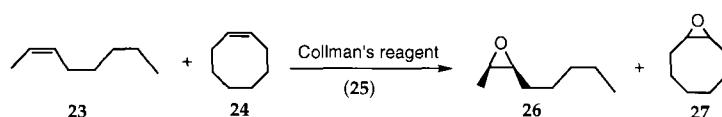
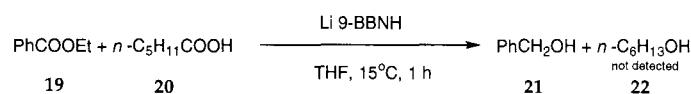
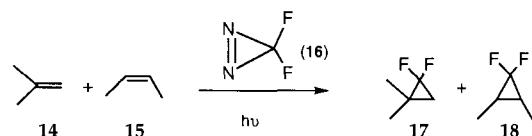
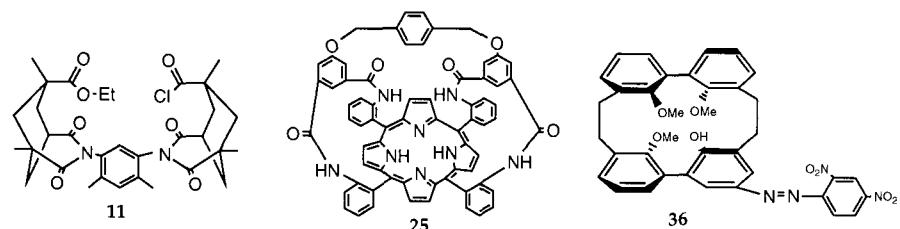
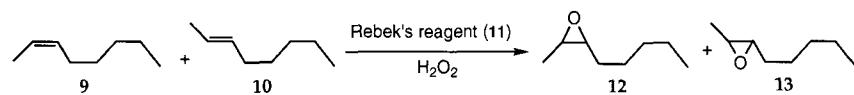
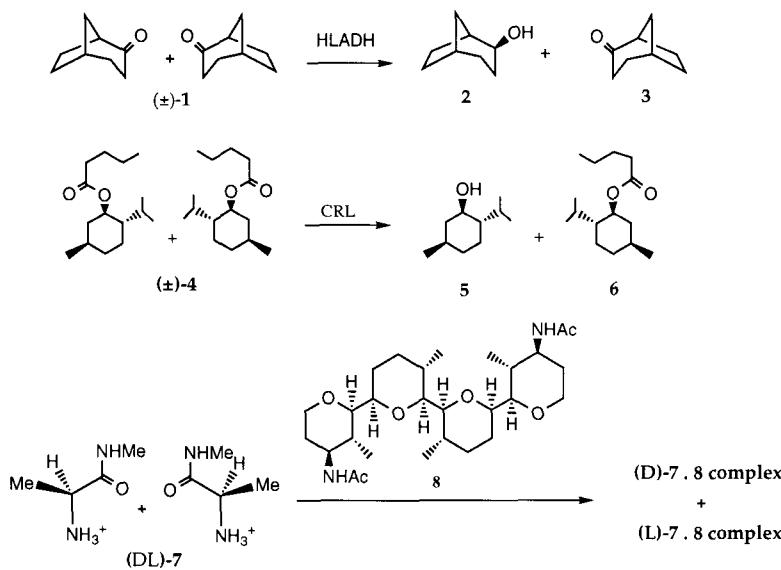
Examples of nonequimorpholytic selectivity<sup>59</sup> include the selective reduction of ethyl benzoate (19) in the presence of hexanoic acid (20), using lithium 9-boratabicyclo[3.3.1]nonane (Li 9-BBNH), and the selective epoxidation of a 1:1 mixture of *cis*-2-octene (23) and *cis*-cyclooctene (24) with Collman's reagent *viz.* Mn(PXYLPBP)(3,5-di-*tert*-butylphenoxyde) (PXYLPBP=25) (ratio of corresponding epoxides 26/27 > 1000/1).<sup>60</sup> Finally, nonequimorpholytic selectivity is observed during the selective epoxidations of 2-octene(28)/1-octene(29) (two isomeric nonequimers) and of 1-methylcyclohexene(32)/cyclohexene(33) (two nonisomeric nonequimers) with MCPBA+ H<sub>2</sub>O<sub>2</sub>; k<sub>28</sub>/k<sub>29</sub>=19.6 , k<sub>32</sub>/k<sub>33</sub>=13.4.<sup>57,61</sup>

In Figure 10.3, we illustrate nonselective and aselective morpholytic processes. The reductions of ( $\pm$ )-3,3,5-trimethylcyclohexanone, ( $\pm$ )-37, with triisobutylaluminum,<sup>62</sup> and of ( $\pm$ )-2-methylcyclohexanone, ( $\pm$ )-40, with Alpine-borane<sup>63</sup> are *morpholytononselective* processes; in each reaction, the two enantiomers are *consumed* at equal rates. Thus, the two enantiomers in racemate ( $\pm$ )-37 react with achiral triisobutylaluminum (36), at *expectedly-equal* rates, to give racemic *cis*-38 plus racemic *trans*-39 (*cis/trans* = 4.8:1). In contradistinction, the two enantiomers in racemate ( $\pm$ )-40 react at *accidentally-equal* rates to give nonracemic *cis*-41 (68% ee) and nonracemic *trans*-42 (68% ee) (*cis/trans* = 1:1). No kinetic resolution of either ( $\pm$ )-37 or ( $\pm$ )-40 takes place.

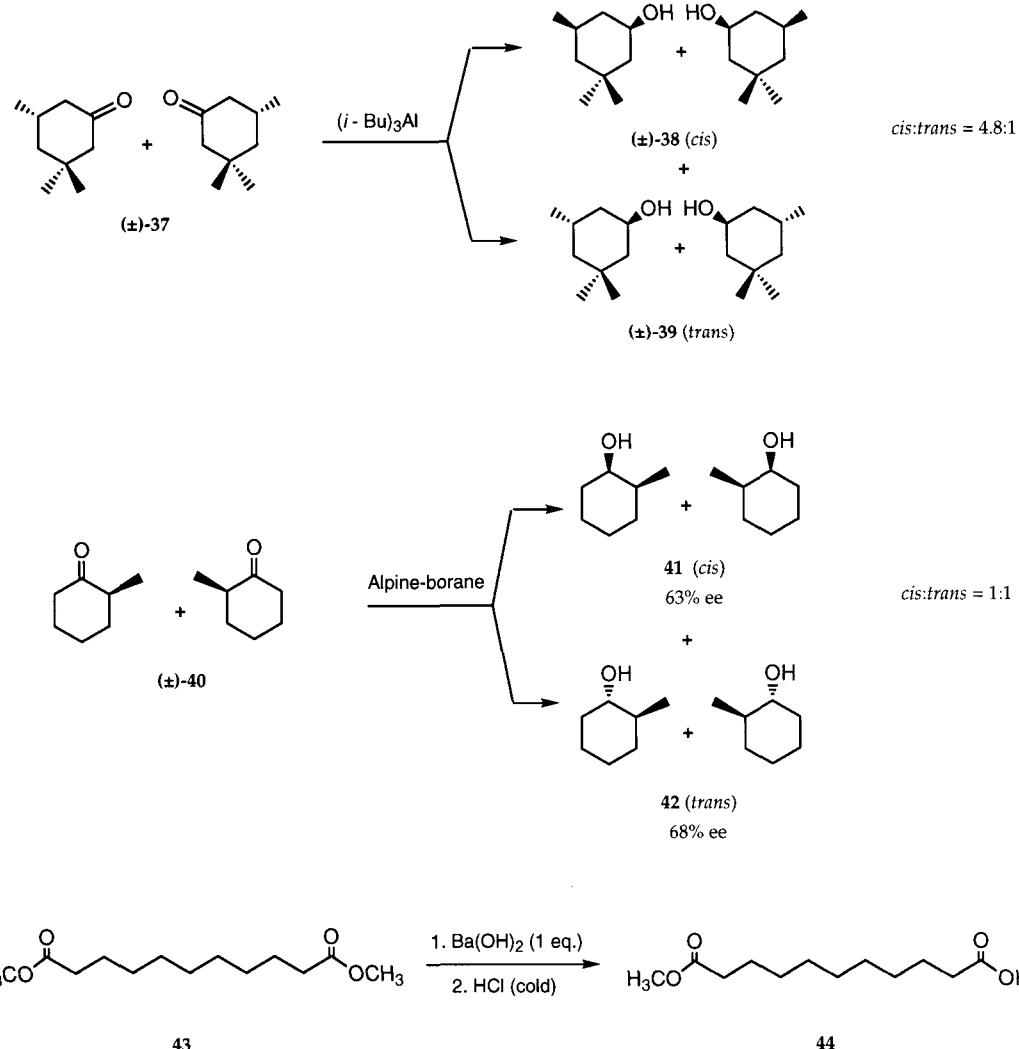
Aselective morpholysis, is exemplified by the controlled saponification of dimethyl cyclohexanedicarboxylate (43) to give monocarboxylic acid 44. The reactant diester reacts at *two* distinct (albeit equivalent) sites within the molecule; however, the relative rates of these processes cannot be ascertained by following the *consumption* of the only substrate.

## B. Morphogenic Selectivity

A given morphogenic process is also subclassified as selective, nonselective, or aselective. A reaction leading to two (or more) products (P<sub>1</sub>,P<sub>2</sub>...) is said to display *selective*



**Figure 10.2.** Examples of Selective Morpholytic Processes



**Figure 10.3.** Examples of Nonselective and Aselective Morpholytic Processes

morphogenesis, if product  $P_1$  is formed in preference to product  $P_2$  ( $P_1 \neq P_2$ ) (Figure 10.1). Here,  $P_1$  and  $P_2$  are distinct, primary products formed through two distinct (nonhomometric) pathways starting from either a single substrate, or two substrates. In contrast, in *nonselective* morphogenesis, the two products  $P_1$  and  $P_2$  are obtained in expectedly- or accidentally-identical rates. In contradistinction, in an *aselective* morphogenic process, selective formation of product(s) is operationally unascertainable, because there forms only *one* product  $P$  (i.e.  $P_1 = P_2 = P$ ), in reactions that may originate from *one* (*or more*) starting material(s). The case involving two reactant substrates converting to a single product may be termed *convergent morphogenesis*.

Where morphogenic selectivity takes place, the type of selectivity is defined on the basis of the morphic relationship between products  $P_1$  and  $P_2$  (*vide infra*). If  $P_1$  and  $P_2$  are stereomeric with respect to each other, then the process is characterized by *stereomorphogenic selectivity*.

More specifically, if P<sub>1</sub> and P<sub>2</sub> are enantiomeric, or, diastereomeric with respect to each other, the process is said to display *enantiomorphogenic selectivity*, or, *diastereomorphogenic selectivity*, respectively. On the other hand, for reactions leading selectively to nonstereomeric products, the processes are characterized by *nonstereomorphogenic selectivity*. Specifically, if P<sub>1</sub> and P<sub>2</sub> are astereomeric or nonequimERIC with respect to each other, the process in question is said to exhibit *astereomorphogenic selectivity*, or, *nonequimorphogenic selectivity*, respectively.

*Selective stereomorphogenesis* is synonymous with *stereoselective synthesis*. More specifically, selective enantiomorphogenesis and diastereomorphogenesis are synonymous with enantioselective and diastereoselective syntheses, respectively. Formation of homomeric substances through competing pathways cannot be ascertained operationally; hence, there is no such thing as selective *homomorphogenesis*. Here too, we note the distinction between *nonstereomorphogenic selectivity* and *stereomorphogenic nonselectivity* (*vide infra*). The former term refers to selectivity in the formation of two products that are nonstereomeric with respect to each other; the latter term refers to the absence of selectivity in a process where products are stereomeric with respect to each other.

Examples of enantiomorphogenic selectivity are provided by the pig liver esterase (PLE) catalyzed hydrolysis of diester 45 to give, by way of intermediate [46], aldehyde 47 (in preference to 48).<sup>64</sup> A non-enzymatic example is provided by the reaction of 2-(2-bromoallyl)-1,3-cyclopentadiene (49) with 2-bromoacrolein (50) in the presence of 10 mol % of catalyst 51 to give 52 (99% ee, *exo/endo* 99:1), en route to key gibberellic acid precursor 53.<sup>65</sup>

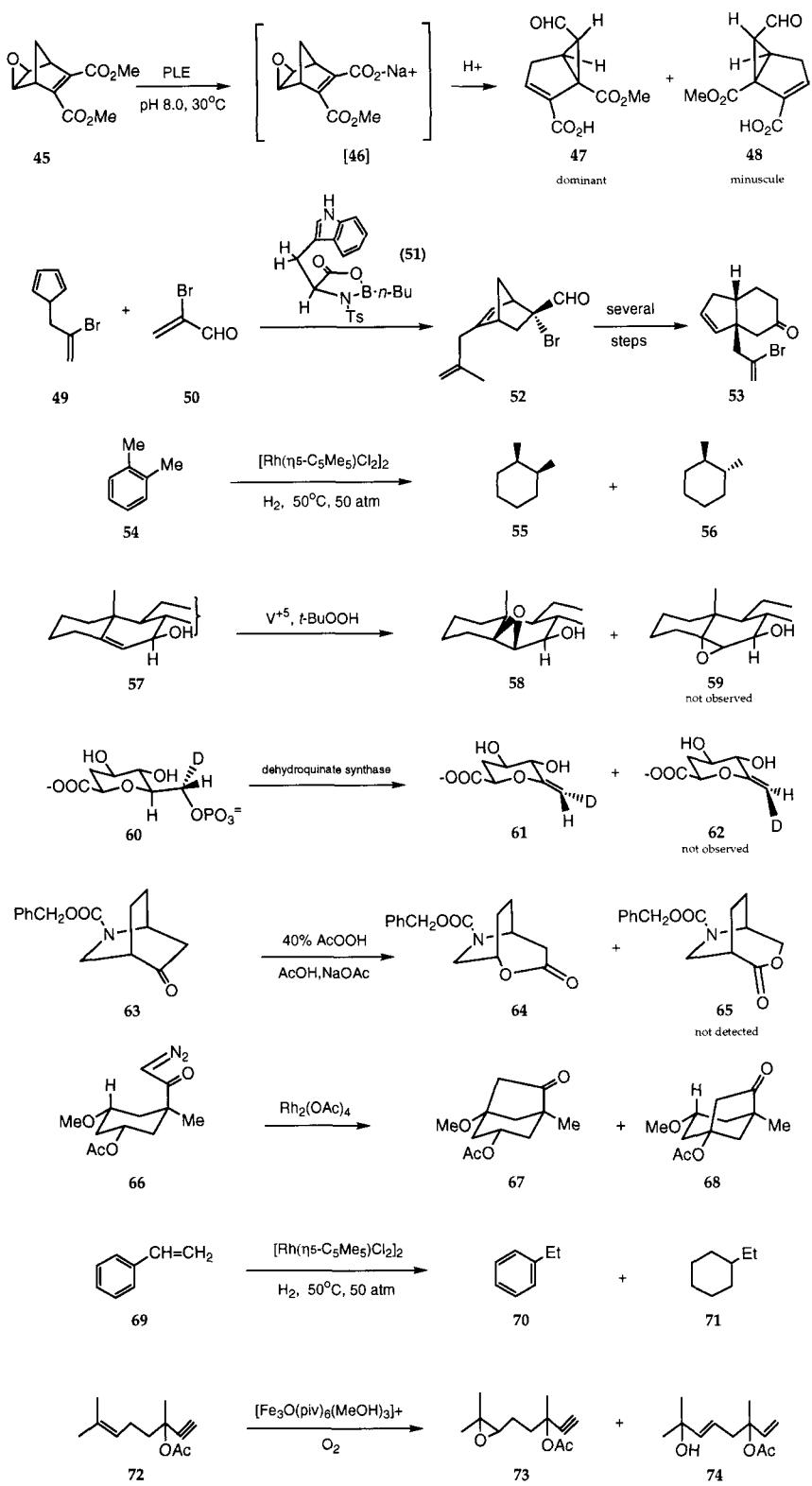
Diastereomorphogenic selectivity is observed in the homogeneous hydrogenation of *o*-xylene (54) in the presence of [Rh( $\eta^5$ -C<sub>5</sub>Me<sub>5</sub>)Cl<sub>2</sub>]<sub>2</sub> at 50°C, 50 atm, to give *cis*- (55) and *trans*-1,2-dimethylcyclohexane (56) in a 6.2:1 ratio.<sup>66</sup> Complete diastereomorphogenic selectivity is observed for the epoxidation of allylic alcohol 57 *viz.* 58/59 = 100:0,<sup>67</sup> and in the dehydroquinate synthase reaction of [7(S)-d]-2-deoxy substrate analog 60, to give 61 rather than 62.<sup>68</sup>

Astereomorphogenic selectivity is exemplified by the Baeyer-Villiger oxidation of 63 to give only 64,<sup>69</sup> and by the Rh(II)-mediated carbonyl C-H insertion of 66 (67/68 > 99:1).<sup>70</sup>

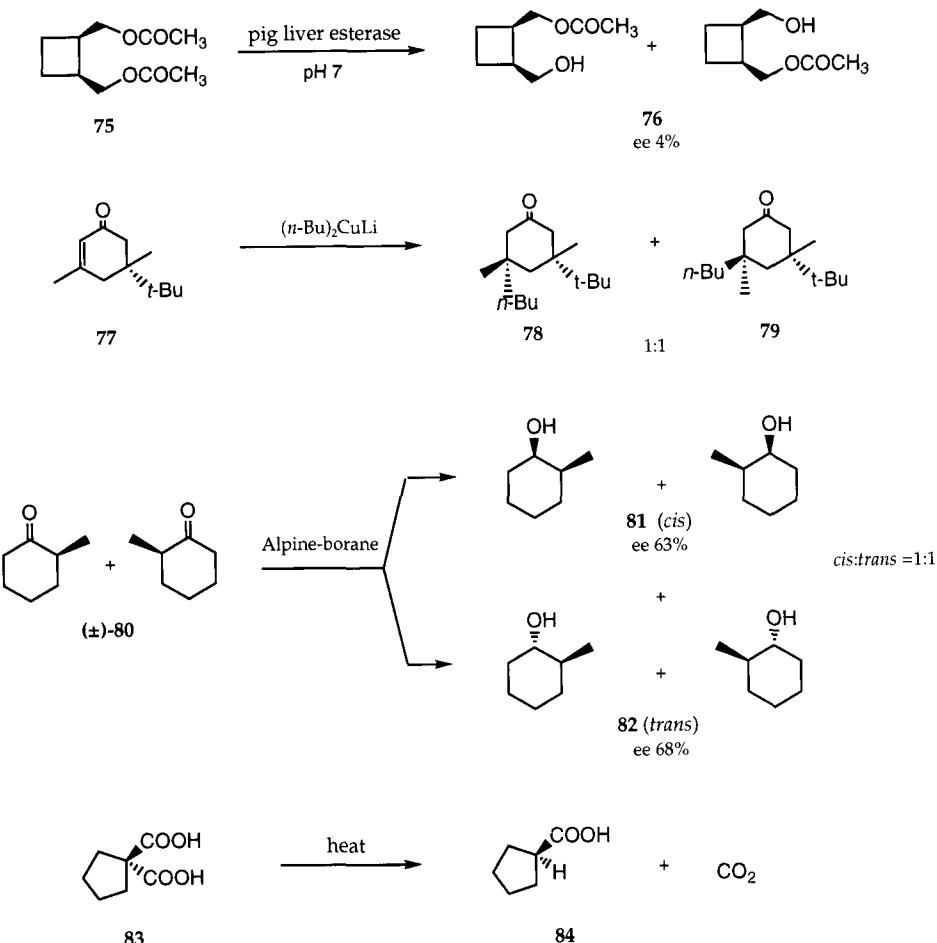
Finally, nonequimorphogenic selectivity is noted in the homogeneous hydrogenation ([Rh( $\eta^5$ -C<sub>5</sub>Me<sub>5</sub>)Cl<sub>2</sub>]<sub>2</sub> at 50°C, 50 atm) of styrene (69) to give 97% ethylbenzene (70) and 3% ethylcyclohexane (71),<sup>66</sup> and in the oxidation of enyne 72, to yield 73 (81%) and 74 (13%).<sup>71</sup>

We now cite examples of nonselective morphogeneses. The pig liver esterase catalyzed hydrolysis of 75 comes very close to being a nonselective enantiomorphogenic process (*vide infra*), as the resulting hydroxyesters 76 are formed as a 48:52 mixture (4% ee);<sup>72</sup> a nonselective transformation would have yielded a 50:50 mixture. The conjugate addition to 77,<sup>73</sup> and the Alpine-borane reduction of ( $\pm$ )-80 represent nonselective diastereomorphogenic processes, since each of the diastereomeric product mixtures - 78/79 and 81/82 - is formed in a 1:1 ratio. It should be pointed out that in the latter case, one does observe *enantiomorphogenic selectivity* for each of 81 and 82 (63% ee for *cis*, and 68% ee for *trans*) by virtue of the fact that Alpine-borane is chiral.<sup>64b</sup> Finally, an *aselective* morphogenic process is typified by the decarboxylation of diacid 83 into monoacid 84; the two carboxyl groups of 83 are homomorphic and therefore their transformations follow two homometric pathways which necessarily converge onto the same product, *viz.* 84.

The above classifications for morpholytic and morphogenic processes are summarized in Figure 10.6 (p.53). Thus, morphoselectivity is categorized into morpholytic and morphogenic types. Each of these types consists of *aselective*, *selective* and *nonselective* subtypes. The selective subtypes are subdivided further into stereomorpholytic/stereomorphogenic vs. nonstereomorpholytic/nonstereomorphogenic groups. In turn, each of the stereomorpholytic/stereomorphogenic groups is divided into enantio- and diastereomorphoselective subgroups, while each of the nonstereomorpholytic/nonstereomorphogenic groups is categorized into astereomorphoselective



**Figure 10.4.** Examples of Selective Morphogenetic Processes



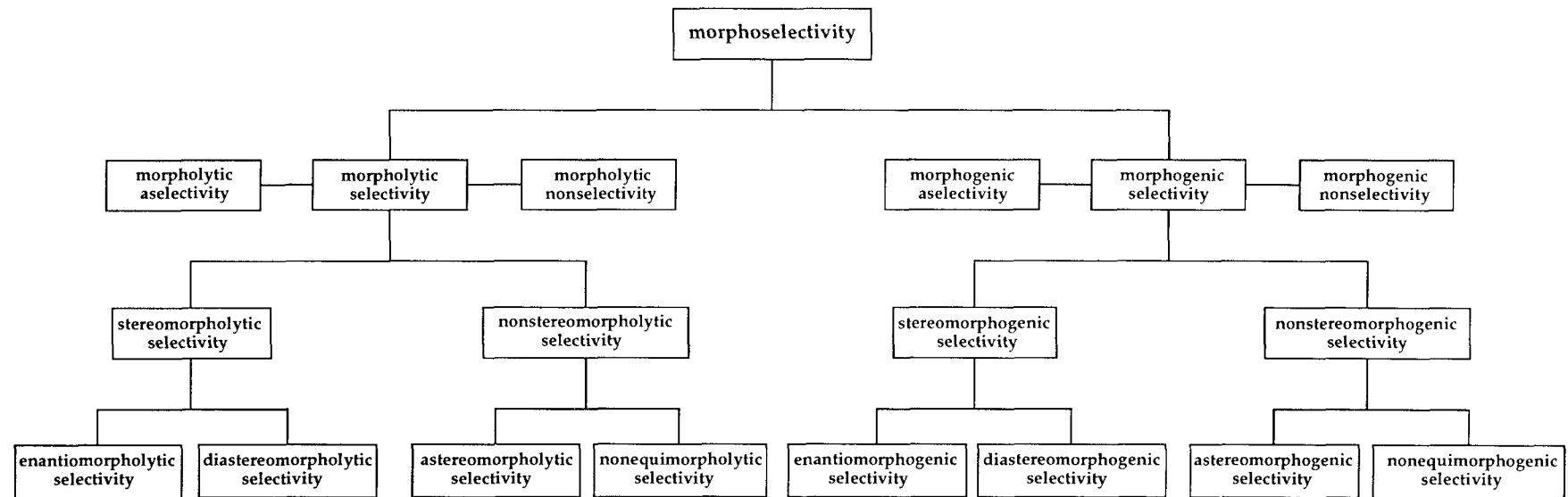
**Figure 10.5.** Examples of Nonselective and Aselective Morphogenic Processes

and nonequimorphoselective subgroups. The terminology advanced here enables one to clearly define, if and when needed, the *specific type of morphoselectivity, at the level of desired distinction*. The terminology may be used to distinguish between the two main classes - morpholytic vs. morphogenic, or, to designate exactly the corresponding enantio-, diastereo-, astereo-, or nonequimorpho- subclasses of selectivity.

## II. Origin of Morphoselectivity - Energetics & Transition States

### A. Morpholytic Processes

The origin of morpholytic selectivity lies in the difference in the free energies of activation  $\Delta\Delta G^\ddagger$  for the competing processes;  $\Delta\Delta G^\ddagger = |\Delta G_{TS} - \Delta G^\ddagger|$  where  $\Delta G_{TS}$  and  $\Delta G^\ddagger$  are the differential energy differences in the transition states and ground states of reactants. Hence, there is no morpholytic selectivity if  $\Delta\Delta G^\ddagger = 0$ . The greater the magnitude of  $\Delta\Delta G^\ddagger$  is, the greater the selectivity would be. The various possibilities for morpholytic processes, and for morphogenic processes are portrayed in Figure 10.7.



**Figure 10.6.** Classification of Morphoselectivity

In an *aselective* morpholytic process (Figure 10.7, cases 1,4,8-10,17,22-24), there is a single reactant, and one obtains one product (case 1) or more than one product (cases 4,8-10,17,22-24). In *nonselective* morpholytic processes (cases 2,3,5-7,11,12,13-15), two reactants are consumed at equal rates - enantiomers (cases 2,3,5-7), diastereomers (cases 11,12,13), astereomers (case 14) and nonequimers (case 15). Finally, in *selective* morpholytic processes (cases 16,18,19-21,25,26,27-29), the reactants are consumed at different rates, and these reactants may be enantiomers (16,18,19-21), diastereomers (cases 25,26,27), astereomers (case 28) or nonequimers (case 29). In sum, the necessary and sufficient condition for morpholytic selectivity to occur, for  $S_1 \neq S_2$ , is that  $\Delta\Delta G^\ddagger$  be greater than 0 (*vide infra*).

### B. Morphogenic Processes

The origin of morphogenic selectivity lies in the difference in the free energies of activation for the competing processes, *viz.*  $\Delta\Delta G^\ddagger$  where  $\Delta\Delta G^\ddagger = |\Delta G_{TS}^\ddagger - \Delta G^\ddagger|$ . Hence, there is no morphogenic selectivity if  $\Delta\Delta G^\ddagger = 0$ .

In *aselective* morphogenic processes (cases 1,12,18,26) there is a single product, but there may be one reactant (case 1) or more than one reactant (cases 12,18,26). In *nonselective* morphogenic processes (cases 3,4,5-7,8-10,11,13-15), two products are formed at equal rates - enantiomers (3,4,11), diastereomers (5,8,13), astereomers (6,9,14) and nonequimers (7,10,15). Finally, in *selective* morphogenic processes (16,17,19-21,22-24,25,27-29), the products are formed at different rates and these products may be enantiomers (16,17,25), diastereomers (19,22,27), astereomers (20,23,28) or nonequimers (21,24,29). In sum, the necessary and sufficient condition for morphogenic selectivity to occur, for  $P_1 \neq P_2$ , is that  $\Delta\Delta G^\ddagger$  be greater than 0 (*vide infra*); the greater the magnitude of  $\Delta\Delta G^\ddagger$ , the greater the ensuing selectivity.

## III. Morphoselectivity and Chirality

### A. Morpholytic Processes

As noted earlier, no morpholytic selectivity is observable (case of morpholytic aselectivity) in the consumption of homomeric reactants  $S_1$  and  $S_2$  ( $S_1 = S_2$ ) (Figure 10.4, cases 1,4,8-10,17,22-24). Morpholytic selectivity is expected to be absent for enantiomeric systems (nonselectivity) undergoing transformations involving achiral reagents and/or achiral media (cases 2,3,5,7). Here, the two pathways are distinct (enantiometric), they are nevertheless traversed with equal probability, and the two enantiomers are consumed at equal rates. In principle, however, enantiomeric systems undergoing transformations with any one of the following combinations - chiral reagent(s)-achiral media, achiral reagent(s)-chiral media, or chiral reagent(s)-chiral media - are subject to enantiomorpholytic selectivity (cases 16,18,19-21). This is true because either  $|\Delta G_{products}^\ddagger| \neq 0$ , and/or  $\Delta\Delta G^\ddagger \neq 0$ , owing to the involvement of diastereometric (expectedly nonisoenergetic)<sup>74</sup> transition states. In accidentally isoenergetic cases, one would observe nonselectivity (case 5).

In the case of diastereomeric, astereomeric, and nonequimERIC systems (all of which are, *a priori*, nonisoenergetic), morpholytic selectivity is possible with either achiral or chiral reagents, and in achiral or chiral media, because reactions may proceed through expectedly-nonisoenergetic transition states (cases 25-29). In accidentally isoenergetic cases, nonselectivity is expected (case 11-15).

The above considerations of morpholytic selectivity (in all relevant cases, barring accidental disappearance of  $\Delta\Delta G^\ddagger$ ), are summarized in Table 10.1 below:

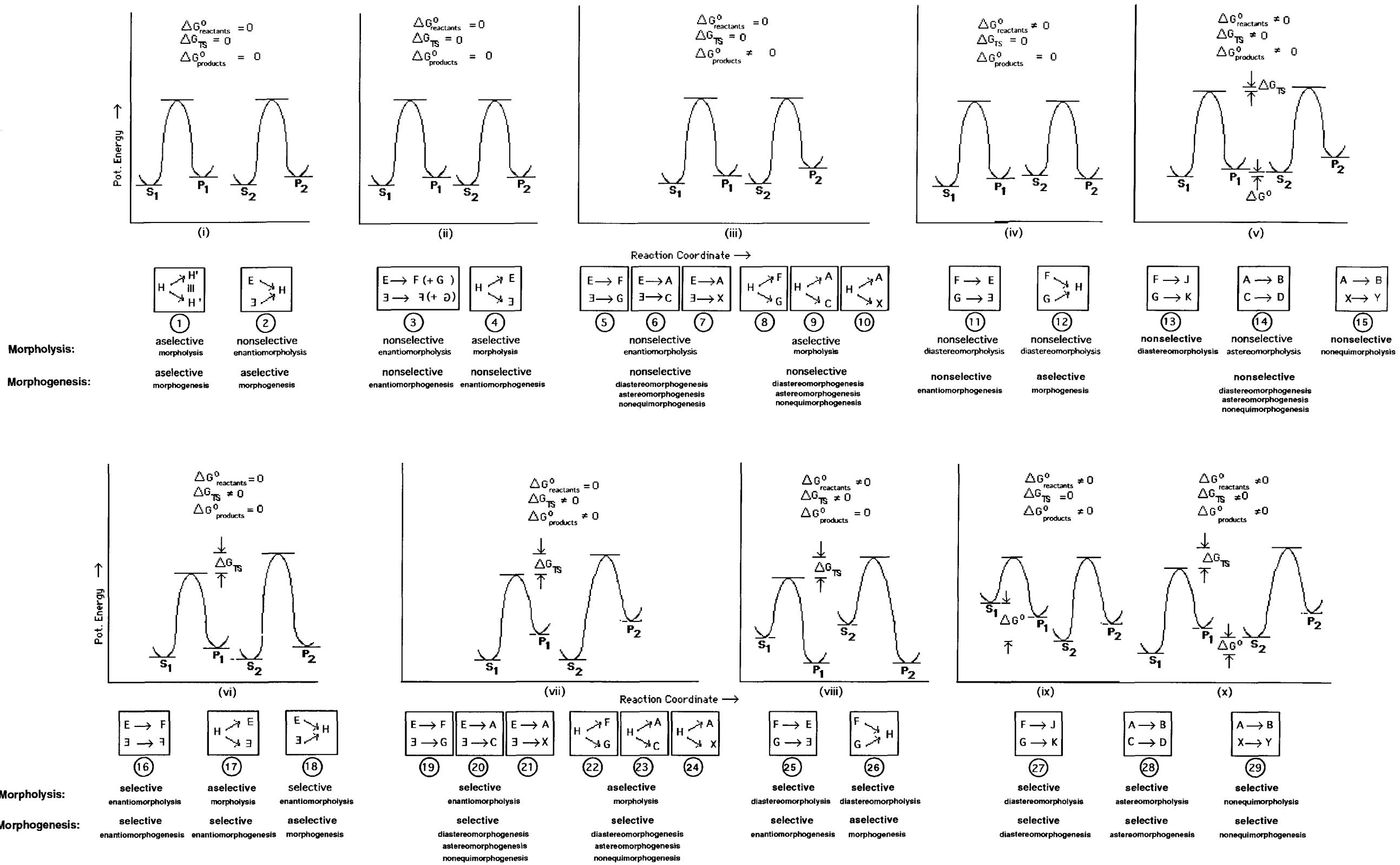


Figure 10.7. Energetics of Morpholytic and Morphogenic Processes

Relationship of Reactants $S_1$ & $S_2$	$S_1$ $S_2$	Achiral Medium		Chiral Medium	
		Achiral Reagent(s)	Chiral Reagent(s)	Achiral Reagent(s)	Chiral Reagents
Homomeric	H H	- <sup>1</sup>	- <sup>1</sup>	- <sup>1</sup>	- <sup>1</sup>
Enantiomeric	E E	- <sup>2</sup>	+ <sup>3</sup>	+ <sup>3</sup>	+ <sup>3</sup>
Diastereomeric	D F	+ <sup>4</sup>	+ <sup>4</sup>	+ <sup>4</sup>	+ <sup>4</sup>
Astereomeric	A C	+ <sup>5</sup>	+ <sup>5</sup>	+ <sup>5</sup>	+ <sup>5</sup>
NonequimERIC	A X	+ <sup>6</sup>	+ <sup>6</sup>	+ <sup>6</sup>	+ <sup>6</sup>

- : not morphoselective (aselective or nonselective cases)  
+ : morphoselective

<sup>1</sup>: homomorpholytic aselective process: cases 1,4,8-10,17,22-24

<sup>2</sup>: enantiomorpholytic nonselective process: cases 2,3,5-7

<sup>3</sup>: enantiomorpholytic selective process: cases 16,18,19-21

<sup>4</sup>: diastereomorpholytic selective process: cases 25-27

<sup>5</sup>: astereomorpholytic selective process: case 28

<sup>6</sup>: nonequimorpholytic selective process: case 29

**Table 10.1.** Selectivity in Morpholytic Processes

### B. Morphogenic Processes

Morphogenic selectivity is not observable (case of morphogenic aselectivity) in the formation of homomeric products  $P_1$  and  $P_2$  ( $P_1 = P_2$ ) (Figure 10.4, cases 1,2,12,18,26). Morphogenic selectivity is expected to be absent in transformations (morphogenic nonselectivity) leading to enantiomeric products if achiral reactants, reagents and/or achiral media are utilized (cases 3,4,11). Here, the two pathways are distinct (enantiometric), they are nevertheless traversed with equal probability, and the two enantiomers are formed at equal rates. In principle, however, enantiomorphogenic selectivity will manifest itself in transformations involving any one of the following combinations: chiral reagent(s)-achiral media, achiral reagent(s)-chiral media, or chiral reagent(s)-chiral media. This is true because  $\Delta\Delta G^\neq \neq 0$  (cases 16,17,25). In accidentally isoenergetic cases, one anticipates nonselective morphogenicity (case 11).

In the case of diastereomeric, astereomeric, and nonequimERIC systems (all of which are, *a priori*, nonisoenergetic), morphogenic selectivity is possible with either achiral or chiral reagents, and in achiral or chiral media, since reactions would proceed through expectedly-nonisoenergetic transition states (cases 19-24,27-29). In accidentally isoenergetic cases, nonselectivity would be observed (cases 5-7,8-10,13-15).

The different scenarios that lead to morphogenic selectivity are summarized in Table 10.2 below:

Relationship of Products $P_1$ & $P_2$	$P_1$ $P_2$	Achiral Medium		Chiral Medium	
		Achiral Reagent(s)	Chiral Reagent(s)	Achiral Reagent(s)	Chiral Reagents
HomomERIC	H H	- <sup>1</sup>	- <sup>1</sup>	- <sup>1</sup>	- <sup>1</sup>
EnantiomERIC	E E	- <sup>2</sup>	+ <sup>3</sup>	+ <sup>3</sup>	+ <sup>3</sup>
DiastereomERIC	D F	+ <sup>4</sup>	+ <sup>4</sup>	+ <sup>4</sup>	+ <sup>4</sup>
AstereomERIC	A C	+ <sup>5</sup>	+ <sup>5</sup>	+ <sup>5</sup>	+ <sup>5</sup>
NonequimERIC	A X	+ <sup>6</sup>	+ <sup>6</sup>	+ <sup>6</sup>	+ <sup>6</sup>

- : not morphoselective (aselective or nonselective cases)

+ : morphoselective

<sup>1</sup>: homomorphogenic aselective process: cases 1,2,12,18,26

<sup>2</sup>: enantiomorphogenic nonselective process: cases 3,4,11

<sup>3</sup>: enantiomorphogenic selective process: cases 16,17,25

<sup>4</sup>: diastereomorphogenic selective process: cases 19,22,27

<sup>5</sup>: astereomorphogenic selective process: cases 20,23,28

<sup>6</sup>: nonequimorphogenic selective process: cases 21,24,29

**Table 10.2.** Selectivity in Morphogenic Processes

Since a given reaction may be looked at in terms of changes in either reactant or product, there would be a correlation between morpholytic and morphogenic processes. Figure 10.8 (p. 58) shows the correlation of cases 1-29 of Figure 10.7.

Thus, an aselective morpholytic process may accompany a morphogenic process that is aselective (case 1), nonselective (cases 4,8,9,10), or selective (cases 17,22,23,24). A nonselective morpholytic process, on the other hand, may go hand in hand with either aselective (cases 2,12) or nonselective morphogenic processes (cases 3,5,6,7,11,13,14,15). Finally, a selective morpholytic process may partake in aselective or selective processes. However, nonselective morpholytic and selective morphogenic processes cannot occur concomitantly; the same is true of simultaneous selective morpholytic and nonselective morphogenic processes.

#### IV. Quantitative Designation of Morphoselectivity

##### A. Morpholytic Processes

The selective or competitive consumption of substrate  $S_1$  as opposed to that of substrate  $S_2$  by a given single reagent, is determined by  $\Delta\Delta G^\ddagger$ , the difference in activation energies of the two competing processes (*vide supra*), and is reflected in  $k_{S_1}/k_{S_2}$ , where  $k_{S_1}$  and  $k_{S_2}$  are the rate constants of the competing processes (kinetic control). The selectivity is denoted by morpholytic selectivity,  $S_{ml}$ , based on a Hammett-type relationship, (Eq. 10.1), or by (morphic) substance excess (se) (Eq. 10.2):

$$S_{ml} = \log(k_{S_1}/k_{S_2}) \quad (10.1)$$

$$se = | \%S_1 - \%S_2 | \quad (10.2)$$

$$\text{where } \%S_1 = \frac{(C_{S_1}^{t^0} - C_{S_1}^t)}{(C_{S_1}^{t^0} - C_{S_1}^t) + (C_{S_2}^{t^0} - C_{S_2}^t)} \quad \%S_2 = \frac{(C_{S_2}^{t^0} - C_{S_2}^t)}{(C_{S_1}^{t^0} - C_{S_1}^t) + (C_{S_2}^{t^0} - C_{S_2}^t)} \quad (10.3a, 10.3b)$$

The  $\%S_1$  and  $\%S_2$  terms are the amounts of  $S_1$  and  $S_2$  that have remained unreacted at  $t = t$ ; the  $C$  terms are the concentrations of reactants  $S_1$  and  $S_2$  in the same reaction mixture that have reacted for the same period of time - from the beginning ( $t=t_0$ ) to the end ( $t=t$ ) of the competitive processes.

If  $S_1$  reacts 10 times more rapidly than  $S_2$ ,  $k_{S_1}/k_{S_2} = 10$ ,  $S_{ml} = \log(10/1) = 1$ ;  $se = | \%S_1 - \%S_2 | = 90.9 - 0.9 = 90\%$ ; if  $k_{S_1}/k_{S_2} = 100$ ,  $S_{ml} = \log(100/1) = 2$ ,  $se = | \%S_1 - \%S_2 | = 99.01 - 0.01 = 99\%$ .

The quantitative expressions for the particular morpholytic selectivities are given by the following equations:

$$\text{enantiomorpholytic selectivity} = S_{eml} = \log(k_E/k_\alpha) \quad (10.4)$$

$$se = ee = \text{enantiomeric excess} = | \%E - \% \alpha | \quad (10.5)$$

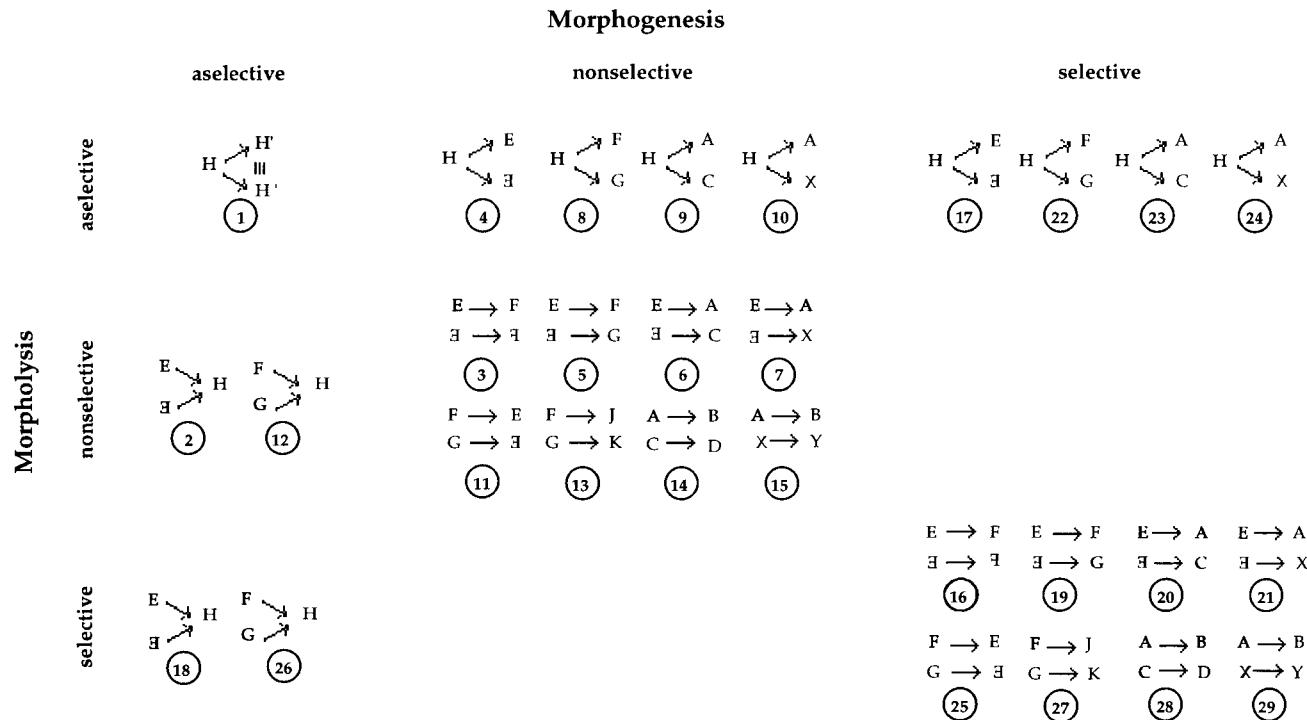


Figure 10.8. Correlations of Morpholytic and Morphogenic Processes

$$\text{diastereomorpholytic selectivity} = S_{\text{dml}} = \log(k_D/k_F) \quad (10.6)$$

$$se = de = \text{diastereomeric excess} = | \%D - \%F | \quad (10.7)$$

$$\text{astereomorpholytic selectivity} = S_{\text{aml}} = \log(k_A/k_C) \quad (10.8)$$

$$se = ae = \text{astereomorphic excess} = | \%A - \%C | \quad (10.9)$$

$$\text{nonequimorpholytic selectivity} = S_{\text{nml}} = \log(k_A/k_X) \quad (10.10)$$

$$se = ne = \text{nonequimorphic excess} = | \%A - \%X | \quad (10.11)$$

In the preceding discussion it was assumed that a single given reagent reacts selectively with two substrates -  $S_1$  and  $S_2$ . The selectivity relationships given above would apply for pairs of substrates. A chemical transformation may involve three or more substrates. Thus, for a three-way competition between substrates  $S_1$ ,  $S_2$ , and  $S_3$  one defines  $\%S_1-\%S_2$ , and  $\%S_2-\%S_3$ . Similarly, for a four-way competition, one has  $\%S_1-\%S_2$ ,  $\%S_2-\%S_3$ , and  $\%S_3-\%S_4$ . Additionally, one may have two reactants  $R_1$  and  $R_2$  (say a racemic form of a chiral reagent) reacting with two substrates  $S_1$  and  $S_2$ , thereby leading to four possible competing pathways -  $R_1+S_1$ ,  $R_1+S_2$ ,  $R_2+S_1$  and  $R_2+S_2$ . We will discuss such cases in Chapters 12 and 13.

### B. Morphogenic Processes

The selective or competitive formation of product  $P_1$  as opposed to that of product  $P_2$  in a given reaction mixture, is determined by  $\Delta\Delta G^\ddagger$ , the difference in activation energies of the two competing processes, and is reflected in  $k_{P_1}/k_{P_2}$ , where  $k_{P_1}$  and  $k_{P_2}$  are the rate constants of the competing processes (kinetic control). The selectivity is denoted by morphogenic selectivity,  $S_{\text{mg}}$ , based on a Hammett-type relationship, (Eq. 10.12), or by % morphic substance excess (se) (Eq. 10.13):

$$S_{\text{mg}} = \log(k_{P_1}/k_{P_2}) \quad (10.12)$$

$$se = | \%P_1 - \%P_2 | \quad (10.13)$$

$$\text{where } \%P_1 = \frac{(C_{P_1}^{\text{f}} - C_{P_1}^{\text{t}})}{(C_{P_1}^{\text{f}} - C_{P_1}^{\text{t}}) + (C_{P_2}^{\text{f}} - C_{P_2}^{\text{t}})} \quad \%P_2 = \frac{(C_{P_2}^{\text{f}} - C_{P_2}^{\text{t}})}{(C_{P_1}^{\text{f}} - C_{P_1}^{\text{t}}) + (C_{P_2}^{\text{f}} - C_{P_2}^{\text{t}})} \quad (10.14\text{a}, 10.14\text{b})$$

The  $\%P_1$  and  $\%P_2$  terms are the amounts of  $P_1$  and  $P_2$  that have formed at  $t=t$ ; the  $C$  terms are the concentrations of reactants  $P_1$  and  $P_2$  in the same reaction mixture that have reacted for the same period of time - from the beginning ( $t=t_0$ ) to the end ( $t=t$ ) of the competitive processes.

If  $P_1$  is formed 10 times more rapidly than  $P_2$ ,  $k_{P_1}/k_{P_2} = 10$ ,  $S_{\text{mg}} = \log(10/1) = 1$ ;  $se = | \%P_1 - \%P_2 | = 90.9 - 0.9 = 90\%$ ; if  $k_{P_1}/k_{P_2} = 100$ ,  $S_{\text{mlh}} = \log(100/1) = 2$ ,  $se = | \%P_1 - \%P_2 | = 99.01 - 0.01 = 99\%$ .

The quantitative expressions for the particular morphogenic selectivities are given by the following equations:

$$\text{enantiomorphogenic selectivity} = S_{\text{emg}} = \log(k_E/k_\Xi) \quad (10.15)$$

$$se = ee = \text{enantiomorphic excess} = | \%E - \% \Xi | \quad (10.16)$$

$$\text{diastereomorphogenic selectivity} = S_{\text{dmg}} = \log(k_D/k_F) \quad (10.17)$$

$$de = \text{diastereomeric excess} = | \%D - \%F | \quad (10.18)$$

$$\text{astereomorphogenic selectivity} = S_{\text{amg}} = \log(k_A/k_C) \quad (10.19)$$

$$ae = \text{astereomorphic excess} = | \%A - \%C | \quad (10.20)$$

$$\text{nonequimorphogenic selectivity} = S_{\text{nmg}} = \log(k_A/k_X) \quad (10.21)$$

$$ne = \text{nonequimorphic excess} = | \%A - \%X | \quad (10.22)$$

The preceding discussion was intended for two-component systems. A wide variety of chemical transformations do yield 3-component or 4-component mixtures. Before the discussion on multicomponent systems, we will first extend the concept of selectivity to encompass situselectivity (Chapter 11), facioselectivity (Chapter 12), and vectoselectivity (Chapter 13). The specification of the various compositions of 2-, 3-, 4-component mixtures was given previously in Addendum A, Volume 1 (p. 143).

### Summary

For a given a molecular transformation, the selective consumption of a reactant  $S_1$ , over  $S_2$ , is characterized by *morpholytic selectivity*, whereas the selective generation of a product  $P_1$ , over  $P_2$ , is characterized by *morphogenic selectivity*. Each of these selectivities was classified further, on the basis of the morphic relationship of the reactants  $S_1$  and  $S_2$ , or of the products  $P_1$  and  $P_2$ . If  $S_1$  and  $S_2$  are stereomeric or nonstereomeric with respect to each other, then the process is characterized by *stereomorpholytic selectivity* or *nonstereomorpholytic selectivity*, respectively. Stereomorpholytic selectivity is subdivided into *enantiomorpholytic selectivity* and *diastereomorpholytic selectivity*. Nonstereomorpholytic selectivity, in turn, is subdivided into *astereomorpholytic selectivity* and *nonequimorpholytic selectivity*.

In a parallel manner, if  $P_1$  and  $P_2$  are stereomeric or nonstereomeric with respect to each other, then the process is characterized by *stereomorphogenic selectivity* or *nonstereomorphogenic selectivity*, respectively. Stereomorphogenic selectivity is subdivided into *enantiomorphogenic selectivity* and *diastereomorphogenic selectivity*. Nonstereomorphogenic selectivity, in turn, is subdivided into *astereomorphogenic selectivity* and *nonequimorphogenic selectivity*.

"The search is for the just word, the happy phrase, that will give expression to the thought, but somehow the thought itself is transfigured by the phrase when found."

Benjamin N. Cardozo, *The Growth of the Law*, 1924.

# 11

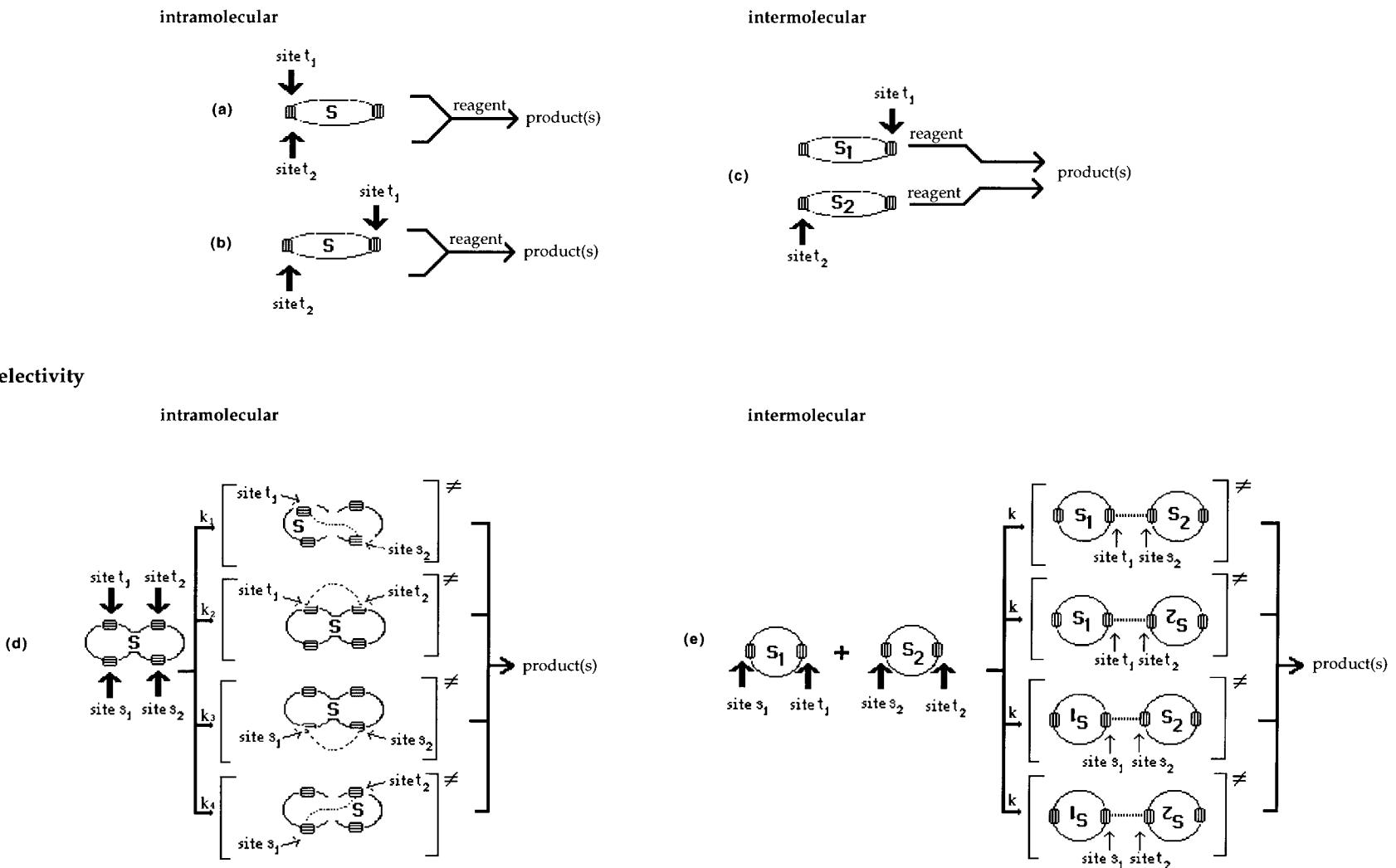
## Situselectivity

In specifying selectivity of ligogenic processes, the focus of attention is on either whole molecules, or, molecular sites. Selectivity for whole molecules is based on their morphic relationships and is termed *morphoselectivity*. In contrast, if the emphasis is on selective transformations at molecular sites, then one is dealing with *situselectivity*.<sup>75</sup> The latter term is synonymous with site selectivity,<sup>76</sup> site specificity,<sup>77</sup> positional selectivity,<sup>46,49</sup> locoselectivity,<sup>78</sup> atroposelectivity,<sup>79</sup> regioselectivity (intramolecular),<sup>69,71,80</sup> regiospecificity,<sup>81</sup> chemoselectivity (intramolecular),<sup>82</sup> intramolecular selectivity,<sup>49,83</sup> functional selectivity,<sup>84</sup> and sequence selectivity.<sup>85</sup> This chapter deals with the concept of situselectivity, and establishes the commonality of all the previous terms.

### I. Situselectivity and Bisituselectivity

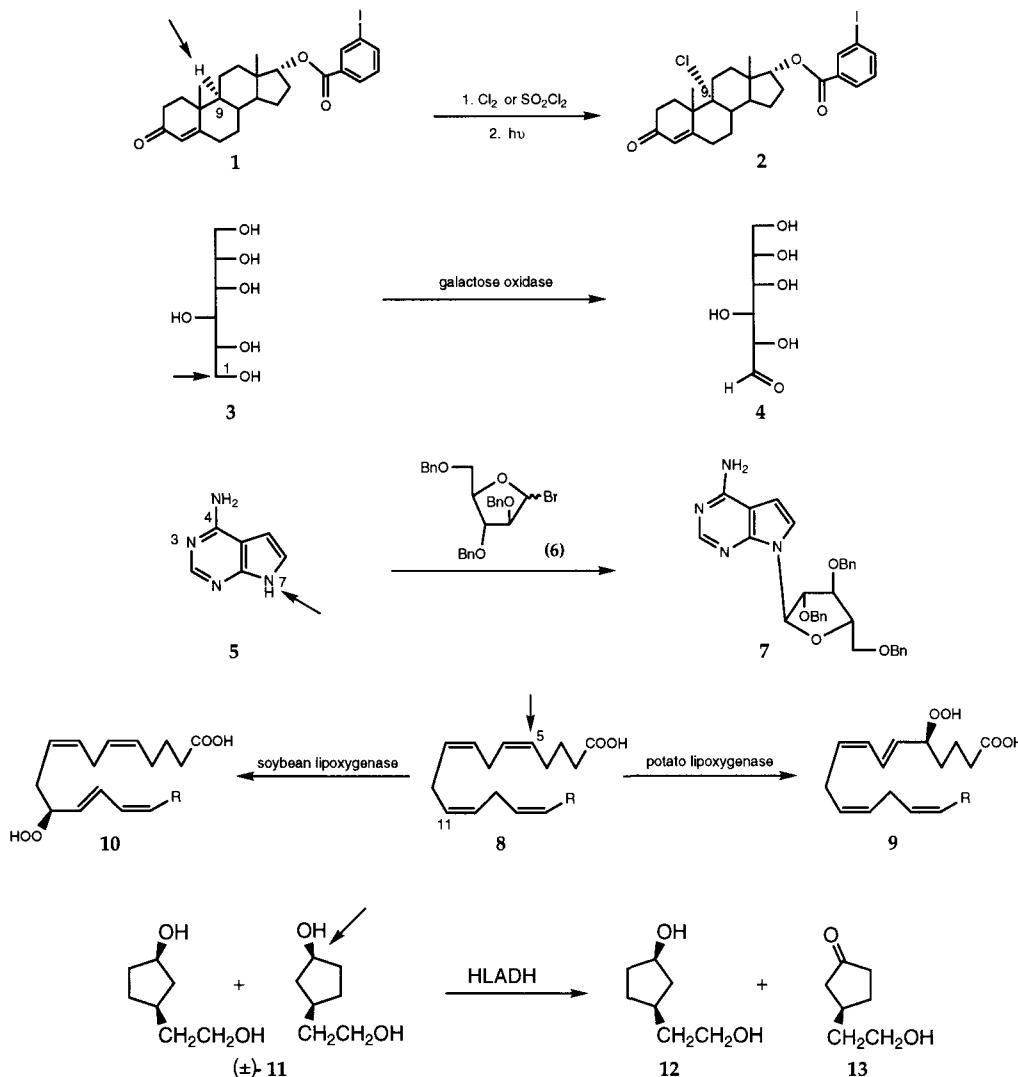
In a geometric figure, a site (L. *situs*, site, place, location; Gr. *topos*, place, position, spot) refers to a point, an edge, a plane, or a geometric segment. In a molecule, a site refers to an atom (with empty, partially filled or completely filled atomic orbitals), a bond, a molecular face,<sup>86</sup> or a molecular segment (the latter being a composite of the said three fundamental sites). There is a direct correspondence between geometric sites in figures, on the one hand, and molecular sites in molecules, on the other. Thus, a point in a geometric figure may correspond to an atom in a molecule, an edge in a figure may correspond to a bond (or the distance between two nonbonded atoms) in a molecule, a plane in a figure may correspond to a planar portion of a molecule, and a geometric segment in a figure would be the counterpart of a molecular moiety. A given chemical transformation, in which reagent/reactant R can react competitively at two molecular sites (or subsites)  $t_1$  and  $t_2$  in a single molecule S (intramolecular case), or at two sites  $t_1$  and  $t_2$  in two nonhomomeric reactant molecules  $S_1$  and  $S_2$  (intermolecular case),<sup>87</sup> respectively, would be characterized by *situselectivity* (Figure 11.1). In instances where two reactants  $S_1$  and  $S_2$  are involved, and there are competing sites  $s_1$  and  $t_1$  in  $S_1$ , and competing sites  $s_2$  and  $t_2$  in  $S_2$ , the process is characterized by bisituselectivity - i.e. site selectivity between  $s_1$  and  $t_1$  in reactant  $S_1$  and concomitant selectivity between sites  $s_2$  and  $t_2$  in reactant  $S_2$  (*vide infra*).<sup>88</sup> Figure 11.1 illustrates idealized situselective and bisituselective transformations.

## siteselectivity



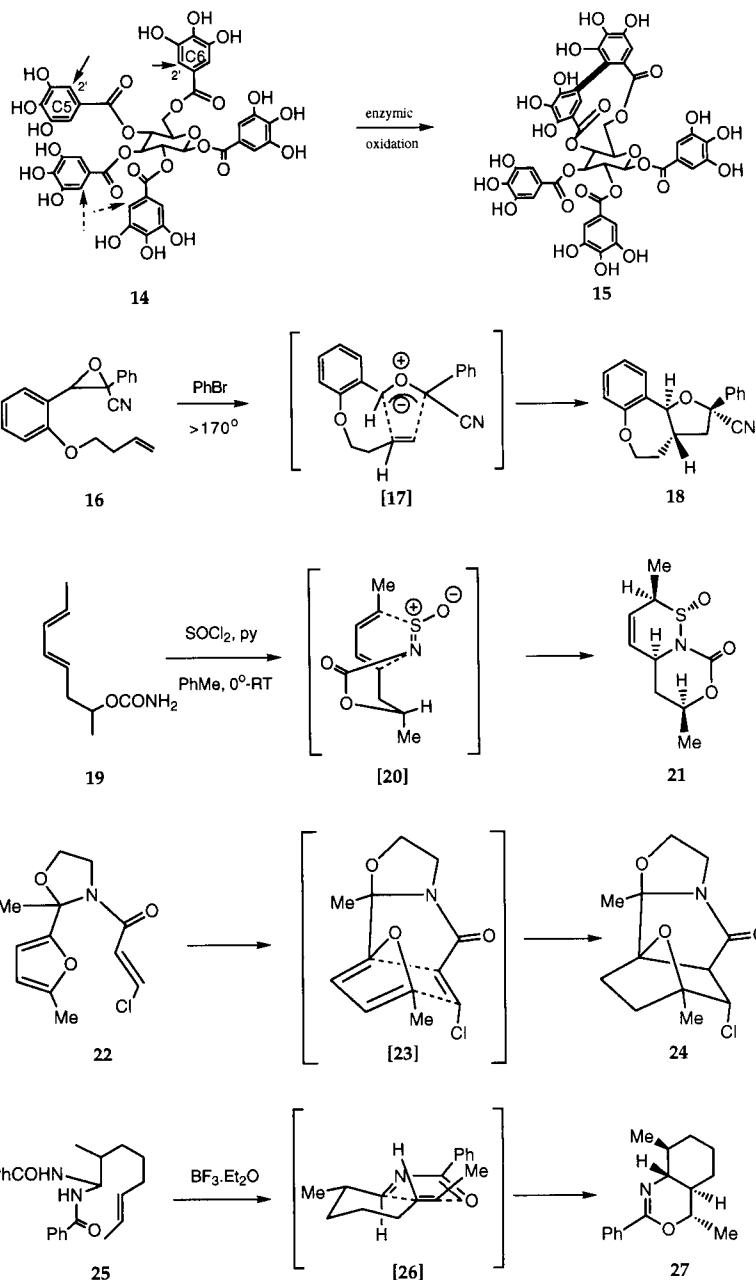
**Figure 11.1.** Idealized Representation of Siteselective and Bisiteselective Transformations

The reactions in Figure 11.2 below illustrate the generalized concept of siteselectivity and bisiteselectivity. Siteselective chlorination of **1** at C-9 yields **2**,<sup>89</sup> whereas siteselective enzymatic oxidation of **3** at C-1 produces L-glucose (**4**).<sup>90</sup> The coupling of halogenose **6** with unprotected 7H-pyrrolo[2,3-d]pyrimidine (**5**) takes place siteselectively at N-7 to give **7**.<sup>91</sup> Enzymatic peroxidation of arachidonic acid (**8**) occurs siteselectively at C-5 with potato lipoxygenase, and at C-11 with soybean lipoxygenase,<sup>92</sup> to give the corresponding hydroperoxides **9** and **10**. The oxidation of racemic diol ( $\pm$ )-**11** with horse liver alcohol dehydrogenase (HLADH)<sup>54</sup> is an example of an intermolecular siteselective transformation.



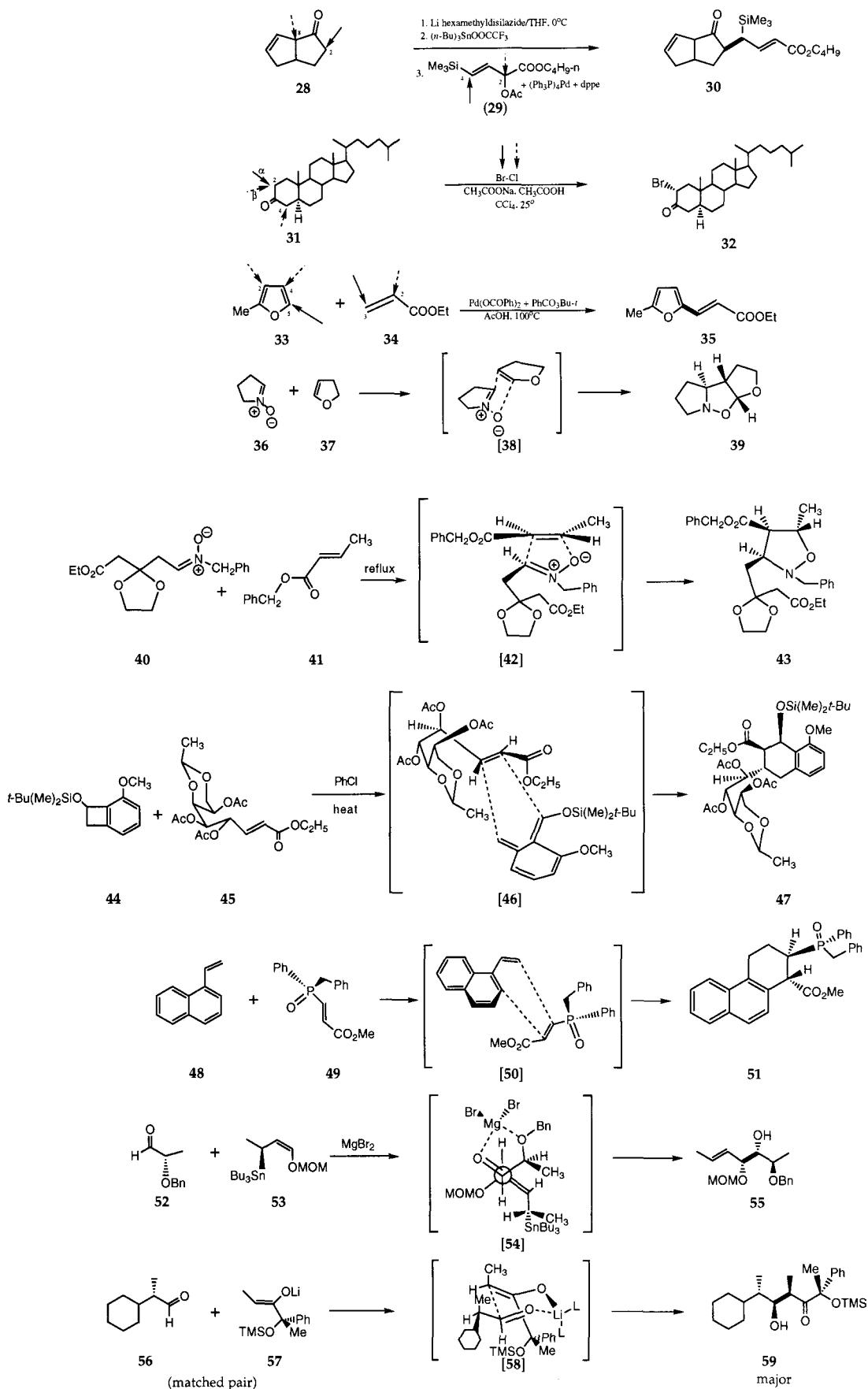
**Figure 11.2.** Examples of Siteselective and Bisituselective Transformations

The enzymatic oxidation in plant of  $\beta$ -pentagalloyl-D-glucose (**14**) to tellimagrandin (**15**)<sup>93</sup> is a (1,1)-junctive bisituselective process linking C-2'(C6 ring) and C-2'(C5 ring) (Figure 11.3). Examples of (2,2)-junctive bisituselective transformations include the intramolecular cyclizations of **16**→[**17**]→**18** (case of edge/face bisituselectivity),<sup>94</sup> and, **19**→[**20**]→**21**,<sup>95</sup> **22**→[**23**]→**24**,<sup>96</sup> and **25**→[**26**]→**27**<sup>97</sup> (all three show face/face bisituselectivity) as shown in Figure 11.3.

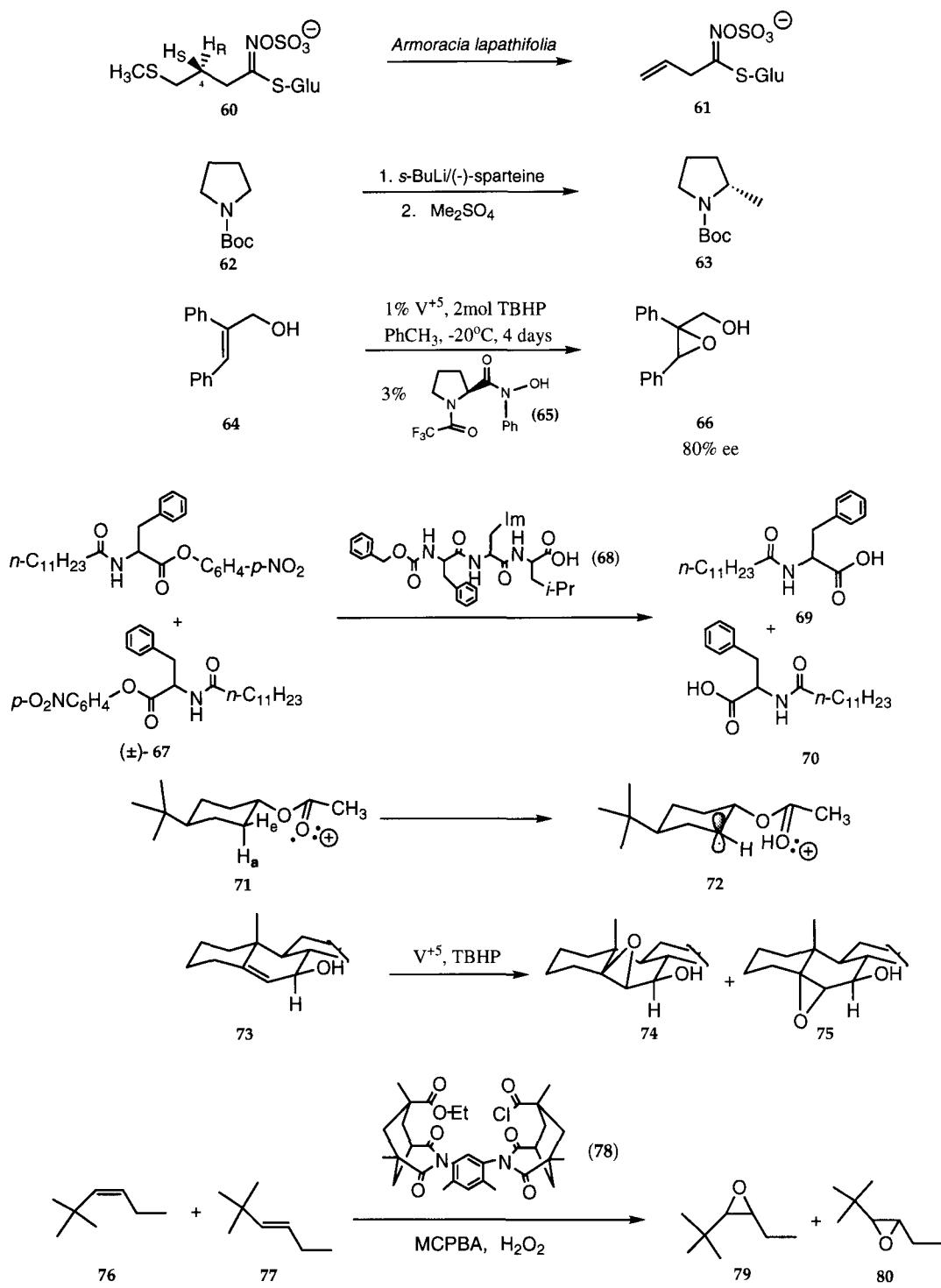


**Figure 11.3.** Examples of Situselective and Bisituselective Transformations

The palladium-catalyzed alkylation of the stannyll enolate of **28** with *n*-butyl 2-acetoxy-4-(trimethylsilyl)-3-butenoate (**29**), to yield **30**,<sup>98</sup> is a (1,1)-junctive process in which the  $sp^3$ - $sp^3$   $\sigma$ -bond is formed bisituselectively between C-2  $\alpha$ -carbon of **28** and C-4 of **29**. Two other bisituselective (1,1)-junctive processes are exemplified by the reaction of **31** with Br-Cl (situselective at C-2 $\alpha$  in substrate **31** and situselective at Br in reagent Br-Cl),<sup>99</sup> and, the coupling of furan **33** with ethyl acrylate (**34**) (bisituselective at C-5 of **33** and C-3 of **34**).<sup>100</sup> The (2,2)-ligogenic transformations **36+37→[38]→39**,<sup>101</sup> **40+41→[42]→43**,<sup>102</sup> **44+45→[46]→47**,<sup>103</sup> **48+49→[50]→51**,<sup>104</sup> constitute, in effect, (2,2)-ligogenic processes, whereas the next two examples - **52+53→[54]→55**,<sup>105</sup> and **56+57→[58]→59**<sup>106</sup> - are (2,2)-junctive processes that end up as overall (1,1)-ligogenic processes.



**Figure 11.4.** Examples of Situselective and Bisituselective Transformations



**Figure 11.5.** Examples of Stereosituselective Transformations

## II. Classification of Situselectivity

### A. Stereosituselectivity and Nonstereosituselectivity

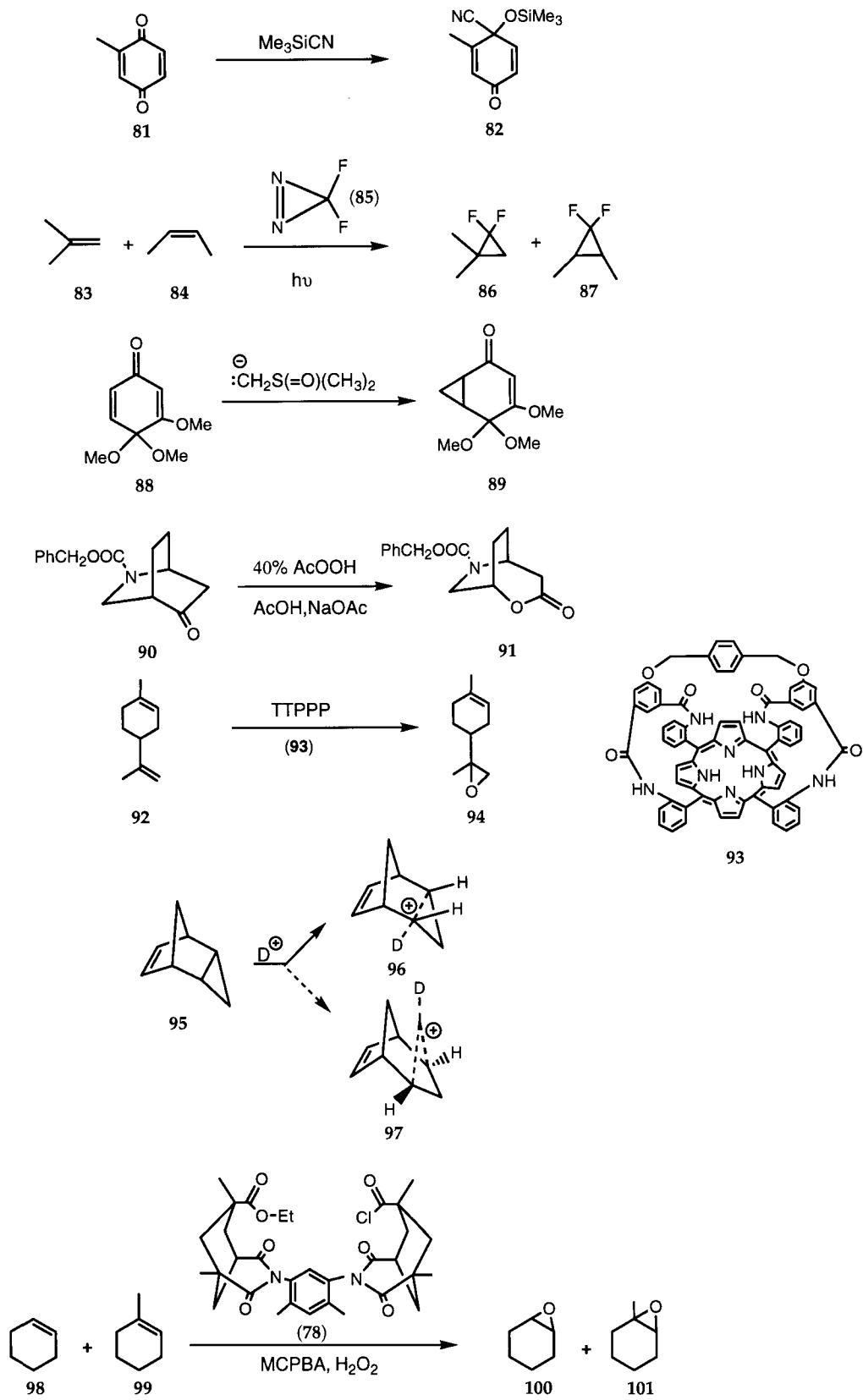
In a chemical transformation of a molecule with two reactive sites (or subsites)  $t_1$  and  $t_2$ , it is the *topic* relationship between the two sites (or subsites) (Volume 1, Chapter 3, p. 35) that determines the exact type of situselectivity (*vide infra*). If  $t_1$  and  $t_2$  are stereotopic with respect to each other, then the process is characterized by *stereosituselectivity* (*stereotopic site selectivity*); if the sites are nonstereotopic, then one has *nonstereosituselectivity* (*nonstereotopic site selectivity*). Stereosituselectivity is subclassified into *enantiosituselectivity* (*enantiotopic site selectivity*) or *diastereosituselectivity* (*diastereotopic site selectivity*), if  $t_1$  and  $t_2$  are enantiotopic, or, diastereotopic with respect to each other, respectively.<sup>107</sup> On the other hand, nonstereosituselectivity is subclassified into *astereosituselectivity* (*nonstereotopic site selectivity*) or *nonequisituselectivity* (*nonstereotopic site selectivity*), depending on whether  $t_1$  and  $t_2$  are astereotopic, or, nonequiptopic with respect to each other, respectively. Figures 11.5 and 11.6 illustrate select examples of stereosituselectivity and nonstereosituselectivity.

Intramolecular enantiosituselectivity is exemplified by the biosynthetic formation of the mustard oil glucoside sinigrin (60) in horseradish,<sup>108</sup> the deprotonation of N-Boc-pyrrolidine (62) with *sec*-butyllithium (*s*-BuLi)/(-)-sparteine, followed by methylation,<sup>109</sup> and, the oxidation of enol 64.<sup>110</sup> Intermolecular enantiosituselective transformations are exemplified by the hydrolysis of racemic N-dodecanoylphenylalanine *p*-nitrophenyl esters (( $\pm$ )-67) in the presence of tripeptide catalyst (Z)-L-Phe-L-His-L-Leu (68),<sup>111</sup> in each of the latter two cases, only one (externally) enantiotopic carbonyl reacts preferentially.<sup>112</sup> It should be pointed out parenthetically, that as a result of the enantiosituselectivity in these transformations, one has, in effect, kinetic resolution of ( $\pm$ )-67. The electron-impact induced elimination in acetate 71,<sup>113</sup> and the oxidation of 73 exemplify intramolecular diastereosituselective transformations.<sup>114</sup> The epoxidation of the mixture 76/77 is an example of an intermolecular diastereosituselective process at the same time that each substrate is subject to enantiositunselectivity of the carbonyl sub-sites.

Intramolecular astereosituselective reactions are exemplified by the selective blocking of the more electron-rich C=O of 81 with trimethylsilyl cyanide to give 82.<sup>115</sup> An example of intermolecular astereosituselectivity is provided by the addition of difluorocarbene to 2-butene (83) and 2-methylpropene (84) ( $k_{38}/k_{39} = 12.8$ ).<sup>58</sup>

Finally, intramolecular nonequisituselective transformations are exemplified by the selective methylenation of quinone ketal 88,<sup>116</sup> the Baeyer-Villiger oxygen insertion in bicyclic ketone 90,<sup>69</sup> and by the epoxidation of the external double bond of limonene (92) with the highly hindered Mn[5,10,15,20-tetrakis(2',4',6'-triphenylphenyl)porphyrin](acetate) = [Mn(TPPPP)(OAc)] catalyst (93),<sup>117</sup> the corner- vs. edge-protonation of *endo*-tricyclo[3.2.1.0<sup>2,4</sup>]oct-6-ene (95).<sup>118</sup> Intermolecular nonequisituselectivity is exemplified by the epoxidation of cyclohexenes (98/99)<sup>57</sup> with Rebek's ester-acid chloride 78, MCPBA and H<sub>2</sub>O<sub>2</sub>.

Nonequisituselective binding is seen in the molecular recognition of DNA, RNA, and other biomolecules.<sup>119</sup> For example, synthetic peptides 2-PyN and 2-ImN bind by antiparallel alignment at 5'-TGTCA-3' and 5'-TGTCA-3' sites in the minor groove of DNA.<sup>120</sup> Similarly, distamycin (D) and 2-ImN bind at the 5'-TGTCA-3' site as an antiparallel heterodimer. On the other hand, covalent peptide heterodimer 2-ImN-C4-P3 binds selectively at the 5'-TGTCA-3' site of a DNA fragment containing all three - 5'-TTTTT-3', 5'-TGTCA-3' and 5'-TGTCA-3'- binding sites. Similarly, enediyne antitumor antibiotics calicheamicin  $\gamma_1$ I and esperamicin A1 bind preferentially to the minor groove of DNA<sup>121,122</sup> while inhibitor [2S-(2R\*,6R\*,9R\*)]-3,4,5,6,8,9-hexahydro-4-hydroxy-11-methyl-6,9-bis(2-methylpropyl)-2,13-ethano-1,5,8,4-benzoxa diaza-phosphacycloundecin-7(2H)-one-4-oxide, monolithium salt, binds selectively at the active site of zinc peptidase thermolysin,<sup>123</sup> and phenol at Leu-57/Ile-91/Asp-72/Pro-237/Gly-235 and Val-121/Val143/Leu-198/Trp-209/Thr-199 in the active site of human carbonic anhydrase II.<sup>124</sup>



**Figure 11.6.** Examples of Nonstereoselective Transformations

## B. Subclassification of Enantiosituselectivity, Diastereosituselectivity, Astereosituselectivity and Nonequisituselectivity

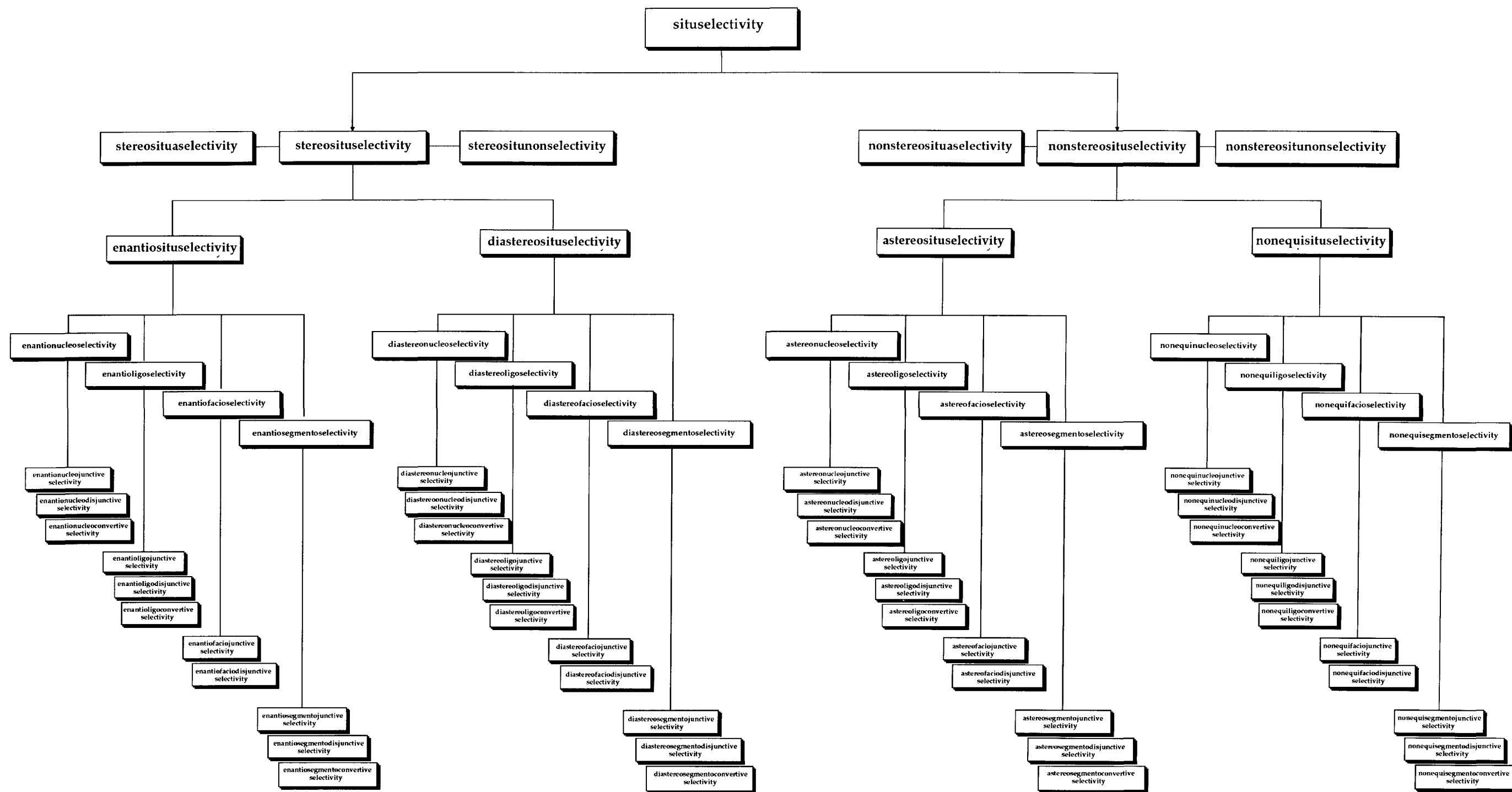
Enantiosituselectivity, diastereosituselectivity, astereosituselectivity and nonequisituselectivity can be further subclassified on the basis of the structural nature of the site undergoing the transformation. Since sites or subsites are atoms, bonds, half-spaces, and segments, it is possible, to subclassify each the four listed types of situselectivity into nucleoselectivity (selectivity between atoms), ligoselectivity (selectivity between ligating bonds), facioselectivity (selectivity between half-spaces of molecular faces), or (segmentoselectivity; L. segmentum, piece, selectivity between molecular segments).

Thus, *enantiosituselectivity* may be subclassified into *enantionucleoselectivity* (selectivity at enantiopic atoms), *enantioligoselectivity* (selectivity at enantiopic bonds), *enantiofacioselectivity* (selectivity at enantiopic molecular faces) and *enantiosegmentoselectivity* (selectivity at enantiopic molecular segments). *Diastereosituselectivity* is similarly subclassified into *diastereonucleoselectivity* (selectivity at diastereotopic atoms), *diastereoligoselectivity* (selectivity at diastereotopic bonds), *diastereofacioselectivity* (selectivity at diastereotopic molecular faces) or *diastereosegmentoselectivity* (selectivity at diastereotopic molecular segments). *Astereosituselectivity* is subclassified into *astereonucleoselectivity* (selectivity at astereotopic atoms), *astereoligoselectivity* (selectivity at astereotopic bonds), *astereofacioselectivity* (selectivity at astereotopic molecular faces) and *astereosegmentoselectivity* (selectivity at astereotopic molecular segments). Finally, *nonequisituselectivity* is subclassified into *nonequinucleoselectivity* (selectivity at nonequitopic nuclei), *nonequiligoselectivity* (selectivity at nonequitopic bonds), *nonequifacoselectivity* (selectivity at nonequitopic molecular faces) and *nonequisegmentoselectivity* (selectivity at nonequitopic molecular segments).

Of the examples given previously, the biosynthetic formation of the mustard oil glucoside sinigrin (60) in horseradish, and the deprotonation of N-Boc-pyrrolidine (62) with sec-butyllithium/(-)-sparteine involve enantioligoselective cleavages. The elimination in acetate 71 constitutes a diastereoligoselective scission, whereas the oxidation of 73 exemplifies a diastereofacioselective transformation, and the oxidation of 76/77 is an intermolecular diastereosegmentoselective process. The methylenation of quinone ketal 88, epoxidation of the external double bond of limonene (92) are nonequisegmentoselective reactions, while the deuteronation of 95 is nonequisituselective. The selectivity seen in the molecular recognition of DNA, RNA, and other biomolecules may be generally described as nonequisegmentoselective complexation. For example, complexation of distamycin (D) and 2-ImN bind at the 5'-TGTAA-3' site as a antiparallel heterodimer, or of covalent peptide heterodimer 2-ImN-C4-P3 at the 5'-TGTAA-3' site of a DNA fragment are nonequisegmentoselective. Similarly, enediyne antitumor antibiotics calicheamicin  $\gamma_1^I$  and esperamicin A1 bind at the minor groove of DNA, nonequisegmentoselectively.

## C. Subclassification of Nucleoselectivity, Ligoselectivity, Facioselectivity and Segmentoselectivity

The subclassifications given in the preceding section can, in principle, be taken a step further, to include a specification of the *type of process* at the particular site. In general, at a given site - atom, bond, face, segment - the type of process may be *junctive* (conjunctive, associative, additive, complexative), *disjunctive* (dissociative, subtractive, decomplexative), or *convertive* (substitutive, transformative; e.g. carbonyl to methylene). It turns out that nucleoselectivity, ligoselectivity and segmentoselectivity are generally *junctive*, *disjunctive* or *convertive*, whereas facioselectivity is either *junctive* or *disjunctive*.



**Figure 11.7 Complete Classification of Siteselectivity**

The biosynthetic formation of the mustard oil glucoside sinigrin (**60**) in horseradish, and the deprotonation of N-Boc-pyrrolidine (**62**) with *sec*-butyllithium (*s*-BuLi)/(-)-sparteine display enantioligodisjunctive selectivity. The elimination in acetate **71** constitutes a selective diastereoligodisjunctive process, while the oxidation of enol **73** exhibits diastereofaciojunctive selectivity. The methylenation of quinone ketal **47** is characterized by nonequisegmentojunctive selectivity, while the bindings of enediyne antitumor antibiotics calicheamicin  $\gamma_1^1$ , and esperamicin A1, at the minor groove of DNA, show nonequisegmentojunctive selectivity,

The complete classification of the different types of selectivity is given in Figure 11.7. Such a classification enables one to specify the type of situselectivity *at the level of detail needed or desired*. At the simplest level, a process at a molecular site is selective (situselective), nonselective (situnonselective), or aselective (situaselective). If situselective, a process is either stereosituselective or nonstereosituselective. At the next level, one may specify the topic relationship between the sites - enantiosituselective vs. diastereosituselective, or astereosituselective vs. nonequisituselective. The next level of detail specifies the type of site e.g. enantionucleoselective vs. enantiofacioselective. Finally, at the highest level, one may specify the type process at the site, e.g. enantiofaciojunctive selectivity vs. enantiofaciodisjunctive selectivity.

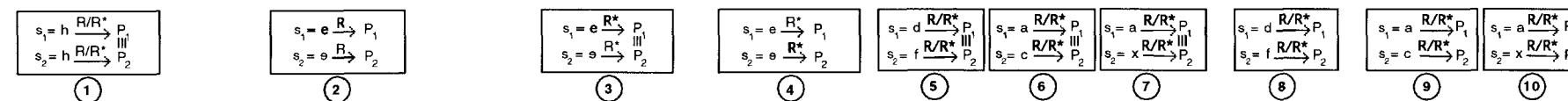
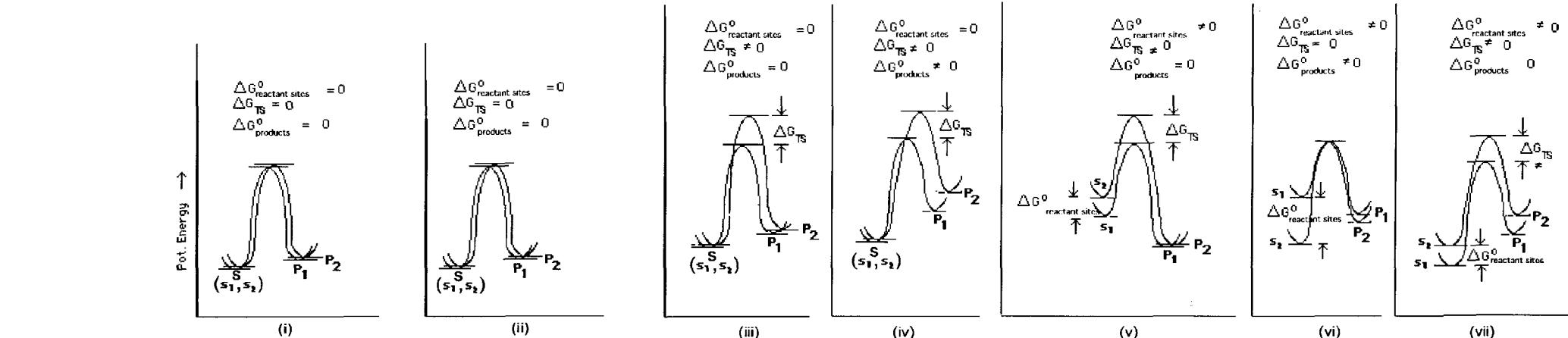
### III. Origin of Situselectivity - Energetics & Transition States

The origin of situselectivity, as for morphoselectivity, lies in the difference in the free energies of activation for the competing processes, *viz.*  $\Delta\Delta G^\ddagger$  (see Vol. 2, p. 52). Destruction or consumption of a site may be referred to as *situlysis*. Note that for intramolecular cases, the ground state of a reactant molecule S is one and the same, despite any possible differences of localized chemical potential energies of competing sites or subsites  $s_1$  and  $s_2$ . Intramolecular situselectivity is generally monitored through the appearance of products  $P_1 \neq P_2$ ,  $\Delta\Delta G^\ddagger > 0$ . Intermolecular situselectivity, on the other hand, is followed by either the disappearance of reactants (morpholysis) -  $S_1 \neq S_2$  and  $\Delta\Delta G^\ddagger > 0$ , or appearance of products (morphogenesis) -  $P_1 \neq P_2$ ,  $\Delta\Delta G^\ddagger > 0$ . The various possibilities for intramolecular and intermolecular situselectivity are portrayed in Figure 11.8. Here, a "ligo" site is in competition with a "nucleo" site; the more general "situ" component is retained to accommodate both type of sites.

Intramolecular situselectivity is operationally undetectable if sites  $s_1$  and  $s_2$  are homotopic, i.e.  $s_1 = s_2$ ; this is the case of aselectivity (case 1). If  $s_1 \neq s_2$  but  $\Delta\Delta G^\ddagger = 0$ , no situselectivity is observed (case 2); this is the case of nonselectivity. If  $s_1 \neq s_2$ , situselectivity would be observed even if ground states are isoenergetic ( $\Delta G^\circ = 0$ ), provided transition states are non-isoenergetic ( $\Delta\Delta G^\ddagger \neq 0$ ), i.e.  $\Delta\Delta G^\ddagger = |\Delta G^\circ - \Delta G_{TS}| > 0$  (cases 3-4). Situselectivity is also possible when ground states are non-isoenergetic ( $\Delta G^\circ \neq 0$ ), and transition states are either isoenergetic ( $\Delta G_{TS} = 0$ , case 8) or nonisoenergetic ( $\Delta G_{TS} \neq 0$ , cases 5-7,9-10). In sum, if  $s_1 \neq s_2$ , the necessary and sufficient condition for situselectivity to occur is that  $\Delta\Delta G^\ddagger$  be greater than 0 (*vide infra*).

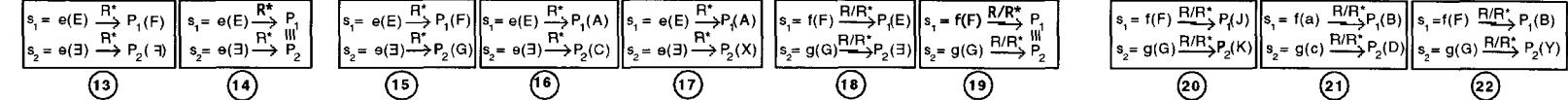
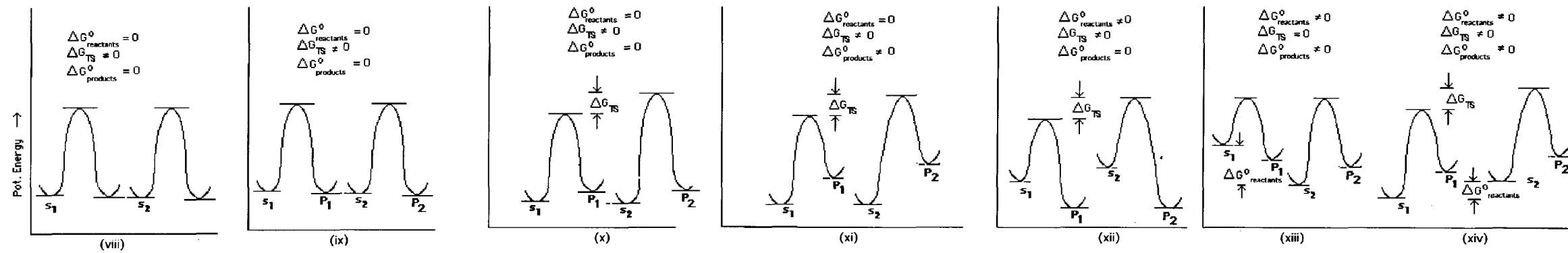
*Intermolecular* situselectivity follows a parallel pattern. If sites  $s_1$  and  $s_2$  are intermolecularly homotopic, i.e.  $s_1 = s_2$ , no selectivity is possible (case 11); this is also true of aselectivity referred to above. If  $s_1 \neq s_2$  and  $\Delta\Delta G^\ddagger = 0$ , no situselectivity is observed (case 12); this is the case of nonselectivity. If  $s_1 \neq s_2$ , situselectivity would be observed if ground states are isoenergetic ( $\Delta G^\circ = 0$ ) or not ( $\Delta G^\circ \neq 0$ ), as long as transition states are non-isoenergetic ( $\Delta\Delta G^\ddagger \neq 0$ ), that is,  $\Delta\Delta G^\ddagger = |\Delta G^\circ - \Delta G_{TS}| > 0$  (cases 13-17). Situselectivity is, of course, possible when ground states are non-isoenergetic ( $\Delta G^\circ \neq 0$ ), and transition states are either isoenergetic ( $\Delta G_{TS} = 0$ , case 20-22-xiii) or

### Intramolecular Cases



Siteselectivity:	'homosituselective'	enantiositounselective	enantiosituselective	enantiosituselective	diastereosituselective	astereosituselective	nonequisituselective	diastereosituselective	astereosituselective	nonequisituselective
Morpholysis:	aselective	aselective	aselective	aselective	aselective	aselective	aselective	aselective	aselective	aselective
Morphogenesis:	aselective	nonselective	aselective	selective	aselective	aselective	aselective	selective	selective	selective

### Intermolecular Cases



Siteselectivity:	homosituselective	enantiositounselective	enantiosituselective	enantiosituselective	enantiosituselective	enantiosituselective	enantiosituselective	enantiosituselective	diastereosituselective	diastereosituselective	astereosituselective	nonequisituselective
Morpholysis:	aselective	nonselective	selective enantiomorpholysis	selective enantiomorpholysis	selective enantiomorpholysis	selective enantiomorpholysis	selective enantiomorpholysis	selective diastereomorpholysis	selective diastereomorpholysis	selective diastereomorpholysis	selective astereomorpholysis	nonequisimorpholysis
Morphogenesis:	aselective	nonselective	selective enantiomorphogenesis	aselective morpholysis	selective diastereomorphogenesis	selective stereomorphogenesis	selective nonequisimorphogenesis	selective enantiomorphogenesis	aselective morphogenesis	selective diastereomorphogenesis	selective stereomorphogenesis	selective nonequisimorphogenesis

**Figure 11.8.** Energetics of Intramolecular and Intermolecular Situselective Processes and Selectivity of Attendant Morphogenesis or Morpholysis

nonisoenergetic ( $\Delta G_{TS} \neq 0$ , cases 18-19, 20-22- xiv). In sum, if  $s_1 \neq s_2$ , the necessary and sufficient condition for situselectivity to occur is that  $\Delta\Delta G^\ddagger$  be greater than 0 (vide infra).

#### IV. Quantitative Designation of Situselectivity

Since the situselectivity of a reaction at sites  $t_1$  and  $t_2$  is determined by  $\Delta\Delta G^\ddagger$  (vide supra) - the difference in activation energies of the two competing processes (intramolecular for substrate S; intermolecular for substrates  $S_1$  and  $S_2$ ) , such selectivity is reflected in  $k_{t_1}/k_{t_2}$ , where  $k_{t_1}$  and  $k_{t_2}$  are the rate constants of the homocompetitive processes. Situselectivity,  $S_{st}$ , may involve any type of site - atom, bond, molecular face or molecular segment (vide infra) and is based on a Hammett-type relationship (Equation 11.1):

$$S_{st} = \log(k_{t_1}/k_{t_2}) \quad (11.1)$$

$$\text{enantiosituselectivity } = S_{et} = \log(k_e/k_\theta) \quad (11.2a)$$

$$\text{diastereosituselectivity } = S_{dt} = \log(k_d/k_f) \quad (11.2b)$$

$$\text{astereosituselectivity } = S_{at} = \log(k_a/k_c) \quad (11.2c)$$

$$\text{nonequisituselectivity } = S_{nt} = \log(k_a/k_x) \quad (11.2d)$$

where  $k_e, k_\theta$  are the rate constants at enantiotopic sites

$k_d, k_f$  are the rate constants at diastereotopic sites

$k_a, k_c$  are the rate constants at astereotopic sites

and  $k_a, k_x$  are the rate constants at nonequitoropic sites.

In practice, the selectivity is determined indirectly by assessing substance excess (se) in either disappearing reactants or formation of products. The quantitative expressions for the particular situselectivities are given for substrates (S) or products (P) by the following equations:

$$se = | \%S_1 - \%S_2 | \quad (11.3)$$

$$se = | \%P_1 - \%P_2 | \quad (11.4)$$

The  $\%S_1$  and  $\%S_2$  terms are the amounts of  $S_1$  and  $S_2$  that have remained unreacted at the end of the reaction (intermolecular case). The  $\%P_1$  and  $\%P_2$  terms are the amounts of products  $P_1$  and  $P_2$  that have formed.<sup>125</sup>

The term se, for  $\%S_1/\%S_2$  or  $P_1/P_2$ , is given by Equations 11.5a-11.5d, depending on the morphic relationship between each given pair.

$$se = ee = \text{enantiomorphic excess} = | \%E - \% \bar{E} |^{126} \quad (11.5a)$$

$$se = de = \text{diastereomeric excess} = | \%D - \%F |^{127} \quad (11.5b)$$

$$se = ae = \text{astereomeric excess} = | \%A - \%C | \quad (11.5c)$$

PAIRED SITES	Topic Relationship of Sites $t_1$ and $t_2$	$t_1$ $t_2$	Achiral Influence/Medium		Chiral Influence/Medium	
			Achiral Reagent(s)	Chiral Reagent(s)	Achiral Reagent(s)	Chiral Reagent(s)
Stereotopic	Homotopic	h   h	- <sup>1</sup>	- <sup>1</sup>	- <sup>1</sup>	- <sup>1</sup>
	Enantiotopic	e   e	- <sup>2</sup>	+ <sup>3</sup>	+ <sup>3</sup>	+
	Diastereotopic	f   g	+ <sup>4</sup>	+ <sup>4</sup>	+ <sup>4</sup>	+ <sup>4</sup>
Nonstereotopic	Astereotopic	a   c	+ <sup>5</sup>	+ <sup>5</sup>	+ <sup>5</sup>	+ <sup>5</sup>
	Nonequitopic	a   x	+ <sup>6</sup>	+ <sup>6</sup>	+ <sup>6</sup>	+ <sup>6</sup>

- : siteselectivity not expected  
+ : siteselectivity expected

- <sup>1</sup>: "homositeselective" transformation; corresponds to case i, Figure 11.8
- <sup>2</sup>: enantiositunselective transformation; corresponds to case i, Figure 11.8
- <sup>3</sup>: enantiositeselective transformation; corresponds to cases iii-vi, Figure 11.8
- <sup>4</sup>: diastereosituselective transformation; corresponds to case iv-vi, Figure 11.8
- <sup>5</sup>: astereosituselective transformation; corresponds to case iv-vi, Figure 11.8
- <sup>6</sup>: nonequisituselective transformation; corresponds to case iv-vi, Figure 11.8

**Table 11.1.** Siteselectivity in Chemical Transformations

If  $S_1$  reacts 10 times faster than  $S_2$ ,  $k_{S_1}/k_{S_2} = 10$ ,  $S_{st} = \log(10/1) = 1$ ;  $se = |%S_1 - %S_2| = 90.9 - 0.9 = 90\%$ ; if  $k_{S_1}/k_{S_2} = 100$ ,  $S_{st} = \log(100/1) = 2$ ,  $se = |%S_1 - %S_2| = 99.01 - 0.01 = 99\%$ . Similarly, if  $P_1$  is formed 10 times faster than  $P_2$ ,  $k_{P_1}/k_{P_2} = 10$ ,  $S_{st} = \log(10/1) = 1$ ;  $se = |%P_1 - %P_2| = 90.9 - 0.9 = 90\%$ ; if  $k_{P_1}/k_{P_2} = 100$ ,  $S_{st} = \log(100/1) = 2$ ,  $se = |%P_1 - %P_2| = 99.01 - 0.01 = 99\%$ .

The preceding discussion dealt only with two-component systems; however, it is extendable to three- and four-component mixtures, as previously discussed.

## V. Situselectivity and Chirality

On the basis of the energetics discussed above, it is clear that no intramolecular or intermolecular situselectivity at homotopic sites ("homosituselectivity") is possible irrespective of the medium and/or reagent(s) (Figure 11.8, cases 1,11). Thus, "homosituselectivity" becomes *aselectivity*; the "two" pathways are isoenergetic and, in effect, there is only one pathway.

Situselectivity at enantiotopic sites (enantiosituselectivity) is also not possible for transformations involving achiral reagents and/or achiral media (Figure 11.8, cases 2 and 12). These cases exemplify *nonselectivity* because while the two pathways are distinct (enantiometric), they are nevertheless traversed with equal probability, and the two enantiotopic (intramolecular or intermolecular) sites react/interact at equal rates. In principle, however, enantiosituselectivity is possible under any one of the following combinations - chiral reagent(s)-achiral media, achiral reagent(s)-chiral media, or chiral reagent(s)-chiral media (Figure 11.8, cases 3,4,13-14,15-17). This is true because  $\Delta\Delta G^\ddagger \neq 0$  as a result of the involvement of diastereomeric (expectedly nonisoenergetic)<sup>75</sup> transition states.

In the case of diastereotopic, astereotopic, and nonequitoropic systems (all of which are found in *a priori* isoenergetic whole molecules (intramolecular case), or in nonisoenergetic molecules (intermolecular case), situselectivity is possible with either achiral or chiral reagents, in achiral or chiral media (cases 5-10,18-22), since reactions may proceed through expectedly nonisoenergetic (or accidentally isoenergetic) transition states.

As noted above, "homosituselectivity" is nonexistent; it is operationally undetectable. Enantiosituselectivity is not possible in the absence of chiral perturbations, but is possible if chiral influences are operative. Finally, diastereosituselectivity, astereosituselectivity and nonequisituselectivity are expected in all other cases. These considerations of situselectivity are summarized in Table 11.1.

In determining bisituselectivity, for each reactant one must take into account all paired reactive sites - stereotopic as well as nonstereotopic. If polysituselectivity is possible, then the selectivity must be specified in pairs (see Volume 1, p. 143, Addendum A). The ensuing selectivities are given in Table 11.2.

The listings in Table 11.2 for  $S_1/S_2$  combinations are indicated as --, -+, +- or ++; the first algebraic sign is for  $S_1$ , and the second one, for  $S_2$  (minus means nonselective and plus means selective).

- (1) The "--" for h/h and h/h\*combinations indicate aselectivity - there is only one path and no selectivity is possible. (Note that the h/h, h/h\*, h\*/h\* combinations are situaselective, whereas the h/e combination is situnoselective (*vide infra*)).

			PAIRED SITES OF REACTANT $S_2$								
			Stereotopic					Nonstereotopic			
			h	$h^*$	e	d	$d^*$	a	$a^*$	n	$n^*$
PAIRED SITES OF REACTANT $S_1$	Stereotopic	h	--	--	--	-+	-+	-+	-+	-+	-+
		$h^*$	--	--	-+	-+	-+	-+	-+	-+	-+
		e	--	+-	++	++	++	++	++	++	++
		d	+-	+-	++	++	++	++	++	++	++
		$d^*$	+-	+-	++	++	++	++	++	++	++
	Nonstereotopic	a	+-	+-	++	++	++	++	++	++	++
		$a^*$	+-	+-	++	++	++	++	++	++	++
		n	+-	+-	++	++	++	++	++	++	++
		$n^*$	+-	+-	++	++	++	++	++	++	++

- : situselective or situnoselective - not selective with respect to either site
- + - : situselective - selective with respect to sites in Substance 1, nonselective with respect to sites in Substance 2
- + : situselective - nonselective with respect to sites in Substance 1, selective with respect to sites in Substance 2
- ++: bisituselective - selective with respect to both reactive sites - one in each of the two reactants

++ : 4 conjunctive states possible  
 +- : 2 conjunctive states possible  
 -- : 1 conjunctive state possible

**Table 11.2.** Bisituselectivity in Chemical Processes Involving Two Ambident Reactants  $S_1$  and  $S_2$   
(Achiral medium)

- (2) The “--” designations for h/e and e/h combinations indicate nonselectivity - there are two identical paths, and both are traversed at equal rates.
- (3) The “-+” designations for h/d, h/d\*, h/a, h/a\*, h/n, h/n\* and h\*/e, h\*/d, h\*/d\*, h\*/a, h\*/a\*, h\*/n, h\*/n\* are monosituselective and the selectivity is in S<sub>2</sub>. Similarly, the +- designations for d/h, d\*/h, a/h, a\*/h, n/h, n\*/h and e/h\*, d/h\*, d\*/h\*, a/h\*, a\*/h\*, n/h\*, n\*/h\* indicate monosituselectivity, the selectivity being in S<sub>1</sub>.
- (4) The “++” designations for the following permutations show bisituselectivity; there is selectivity in each of S<sub>1</sub> and S<sub>2</sub>:

e/e, e/d, e/d\*, e/a, e/a\*, e/n, e/n\*  
 d/d, d/d\*, d/a, d/a\*, d/n, d/n\*  
 d\*/d\*, d\*/a, d\*/a\*, d\*/n, d\*/n\*  
 a/a, a/a\*, a/n, a/n\*  
 a\*/a\*, a\*/n, a\*/n\*  
 n/n, n/n\*  
 n\*/n\*.

Table 11.2 indicates that reactions between two reactants that utilize combinations of *only* h, h\* sites *cannot* exhibit bisituselectivity. Two reactants that utilize combinations of *only* h\* sites in one, and e/d/d\*/a/a\*/n/n\* sites in the other, or, of *only* h sites in one, and d/d\*/a/a\*/n/n\* sites in the other, always exhibit (mono)situselectivity. It is reactions between two reactants that utilize combinations of *only* e/d/d\*/a/a\*/n/n\* sites in *both* reactants that will exhibit bisituselectivity.

### Summary

*Situselectivity* is a simple, unambiguous, and euphonious term to describe molecular site selectivity in a chemical transformation. (If each of two reactant molecules/moieties has a preferred site of attack, the transformation is *situselective* with respect to each, and the overall transformation is therefore *bisituselective* i.e. situselective with respect to each reactant/moiety). Situselectivity in a reactant can be subclassified into *stereosituselectivity* (stereotopic site selectivity) and *nonstereosituselectivity* (nonstereotopic site selectivity). The former consists of *enantiosituselectivity* and *diastereosituselectivity*, whereas the latter includes *astereosituselectivity* and *nonequisituselectivity*. The original definition of regioselectivity<sup>128</sup> and the subsequent IUPAC recommendation<sup>129</sup> encompass two conceptually distinct ideas. Where the focus of attention is on *site* selectivity, the correct term is *situselectivity* and *not regioselectivity*. In this respect, the latter term is inapplicable and should be abandoned. In contradistinction, selectivity in the “Markovnikov-sense” alignment/bonding/association of “unsymmetrical” reagents with “unsymmetrical” substrates is properly termed *regioselectivity*. This is discussed in detail in Chapter 11.

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"God fills the gaps of human need,  
Each crisis brings its word and deed."

John Greenleaf Whittier, *The Lost Occasion*, 1880.

# 12

## Facieselectivity

In organic, organometallic and biochemical reactions involving paired molecular (stereotopic) faces, one is confronted with two fundamental types of selectivity - *facieselectivity* and *vectoselectivity*. Facioselectivity characterizes the preferential reaction at molecular faces, and will be discussed in this chapter. Vectoselectivity refers to the relative alignment of reactants, and will be covered in the following chapter.

### I. Stereotopic Molecular Faces h1-h6, e, d1-d4

In order to discuss facioselectivity concisely, one needs to classify molecular faces (half-spaces).<sup>130</sup> In 1975, we categorized time-resolved/time-averaged planar stereotopic molecular faces into homotopic, enantiotopic, and diastereotopic classes.<sup>131</sup>

Stereotopicity and chirotopicity are deemed *independent* attributes of molecular sites – be it ligands, bonds, molecular faces or molecular segments. The former attribute is defined by a specific topic relationship between two given sites, whereas the latter attribute describes the chirality/achirality of the molecular field. Indeed, two molecular sites are, with respect to one another, either stereotopic or nonstereotopic, *irrespective* of the achirality/chirality of the molecule in which they are situated. Conversely, a molecular site is either achirotopic or chirotopic, *regardless* of any stereotopic or nonstereotopic relationship(s) it may bear with respect to another (or other) intramolecular site(s).

Despite the independent nature of these two attributes, stereotopicity and chirotopicity of intramolecular sites are intimately intertwined. When molecular half-spaces are considered in terms of these two attributes, one finds five types of molecular faces: two that are homotopic - *achirohomotopic* (H,H) and *chirohomotopic* (H\*,H\*), *enantiotopic* faces (E\*,\*E), and two types of diastereotopic faces – *achirodiastereotopic* (D,F) and *chirodiastereotopic* (D\*,F\*) (Figure 12.1).<sup>132</sup> Of these five types of molecular faces, types (H,H), (E\*,\*E) and (D,F) are found only in achiral molecules, while (H\*,H\*) and (D\*,F\*) faces are found only in chiral molecules.

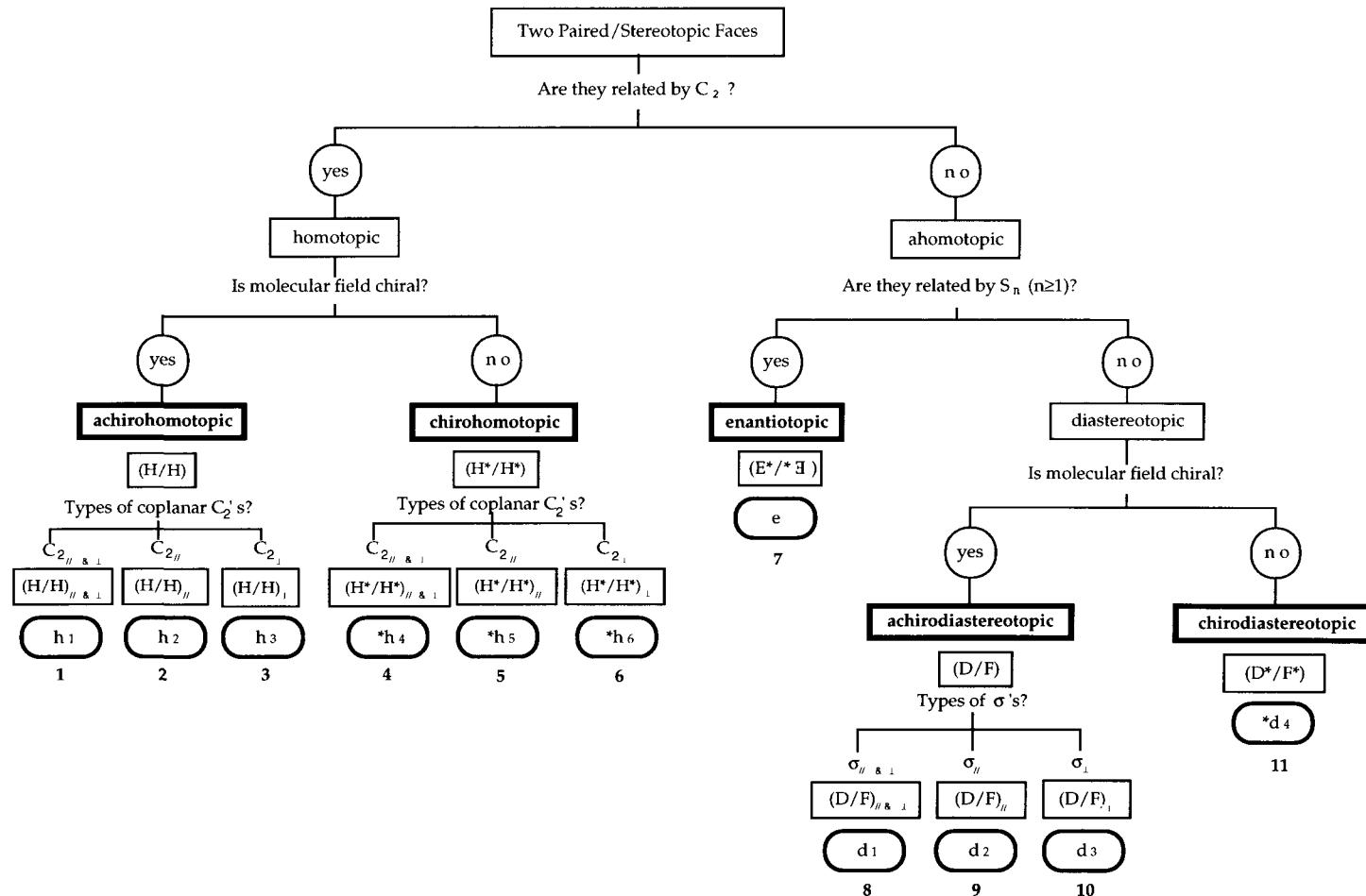


Figure 12.1. Complete Classification of Stereotopic Molecular Faces

Further, if one also considers C<sub>2</sub> axes (*coplanar* with the molecular faces in question) and σ planes (orthogonal to the molecular faces at hand), one uncovers eleven subclasses of molecular faces - six homotopic ones (h<sub>1</sub>-h<sub>6</sub>), one enantiotopic subclass (e), and four that are diastereotopic (d<sub>1</sub>-d<sub>4</sub>) (Figure 12.1). It is, indeed, somewhat ironic that the simplest class - homotopic - has the largest number (6) of subclasses. However, this is a consequence of the higher levels of symmetry attainable with this class. Homotopic molecular faces correspond to (H/H)<sub>//&⊥</sub>, (H/H)<sub>//</sub>, (H/H)<sub>⊥</sub>, and (H<sup>\*</sup>/H<sup>\*</sup>)<sub>//&⊥</sub>, (H<sup>\*</sup>/H<sup>\*</sup>)<sub>//</sub>, (H<sup>\*</sup>/H<sup>\*</sup>)<sub>⊥</sub>, respectively, depending on whether or not a C<sub>2//</sub> axis and/or a C<sub>2⊥</sub> is/are present; they represent face subclasses h<sub>1</sub>-h<sub>6</sub>. The former three subclasses are present in achiral molecules, and the latter three, in chiral molecules.<sup>133</sup> Enantiotopic faces (E<sup>\*</sup>, Ē) are always chirotopic and are found only in *achiral* molecules; they represent face type "e". Finally, diastereotopic faces (D/F)<sub>//&⊥</sub>, (D/F)<sub>//</sub>, (D/F)<sub>⊥</sub> respectively, constitute subclasses d<sub>1</sub>-d<sub>3</sub>; they have parallel and/or perpendicular plane(s) of symmetry (both σ-planes are orthogonal to the plane of the molecular faces), and are found in achiral molecules; diastereotopic molecular faces (D<sup>\*</sup>, F<sup>\*</sup>) lack parallel and/or perpendicular plane(s) of symmetry, constitute subclass d<sub>4</sub>, and are situated only in chiral molecules.<sup>134</sup> Table 12.1 lists the 11 subclasses by subclass number, subclass designation, simplified and complete face descriptors, and the achirality/chirality of the molecular field.

Examples of molecules with stereotopic faces in all eleven subclasses are shown in Figure 12.2. In these figures a,b,c,d represent achirotopic ligands (e.g. H, D, CH<sub>3</sub>); g<sup>+</sup> is a chirotopic ligand (e.g. -CHDT with an R configuration at the carbon) and ḡ is its enantiomeric counterpart (e.g. -CDHT with an S configuration at the carbon). Also, the 3-membered cyclic examples are delocalized cyclopropylum ions, the cyclobutadienes are hypothetical delocalized squares, and the 5-membered rings are cyclopentadienide anions.

Homotopic faces are present in molecules 1-33. Achirohomotopic faces H/H are found in achiral molecules of subclasses h<sub>1</sub> (1,2), h<sub>2</sub> (3,4), h<sub>3</sub> (5-13), whereas chirohomotopic faces H<sup>\*</sup>/H<sup>\*</sup> are present in chiral molecules belonging to subclasses \*h<sub>4</sub> (14,15), \*h<sub>5</sub> (16,17), and \*h<sub>6</sub> (18-33). Enantiotopic faces (E<sup>\*</sup>, Ē) are exemplified by molecules 34-48 all of which are achiral; no enantiotopic faces can exist in chiral molecules. Diastereotopic faces are found in molecules 49-70. Achirodiastereotopic faces D/F are observed in achiral molecules of subclasses d<sub>1</sub> (49), d<sub>2</sub> (50-52), d<sub>3</sub> (53-61) while chirodiastereotopic faces D<sup>\*</sup>, F<sup>\*</sup> are present in chiral molecules of subclass \*d<sub>4</sub> (62-70).

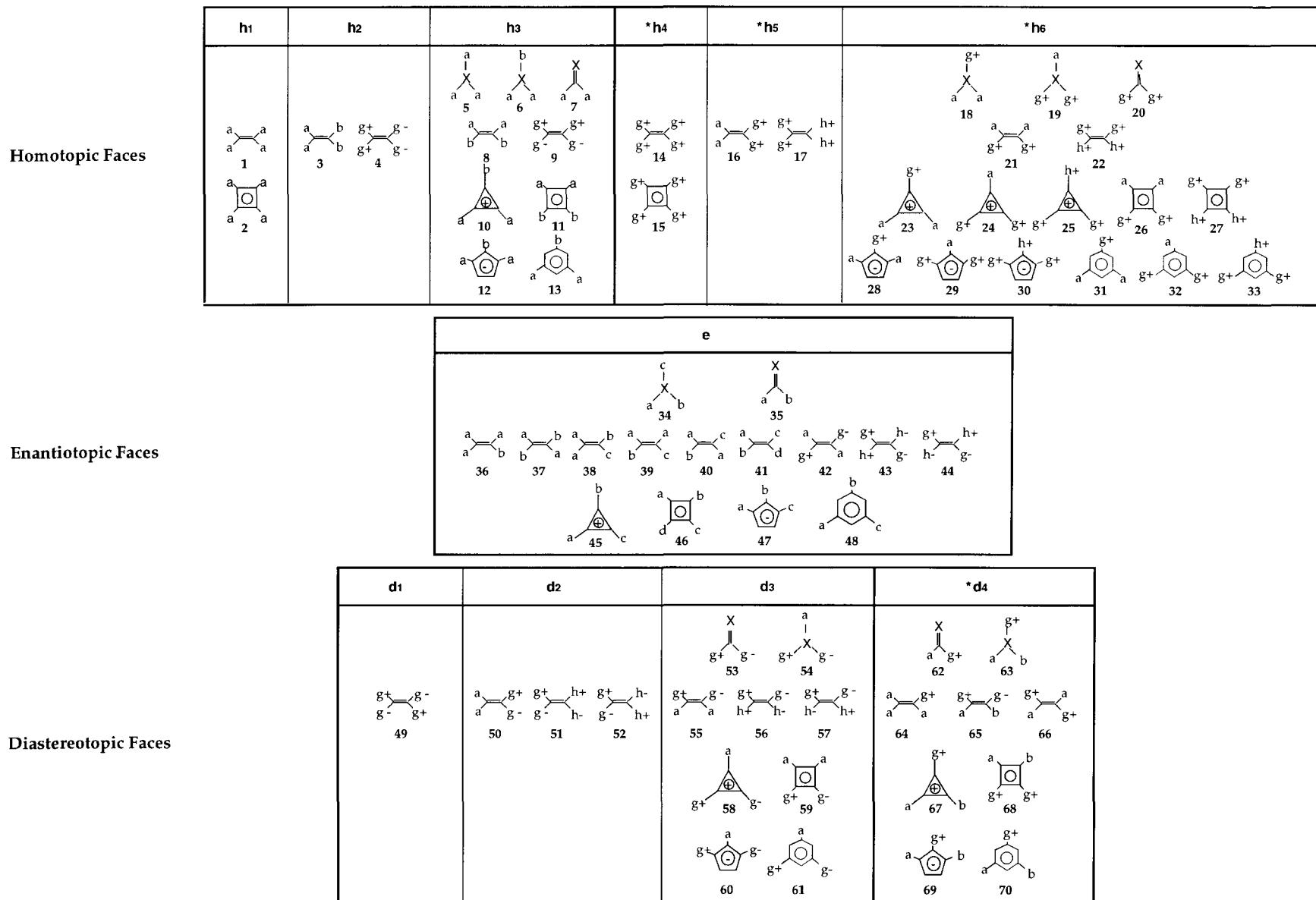
In sum, molecular faces of achiral molecules fall in seven subclasses - h<sub>1</sub> (1,2), h<sub>2</sub> (3,4), h<sub>3</sub> (5-13), e (34-48), d<sub>1</sub> (49), d<sub>2</sub> (50-52), d<sub>3</sub> (53-61). Molecular faces of chiral molecules, in contrast, belong to four subclasses - h<sub>4</sub><sup>\* (14,15), h<sub>5</sub><sup>\* (16,17), h<sub>6</sub><sup>\* (18-33), and d<sub>4</sub><sup>\* (62-70). In this chapter, we will use the simplified face descriptors H,H, H<sup>\*</sup>,H<sup>\*</sup>, E<sup>\*</sup>, Ē, D,F, and D<sup>\*</sup>,F<sup>\*</sup> of Figure 12.1. We will refer to the face descriptors of Figure 12.1 in this chapter and in Chapters 13, 17, and 18, in connection with the attendant chemical reactivity of all eleven types of molecular faces.</sup></sup></sup></sup>

## II. Conjunctive States in Facioselective Processes

The reaction at a paired set of molecular faces, in principle, may proceed through four pathways, or a quartet of conjunctive transition states (or four conjunctive products) m<sub>1</sub>, m<sub>1</sub>, m<sub>2</sub>, m<sub>2</sub>. Thus, the analysis of these pathways centers on the maximum level of structural complexity attainable - that of the incipient transition states - along the pathways. Each conjunctive state (transition state or product) is chiral (dark circle) or achiral (open circle).

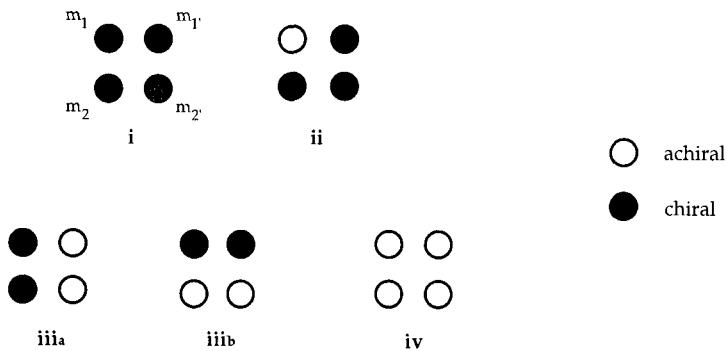
		Subclass Number	Subclass Designation	Simplified Face Descriptor	Complete Face Descriptor	Molecular Field
<b>Homotopic</b>	<b>Achirohomotopic</b>	1	h1	(H/H)	(H/H) <sub>// &amp; ⊥</sub>	achiral
		2	h2	(H/H)	(H/H) <sub>//</sub>	achiral
		3	h3	(H/H)	(H/H) <sub>⊥</sub>	achiral
	<b>Chirohomotopic</b>	4	h <sup>*</sup> 4	(H <sup>*</sup> /H <sup>*</sup> )	(H <sup>*</sup> /H <sup>*</sup> ) <sub>// &amp; ⊥</sub>	chiral
		5	h <sup>*</sup> 5	(H <sup>*</sup> /H <sup>*</sup> )	(H <sup>*</sup> /H <sup>*</sup> ) <sub>//</sub>	chiral
		6	h <sup>*</sup> 6	(H <sup>*</sup> /H <sup>*</sup> )	(H <sup>*</sup> /H <sup>*</sup> ) <sub>⊥</sub>	chiral
<b>Enantiotopic</b>	<b>Enantiotopic</b>	7	e	(E <sup>*</sup> , E <sup>*</sup> )	(E <sup>*</sup> , E <sup>*</sup> )	chiral
<b>Diastereotopic</b>	<b>Achirodiastereotopic</b>	8	d1	(D/F)	(D/F) <sub>// &amp; ⊥</sub>	achiral
		9	d2	(D/F)	(D/F) <sub>//</sub>	achiral
		10	d3	(D/F)	(D/F) <sub>⊥</sub>	achiral
	<b>Chirodiastereotopic</b>	11	d <sup>*</sup> 4	(D <sup>*</sup> , F <sup>*</sup> )	(D <sup>*</sup> , F <sup>*</sup> )	chiral

**Table 12.1.** Classification of Stereotopic Molecular Faces



**Figure 12.2.** Examples of Molecules with all Subclasses of Stereotopic Molecular Faces

There emerge the following four types of quartets: four chiral states (i), one achiral/three chiral states (ii), two achiral/two chiral states (two different arrangements - iii<sub>a</sub> and iii<sub>b</sub>), or four achiral states (iv) (Figure 12.3). States m<sub>1</sub> and m<sub>1'</sub> are for the *top* molecular face; m<sub>2</sub> and m<sub>2'</sub> are for the *bottom* face. In going from m<sub>1</sub> to m<sub>1'</sub> the relative vectorial direction is reversed; the same is true in going from m<sub>2</sub> to m<sub>2'</sub>.



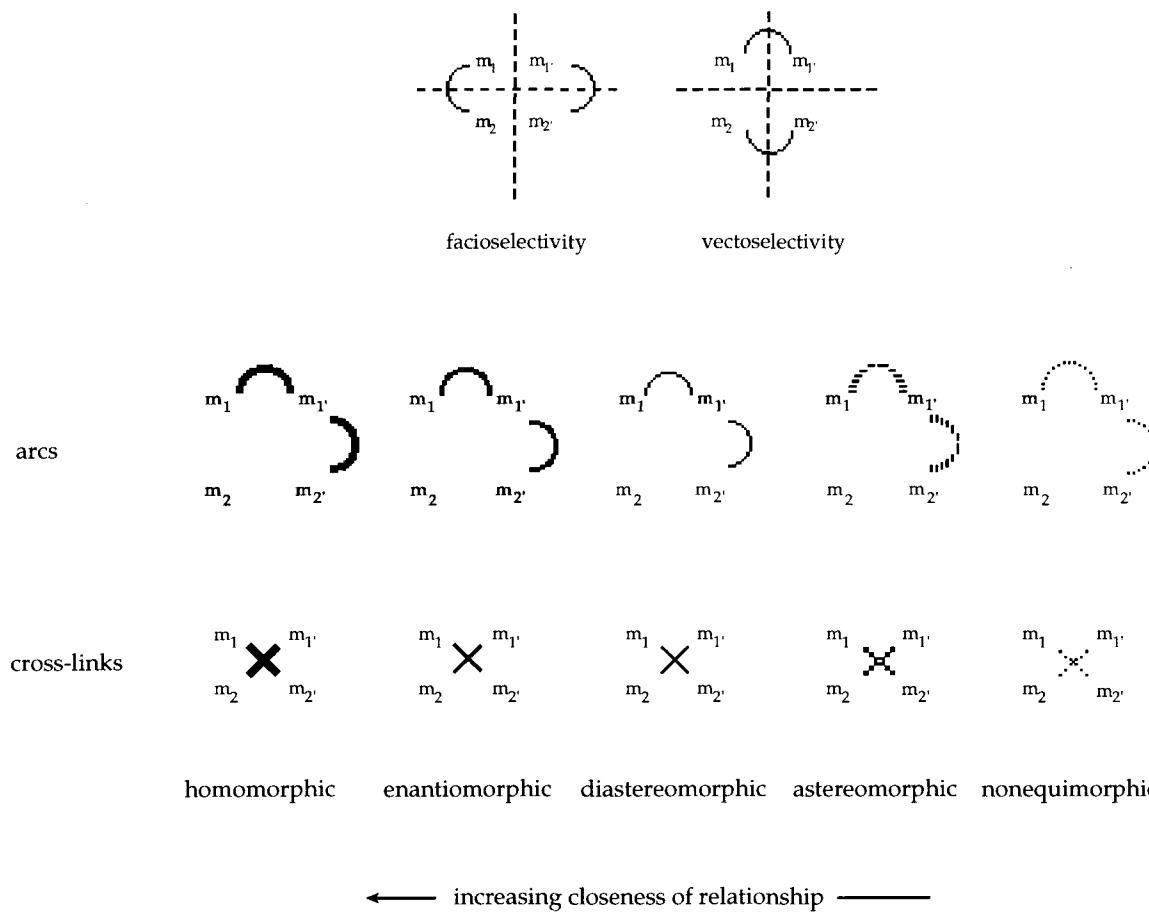
**Figure 12.3.** Possible Permutations of Achiral/Chiral States in Conjunctive Processes

Within each quartet, the morphic relationship between any pair of circles (representing distinct conjunctive states) is marked by an arc or a cross-link (arcs are for m<sub>1</sub>-to-m<sub>1'</sub>, m<sub>1</sub>-to-m<sub>2</sub>, m<sub>1</sub>-to-m<sub>2'</sub>, and m<sub>2</sub>-to-m<sub>2'</sub>; cross-links are for m<sub>1</sub>-to-m<sub>2</sub> and m<sub>1</sub>-to-m<sub>2'</sub>). Once the morphic relationships for the arcs are picked, those for the cross-links follow suit. The arcs and cross-links are drawn very thick, thick, and thin for homomeric, enantiomeric, and diastereomeric relationships, respectively; the arcs and cross-links are dashed and dotted for astereomeric and nonequimorphic relationships, respectively. For a given quartet of circles, every arc or cross-link may reflect any one of the five fundamental morphic relationships (Figure 12.4).

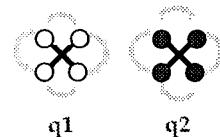
We have systematically analyzed the outcome of a wide variety of (1,2)-atom-face and (2,2)-bond-face ligogenic reactions of prototype alkenes, belonging to the eleven fundamental subclasses, with monoconjunctive/bijunctive C<sub>2</sub>-symmetric/non-C<sub>2</sub>-symmetric, achiral/chiral reagents of general types :Cab, :C=Cxy, :C=C=Cxy, and x-y, (x=y and x≠y; x,y= achiral or chiral ligands). We have also examined (2,2)-face-face ligogenic processes based on [2+2] and [2+4] cycloadditions – those involving reactants of types xyC=Cwz and xyC=Ca-Cb=Cwz.

These reactions bring out important and interesting consequences of the HED classification in the context of facioselectivity and difacioselectivity. Other consequences relating to stereoselectivity, stereospecificity, rotativity, stereotopoprocesses, and chirotopoprocesses, will be given in Volume 3, Chapters 17 and 18. Figure 12.5 represents the 45 quartets that emerge from our analyses.

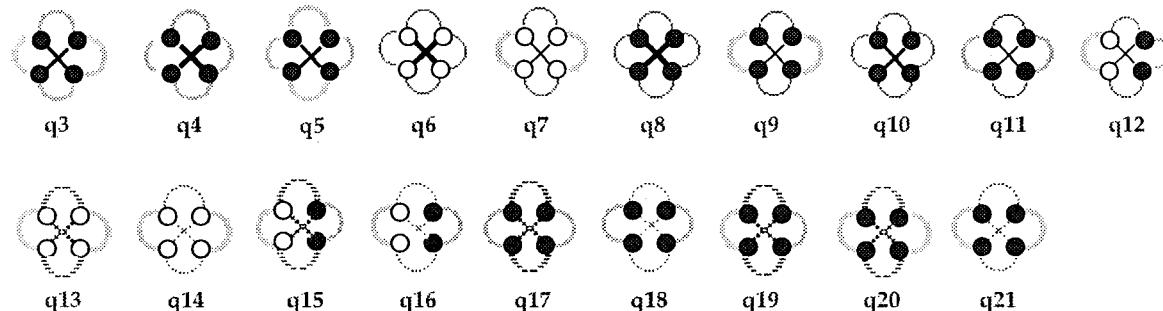
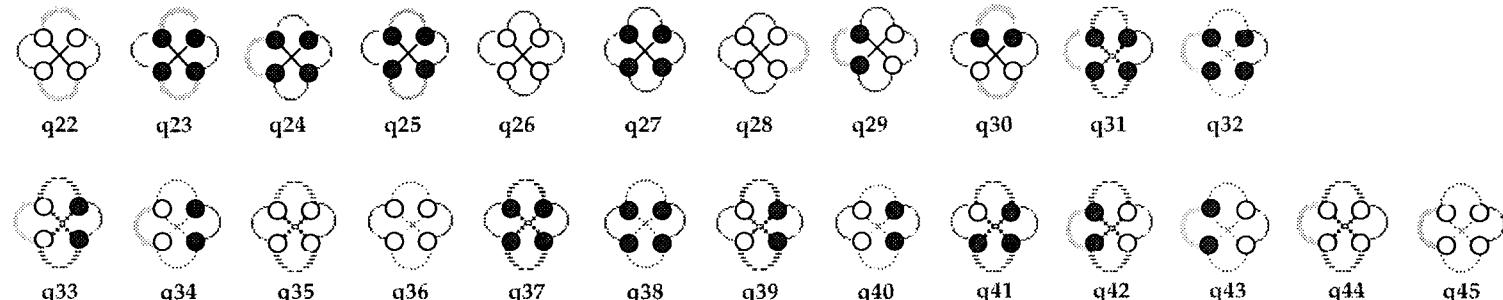
Table 12.2 lists the quartet number (*q* number), quartet component designation, and quartet composition of each of the 45 quartets. The quartets are subclassified into three categories - facioaselective, faciononselective and facioselective (*vide infra*).



**Figure 12.4.** Morphic Relationships in (1,1)-, (1,2)-, and (2,2)-Conjunctive Processes

**Facioselective**

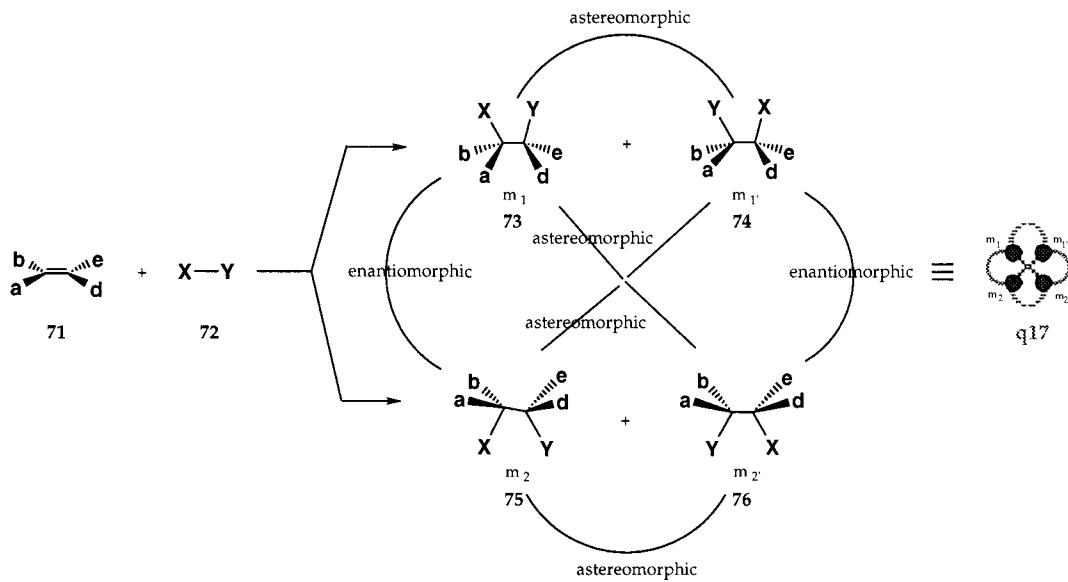
$\times$		homomorphic relationship
$\times$		enantiomeric relationship
$\times$		diastereomeric relationship
$\times$		astereomeric relationship
$\times$		nonequimorphic relationship
		○ achiral conjunctive state ● chiral conjunctive state

**Faciononselective****Facioselective****Figure 12.5.** Quartets q1-q45 for all Permutations of Conjunctive States in Junctive Processes

Quartet	Quartet Component Designation	Quartet Composition
q1	H	1 achiral substance
q2	H*	1 chiral substance
q3	E*/E	2 enantiomers
q4	E*/E*	2 enantiomers
q5	E*/E	2 enantiomers
q6	D,F	2 achiral diastereomers
q7	D,F	2 achiral diastereomers
q8	D*,F*	2 chiral diastereomers
q9	D*,F*	2 chiral diastereomers
q10	E*/E,D*/D*	2 pairs diastereomeric enantiomers
q11	E*/E,D*/D	2 pairs diastereomeric enantiomers
q12	E*/E,D	2 enantiomers + 1 achiral diastereomer
q13	A,N	2 achiral astereomers
q14	A,X	2 achiral nonequimers
q15	E*/E,N	2 enantiomers + 1 achiral astereomer
q16	E*/E,X	2 enantiomers + 1 achiral nonequimer
q17	E*/E,N*	2 enantiomers + 1 common chiral astereomer
q18	E*/E,N*/N	2 pairs astereomeric enantiomers
q19	E*/E,Z*/Z	2 pairs nonequimERIC enantiomers
q20	A*,N*	2 chiral astereomers
q21	A*,X*	2 chiral nonequimers
q22	D,F	2 achiral diastereomers
q23	D*,F*	2 chiral diastereomers
q24	D*,F*,G*	3 chiral diastereomers
q25	E*/E,D*/D*	2 pairs diastereomeric enantiomers
q26	D,F,G,J	4 achiral diastereomers
q27	D*,F*,G*,J*	4 chiral diastereomers
q28	D,F,G	3 achiral diastereomers
q29	D*,F,G	3 diastereomers (1 chiral, 2 achiral)
q30	D*,F	2 diastereomers (1 chiral, 1 achiral)
q31	D*,F*,N*	2 chiral diastereomers + 1 chiral astereomer
q32	D*,F*,X*	2 chiral diastereomers + 1 chiral nonequimer
q33	D*,F*,N	2 chiral diastereomers + 1 achiral astereomer
q34	D*,F*,X	2 chiral diastereomers + 1 achiral nonequimer
q35	D,F,M,N	2 pairs achiral astereomeric diastereomers
q36	D,F,X,Y	2 pairs achiral nonequimERIC diastereomers
q37	D*,F*,M*,N*	2 pairs chiral astereomeric diastereomers
q38	D*,F*,X*,Y*	2 pairs chiral nonequimERIC diastereomers
q39	D*,F*,M,N	2 pairs astereomeric diastereomers (1 pair chiral, 1 pair achiral)
q40	D*,F*,X,Y	2 pairs chiral nonequimERIC diastereomers (1 pair chiral, 1 pair achiral)
q41	D*,F*,M*,N	2 pairs astereomeric diastereomers (1 pair chiral, 1 pair mixed achiral/chiral)
q42	D,F,N*	2 achiral diastereomers + 1 chiral astereomer
q43	D,F,X*	2 achiral diastereomers + 1 chiral nonequimer
q44	D,F,M	2 achiral diastereomers + 2 achiral astereomer
q45	D,F,X	2 achiral diastereomers + 1 achiral nonequimer

**Table 12.2.** Quartets of Conjunctive States (q1-q45), Quartet Component Designations, and Quartet Compositions in (1,2)- and (2,2)-Ligogenic Processes

To illustrate the approach given above, we consider the reaction of X-Y with abC=Cde (Figure 12.6). Of the four possible conjunctive states,  $m_1$  and  $m_1'$  (formed at the top face) are astereomeric with respect each other; so are  $m_2$  and  $m_2'$  (formed at the bottom face). In the quartet, each of these two relationships is represented by a *dashed arc* - one joining  $m_1$  to  $m_1'$ , and the other,  $m_2$  and  $m_2'$ . Further, one finds that  $m_1$  and  $m_2$  are enantiomeric with respect to each other; as are  $m_1'$  and  $m_2'$ . In quartet q17 each of these two relationships is shown by a *thick-lined arc* - one joining  $m_1$  to  $m_2$ , and the other,  $m_1'$  to  $m_2'$ . It follows that  $m_1$  and  $m_2'$  are astereomeric with respect to each other (the same is true of  $m_2$  and  $m_1'$ ); hence, the corresponding cross-links -  $m_1$  to  $m_2'$ , and  $m_2$  to  $m_1'$  - are also dashed. The overall reaction is thus represented by quartet q17.



**Figure 12.6.** The Addition of XY to abC=Cde

For the example above, facioselectivity would be given by either Equation 12.1a (as a difference) or Equation 12.1b (as a ratio):<sup>138</sup>

$$\% \text{ facioselectivity} = |(m_1 + m_1') - (m_2 + m_2')| \times 100 \quad (12.1\text{a})$$

$$\% \text{ facioselectivity} = |(m_1 + m_1') / (m_2 + m_2')| \times 100. \quad (12.1\text{b})$$

### III. Modes of Facioselectivity - Facioselectivity, Faciononselectivity, Stereofacoselectivity

Facioselectivity characterizes the preferential reaction at molecular face 1 (top) as opposed to reaction at paired face 2 (bottom).<sup>135</sup> A reaction is said to be *facioselective*<sup>136</sup> if (a) every pathway (transition state) involved in the reaction at face 1 has an isoenergetic counterpart at face 2, and (b) both transition states of every isoenergetic pair are *homomorphic*. Quartets q1,q2 represent facioselective transformations. Operationally, in an facioselective transformation, the product(s) obtained from face 1 will be exactly identical (in structure and relative amounts) with that(those) obtained from face 2.

A *faciononselective* reaction is one in which (a) every pathway (transition state) involved in the reaction at face 1 has an *isoenergetic* counterpart at face 2 (the corresponding transition state pairs are either homomorphic or enantiomeric), and (b) at least one isoenergetic pair of *enantiomeric* transition states is involved (the other(s) being homomorphic). Faciononselective processes are represented by quartets q3-q21. In real terms, the product(s) from face 1 will be formed in amounts identical with that(those) from face 2; if one of the products (or the only product) from face 1 is chiral, then an equivalent amount of the enantiomeric counterpart will result from face 2.

A reaction is said to be *facioselective (stereofacoselective)* if the reaction, with a given reagent, at face 1 involves at least one pathway with a transition state that has *no* isoenergetic counterpart for the reaction at face 2; that is, there is at least one pair of corresponding diastereomeric transition states. The unique transition state at face 1 is nonhomomorphic or nonenantiomeric with respect to every transition state of face 2. To the extent that each pathway contributes to the overall rate of the reaction, this means that, in principle, the overall reaction rate at face 1 will differ from that at face 2. Stereofacoselective processes proceed through quartets q22-q45.<sup>137</sup> In reality, the result of a stereofacoselective process will consist of one (or more) pair(s) of diastereomeric products, or, in non-conjunctive cases, one (or more) pair(s) of unequal amounts of enantiomeric products. The exact compositions for all the quartets can be gleaned from Table 12.2 above.

It is to be noted that we deal here with paired faces. There may be selectivity also between faces that are not paired, i.e. nonstereofaces, that belong to different planar moieties within the same molecule or different molecules. Such selectivity would be nonstereofacoselectivity which may reduce to nonstereofacioselectivity, or nonstereofaciononselectivity. We will not deal with these.

Figure 12.7 below portrays all types of facioselectivity, faciononselectivity and facioselectivity and the pertinent quartets.

The quantitative expressions for facioselectivity for the three subclasses are as follows:

Type of Facioselectivity	Quartets Involved	% Facioselectivity
facioselectivity	q1-q3	facioselectivity not possible $(m_1 = m_1' = m_2 = m_2')$
faciononselectivity	q4-q21	$=  (m_1 + m_1') - (m_2 + m_2')  = 0$ or $=  (m_1 + m_1') / (m_2 + m_2')  \times 100$
stereofacoselectivity	q22-q45	$=  (m_1 + m_1') - (m_2 + m_2')  \neq 0^{138}$ or $=  (m_1 + m_1') - (m_2 + m_2')  \times 100$

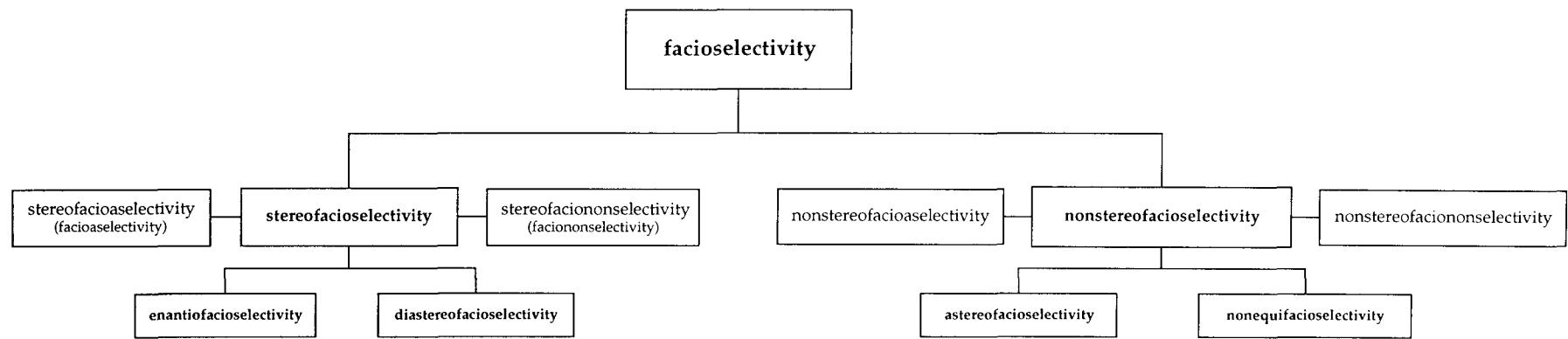


Figure 12.7. Classification of Facioselectivity

#### IV. Facioselectivity at Stereotopic Molecular Faces

We now examine, in detail, aspects of facioselectivity at the eleven fundamental paired molecular faces - h<sub>1</sub>-h<sub>6</sub>, e, and d<sub>1</sub>-d<sub>4</sub>. These results are summarized in Table 12.3.

##### A. Homotopic Faces h<sub>1</sub>-h<sub>6</sub>

1. Reactions of homotopic faces h<sub>1</sub> and h<sub>4</sub> are always afacoselective, with achiral or chiral reagents (q<sub>1</sub>,q<sub>2</sub>).
2. Reactions of h<sub>2</sub> and h<sub>3</sub> can be afacoselective (q<sub>1</sub>-q<sub>3</sub>) or nonfacioselective with achiral or chiral reagents (q<sub>4</sub>,q<sub>6</sub>,q<sub>7</sub>,q<sub>8</sub>,q<sub>9</sub>,q<sub>13</sub>,q<sub>14</sub>,q<sub>20</sub>,q<sub>21</sub>).
3. Reactions of h<sub>5</sub> and h<sub>6</sub> are afacoselective (q<sub>1</sub>,q<sub>2</sub>) or nonfacioselective (q<sub>8</sub>,q<sub>9</sub>,q<sub>20</sub>,q<sub>21</sub>) with achiral or chiral reagents.

In sum, (a) h<sub>1</sub>-h<sub>6</sub> can all be afacoselective, with any reagent; (b) only h<sub>2</sub>,h<sub>3</sub>,h<sub>5</sub>,h<sub>6</sub> can be nonfacioselective, with any reagent; and (c) none of them can be facioselective, with any reagent.

##### B. Enantiotopic Faces e

Reactions of enantiotopic faces "e" are either afacoselective (q<sub>1</sub>) or nonfacioselective with achiral reagents (q<sub>10</sub>,q<sub>11</sub>,q<sub>12</sub>,q<sub>15</sub>,q<sub>16</sub>,q<sub>17</sub>,q<sub>18</sub>), but *stereofaciocoselective* (*enantiofacioselective*) with chiral reagents (q<sub>23</sub>,q<sub>24</sub>,q<sub>27</sub>,q<sub>37</sub>,q<sub>38</sub>,q<sub>41</sub>). With only enantiofacioselectivity at work, and no role for vectoselectivity - e.g. with C<sub>2</sub>-symmetric reagents - one would expect two chiral diastereomers (q<sub>23</sub>). With non-C<sub>2</sub>-symmetric reagents, vectoselectivity would come into play, and more complex mixtures may result (*vide infra*). Here, *enantiofacioselectivity* refers to the face type in the *reactant* substrate.

For enantiotopic faces, enantiofacioselectivity is given by:

$$\text{enantiofacioselectivity} = |(\%m_1 + \%m_1') - (\%m_2 + \%m_2')| \neq 0. \quad (12.2a)$$

or

$$\text{enantiofacioselectivity} = |(\%m_1 + \%m_1')| / |(\%m_2 + \%m_2')|. \quad (12.2b)$$

##### C. Diastereotopic Faces d<sub>1</sub>-d<sub>4</sub>

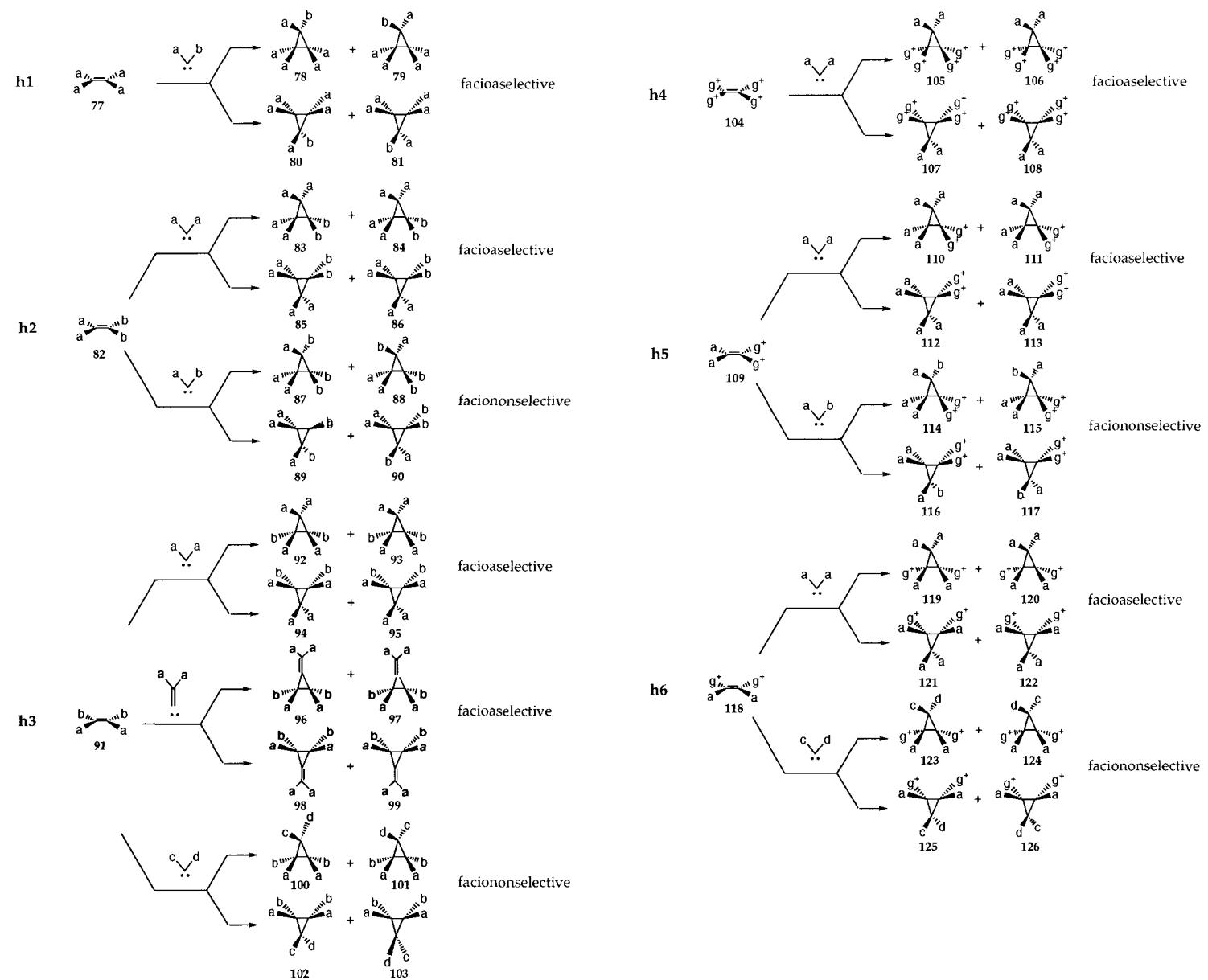
Reactions of d<sub>1</sub>-d<sub>4</sub> are not always facioselective (diastereofaciocoselective); they can also be afacoselective or nonfacioselective as noted below.

1. Reactions of d<sub>1</sub> are always diastereofaciocoselective, with achiral or chiral reagents (q<sub>22</sub> and q<sub>23</sub>, respectively).
2. Reactions of face d<sub>2</sub> can be afacoselective with achiral (q<sub>1</sub>,q<sub>3</sub>) or chiral reagents (q<sub>2</sub>), or diastereofaciocoselective with achiral (q<sub>22</sub>,q<sub>25</sub>,q<sub>26</sub>,q<sub>28</sub>,q<sub>35</sub>,q<sub>36</sub>) or chiral reagents (q<sub>23</sub>,q<sub>27</sub>,q<sub>31</sub>,q<sub>32</sub>,q<sub>37</sub>,q<sub>38</sub>).
3. Reactions of d<sub>3</sub> can be afacoselective only with achiral reagents (q<sub>1</sub>,q<sub>3</sub>), nonfacioselective with chiral reagents (q<sub>9</sub>), or diastereofaciocoselective with achiral (q<sub>22</sub>,q<sub>25</sub>,q<sub>26</sub>,q<sub>28</sub>) or chiral reagents (q<sub>23</sub>,q<sub>24</sub>,q<sub>27</sub>).
4. Reactions at faces of type d<sub>4</sub> can be afacoselective with achiral or chiral reagents (q<sub>2</sub>), nonfacioselective with achiral (q<sub>19</sub>) or chiral (q<sub>20</sub>,q<sub>21</sub>) reagents, or , diastereofaciocoselective with achiral (q<sub>22</sub>,q<sub>23</sub>,q<sub>24</sub>,q<sub>27</sub>,q<sub>29</sub>,q<sub>31</sub>,q<sub>35</sub>,q<sub>37</sub>,q<sub>39</sub>,q<sub>32</sub>), or chiral (q<sub>22</sub>,q<sub>23</sub>,q<sub>24</sub>,q<sub>27</sub>,q<sub>31</sub>,q<sub>37</sub>,q<sub>39</sub>,q<sub>42</sub>,q<sub>44</sub>,q<sub>45</sub>) reagents.

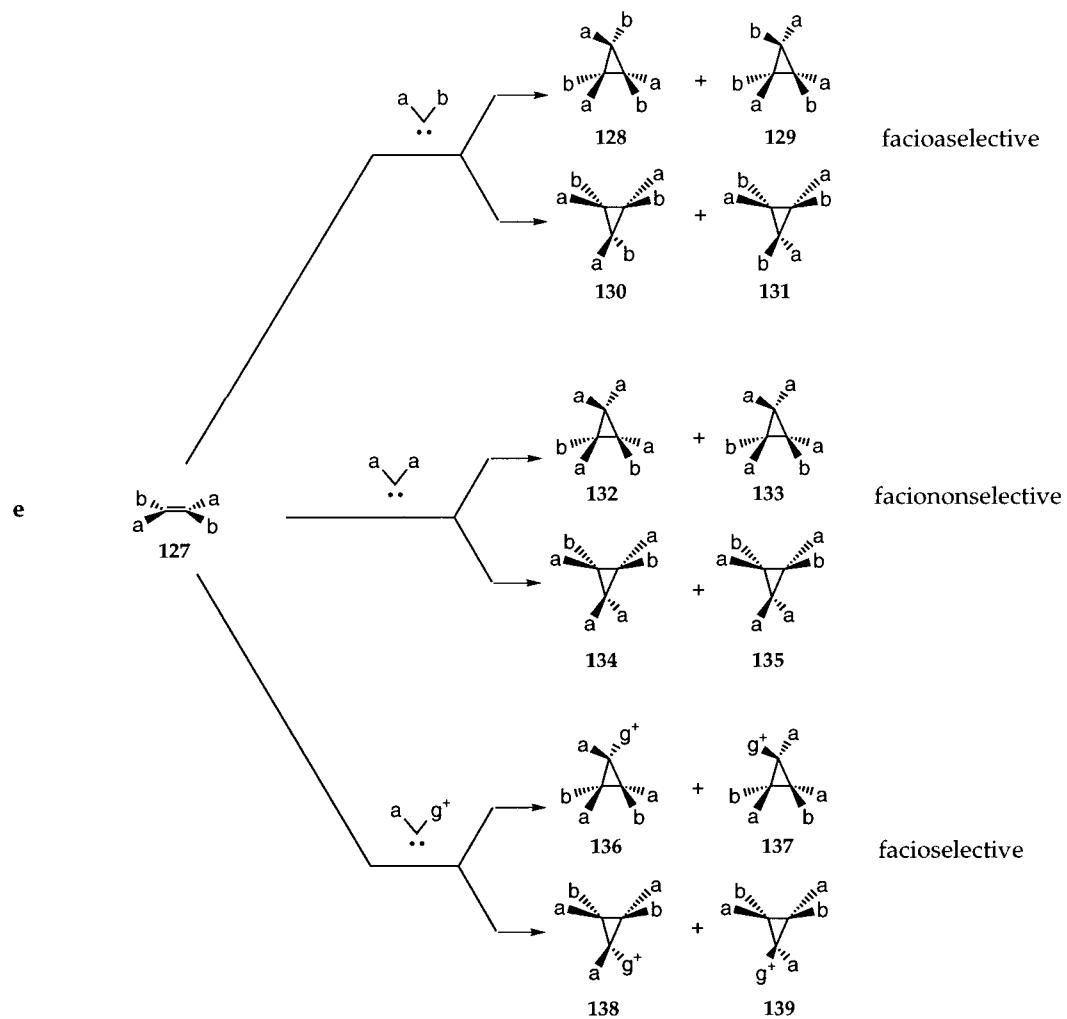
Quartet Mode	Selectivity	Quartets	h1		h2		h3		h4		h5		h6		e		d1		d2		d3		d4	
			ac	c	ac	c	ac	c	ac	c	ac	c	ac	c	ac	c	ac	c	ac	c	ac	c	ac	c
A	Facioselectivity	q1-q3	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+	+		+	+	
N	Faciononselectivity	q4-q21			+	+	+	+			+	+	+	+	+							+	+	+
S	Facioselectivity	Enantiofacioselectivity	q22-q24 and q26-q45														+							
		Diastereofacioselectivity	q22-q45															+	+	+	+	+	+	+

ac : achiral reagent  
c : chiral reagent

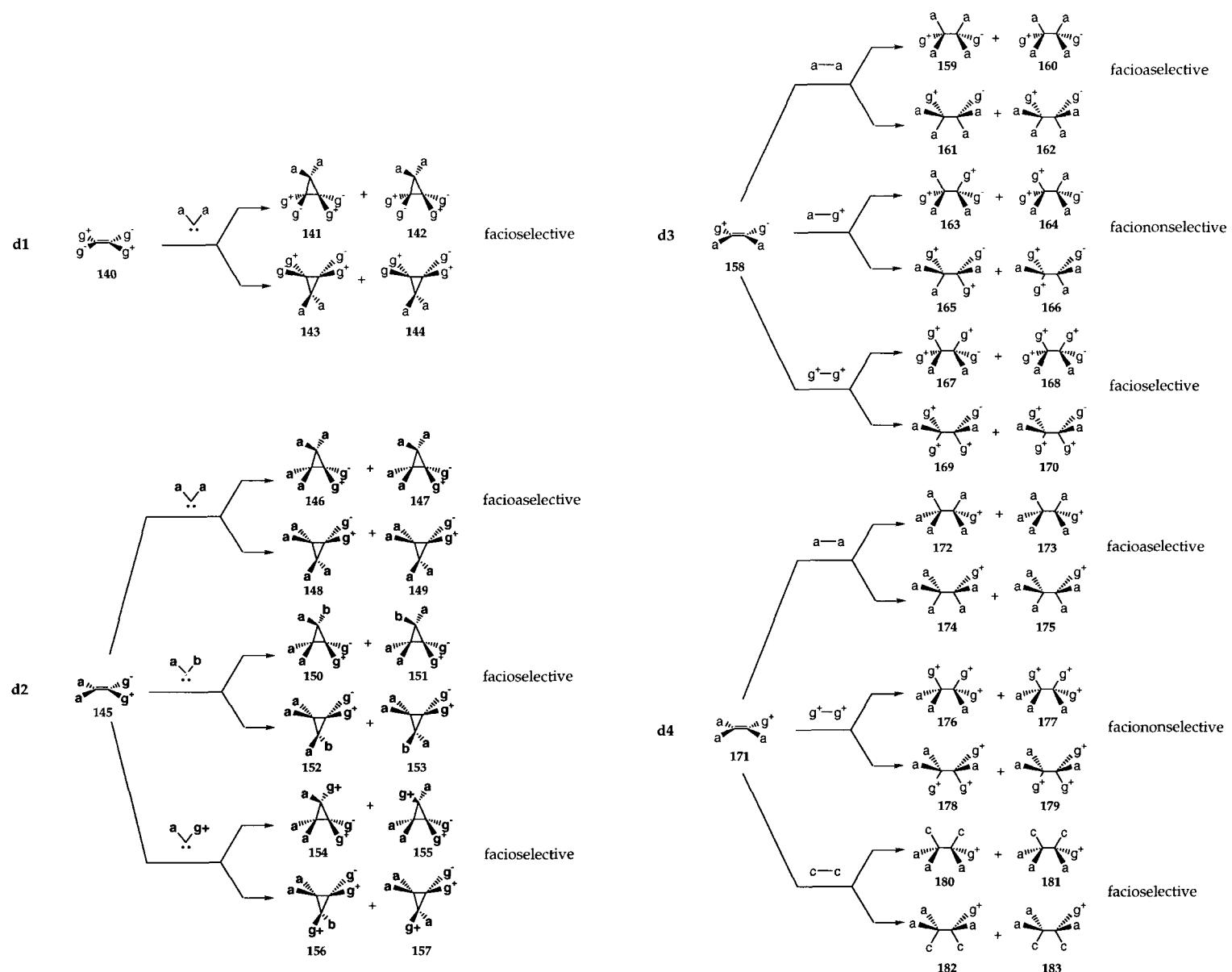
**Table 12.3.** Facioselectivity in Conjunctive Processes Involving Achiral and Chiral Reagents



**Figure 12.8.** Examples of Facioselectivity and Faciononselectivity at Homotopic Faces



**Figure 12.9.** Examples of Facioselectivity, Faciononselectivity and Facioselectivity at Enantiotopic Faces



**Figure 12.10.** Examples of Facioselectivity, Faciononselectivity and Facioselectivity at Diastereotopic Faces

In sum, (a) only d<sub>2</sub>, d<sub>3</sub>, d<sub>4</sub> can be afacioselective with achiral reagents, and only d<sub>2</sub> and d<sub>4</sub> can be afacioselective with chiral reagents; (b) only d<sub>3</sub> can be nonfacioselective and with only chiral reagents, while d<sub>4</sub> can be nonfacioselective with both achiral and chiral reagents; (c) all of d<sub>1</sub>-d<sub>4</sub> can be diastereofacioselective with achiral or chiral reagents.

Diastereofacioselectivity of the substrate say with C<sub>2</sub>-symmetric reagents, and therefore with no role for vectoselectivity, would yield two achiral diastereomers (q22), two chiral diastereomers (q23), or two diastereomeric enantiomeric pairs (q25). The reaction of faces d<sub>1</sub>-d<sub>4</sub> with non-C<sub>2</sub>-symmetric reagents would entail considerations of vectoselectivity, and more complex mixtures may result (*vide infra*). Here, *diastereofacioselectivity* refers to the face type in the *reactant* substrate.

In every case, diastereofacioselectivity is given by the expressions:

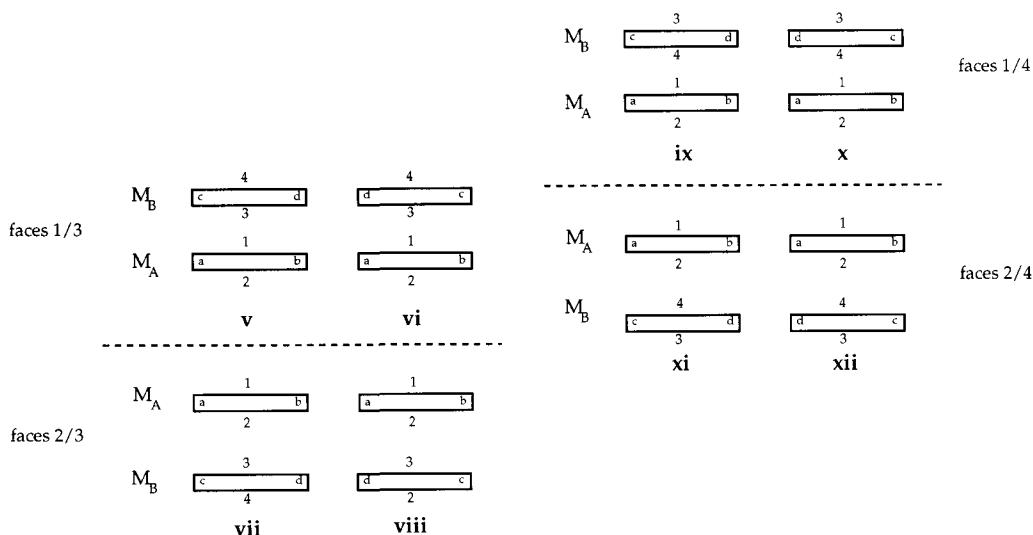
$$\text{diastereofacioselectivity} = |(\%m_1 + \%m'_1) - (\%m_2 + \%m'_2)| \neq 0 \quad (12.2\text{c})$$

or

$$\text{diastereofacioselectivity} = |(\%m_1 + \%m'_1)| / |(\%m_2 + \%m'_2)|. \quad (12.2\text{d})$$

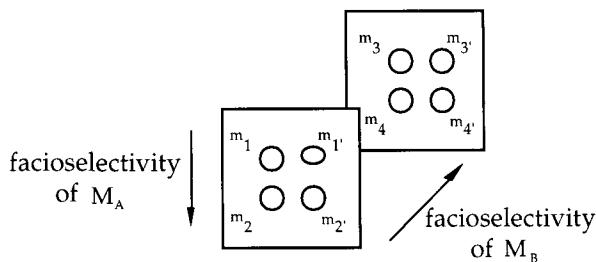
## V. Difacioselectivity

In a (2,2)-face/face ligogenic process involving molecules M<sub>A</sub> and M<sub>B</sub>, facioselectivity is possible at each of the faces of molecule M<sub>A</sub> (faces 1 and 2), and at each of the faces of molecule M<sub>B</sub> (faces 3 and 4) thereby generating four face-face combinations - face1-face3, face2-face3, face1-face4, and face2-face4. When vectoselectivity is also taken into account, such a process would lead to a maximum of eight conjunctive states (v)-(xii) as portrayed in Figure 12.11 below:



**Figure 12.11.** The Eight Conjunctive Permutations in (2,2)-Ligogenic Face-Face Processes

The overall process can be represented by an octet (=two quartets)  $m_1, m_1', m_2, m_2', m_3, m_3', m_4, m_4'$ .



**Figure 12.12.** Facioselectivities of  $M_A$  and  $M_B$  in Face-Face Conjunctive Processes

Facioselectivity at the two faces of  $M_A$  - moving top to bottom - is defined by:

$$\begin{aligned} \text{Facioselectivity of } M_A \text{ (parent)} \\ = (\%m_1 + \%m_1' + \%m_3 + \%m_3') / (\%m_2 + \%m_2' + \%m_4 + \%m_4'). \end{aligned} \quad (12.3)$$

Facioselectivity at the two faces of  $M_B$  - moving front to back - is defined by:

$$\begin{aligned} \text{Facioselectivity of } M_B \text{ (reagent)} \\ = (\%m_1 + \%m_1' + \%m_2 + \%m_2') / (\%m_3 + \%m_3' + \%m_4 + \%m_4'). \end{aligned} \quad (12.4)$$

According to Masamune and coworkers,<sup>139</sup> the degree of double asymmetric induction is approximated by  $ds_1 \times ds_2$  for a matched pair, and by  $ds_1/ds_2$  for a mismatched pair, where  $ds_1$  and  $ds_2$  are the diastereoselectivities for the two chiral reactants, respectively.

Vectoselectivity between  $M_A$  and  $M_B$  - moving left to right - is defined by:

$$\text{Vectoselectivity} = (\%m_1 + \%m_2 + \%m_3 + \%m_4) / (\%m_1' + \%m_2' + \%m_3' + \%m_4'). \quad (12.5)$$

The arcs represent morphic relationships  $m_1/m_3, m_1'/m_3', m_2/m_2'$  and  $m_4/m_4'$ . Each of these relationships is homomorphic, enantiomeric, or diastereomeric.

We have explored the various combinations in [2+2] and [2+4] cycloadditions with a wide variety of alkenes and 1,3-dienes, and discovered 45 fundamental octets governing these face-face combinations. These are presented in Figure 12.14 below. The blown-up octet depicted in Figure 12.15 is for the reaction between *cis*-ag<sup>+</sup>C=Cag<sup>-</sup> and a<sub>2</sub>C=C=cb<sub>2</sub>.

The octets can be grouped into six modes, based on facioselectivity of  $M_A$  and facioselectivity of  $M_B$ . This is given in Table 12.4 below.

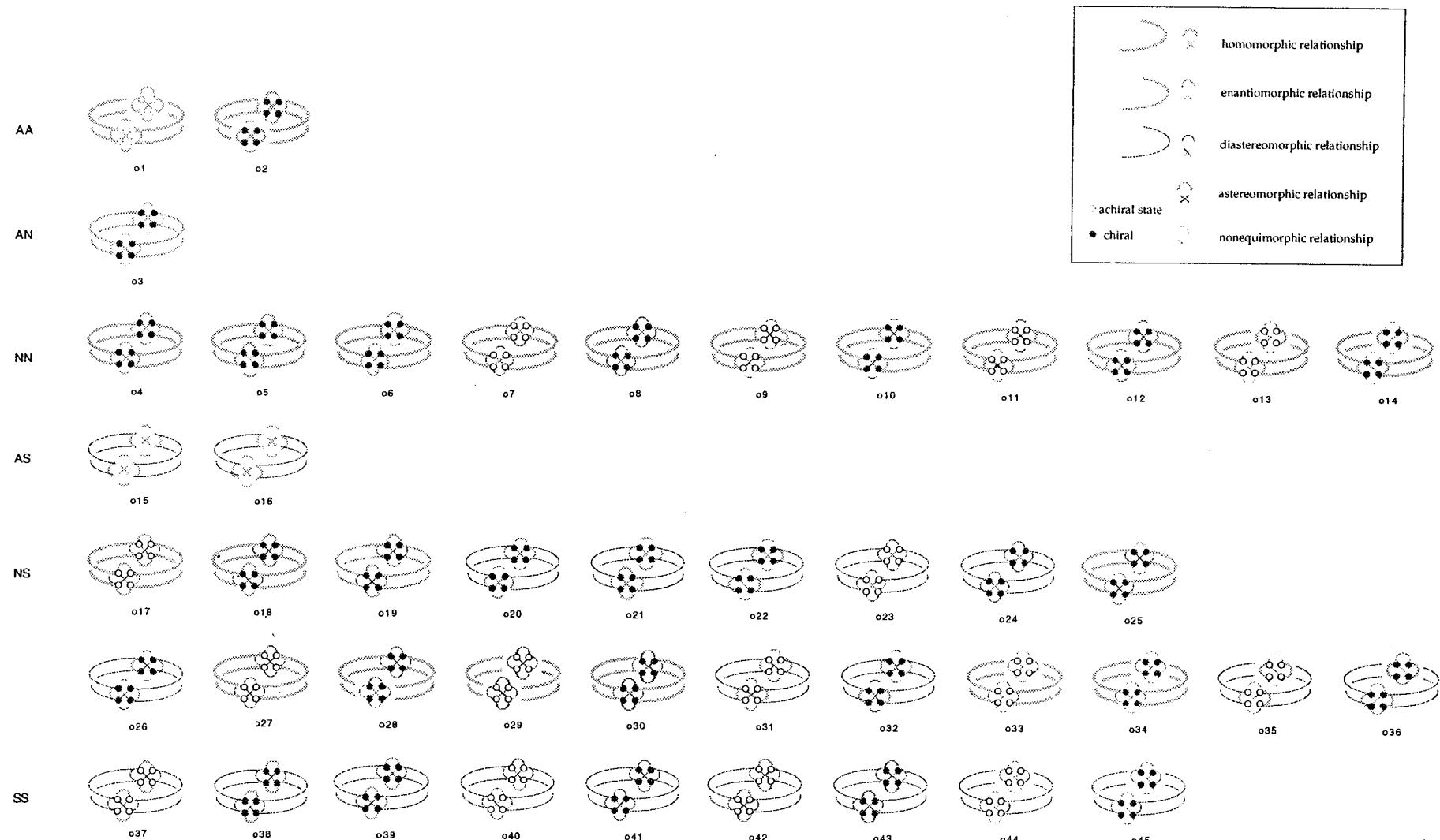
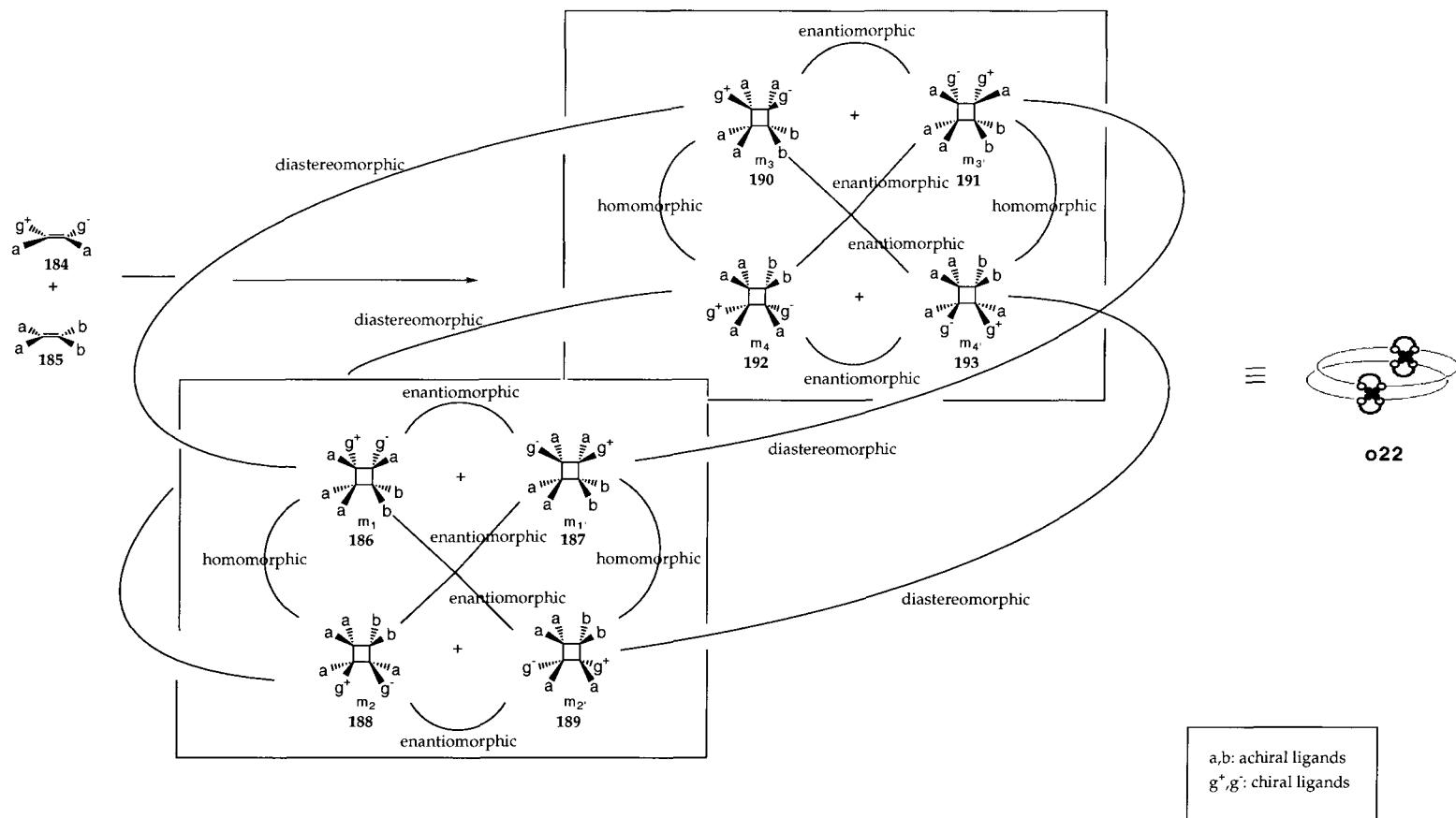


Figure 12.13. The 45 Octets of Face-Face Conjunctive Processes



**Figure 12.14.** The Addition of  $a_2C=Cb_2$  to  $ag^+ C=Cag^-$

When the eleven types of faces ( $h_1$ - $d_4$ ) of  $M_A$  are pitted against the eleven types of faces of  $M_B$ , there emerge six classes of selectivity - facioselective-facioselective (AA), faciononselective-faciononselective (NN), facioselective-faciononselective (AN), facioselective-facioselective (AS), faciononselective-facioselective (NS), and facioselective-facioselective (SS). Table 12.5 shows these correlations between the faces.

Figure 12.15 illustrates one example of each of these six classes of difacioclectivity and the type of octet it represents:

AA	<b>o1,o2</b>
AN	<b>o3</b>
NN	<b>o4-o14</b>
AS	<b>o15, o16</b>
NS	<b>o17-o36</b>
SS	<b>o37-o45</b>

It can be seen from the above cases that of the homotopic subclasses,  $h_1$  and  $h_4$  are facioselective towards  $h_1$ - $h_6$ , e and  $d_1$ - $d_4$ , and, faciononselective towards e and  $d_1$ - $d_4$ . However,  $h_2$ ,  $h_3$ ,  $h_5$  and  $h_6$  are facioselective towards  $h_1$ ,  $h_4$ , e and  $d_1$ , and, faciononselective towards  $h_2$ ,  $h_3$ ,  $h_5$ ,  $h_6$ , e and  $d_1$ - $d_4$ .

Enantiotopic faces e are facioselective towards  $h_1$ - $h_6$ , faciononselective towards  $h_1$ - $h_6$ , e and  $d_1$ - $d_3$ , and, facioselective towards  $d_4$ .

In the case of diastereotopic faces, one finds that  $d_1$  is facioselective towards  $h_1$ - $h_6$ , faciononselective towards  $h_1$ - $h_6$  and e, and, facioselective towards  $d_1$ - $d_4$ . In contradistinction,  $d_2$  and  $d_3$  are facioselective towards  $h_1$  and  $h_4$ , faciononselective towards  $h_1$ - $h_6$  and e, and, facioselective towards  $d_1$ - $d_4$ . Finally,  $d_4$  is facioselective towards  $h_1$  and  $h_4$ , faciononselective towards  $h_1$ - $h_6$ , and, facioselective towards e and  $d_1$ - $d_4$ .

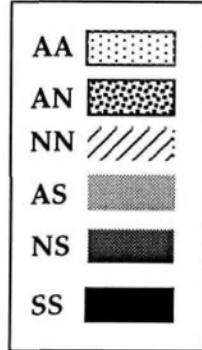
### Summary

To clarify selectivity at faces of planar molecular fragments, or *facioselectivity*, we presented a complete classification of all eleven types of stereotopic molecular faces. We defined the different modes of facioselectivity *viz.* facioselectivity, faciononselectivity and stereofacioclectivity at each type of molecular face. We also discussed *difacioclectivity* for conjunctive processes involving the interactions of two molecular faces.

Octet Mode	Octets	Facioselectivity of $M_A$			Facioselectivity of $M_B$		
		Facioselectivity	Faciononselectivity	Facioselectivity	Facioselectivity	Faciononselectivity	Facioselectivity
AA	o1,o2	+			+		
AN	o3	+				+	
NN	o4-o14		+			+	
AS	o15,o16	+					+
NS	o17-o36		+				+
SS	o37-o45			+			+

**Table 12.4.** The Six Modes of Difacioselectivity in Conjunctive Processes

	h1	h2	h3	h4	h5	h6	e	d1	d2	d3	d4
h1	AA	AA	AA	AA	AA	AA	AN	AS	AS	AS	AS
h2		NN	NN	NN	NN	NN	AN	AS	AS	AS	AS
h3					NN	NN		AS	AS	AS	AS
h4				NN	NN	NN		AS	AS	AS	AS
h5					NN	NN		AS	AS	AS	AS
h6						NN		AS	AS	AS	AS
e							AN				
d1								SS			
d2									SS		
d3										SS	
d4											SS


**Table 12.5.** Difacieselectivity in Conjunctive Processes

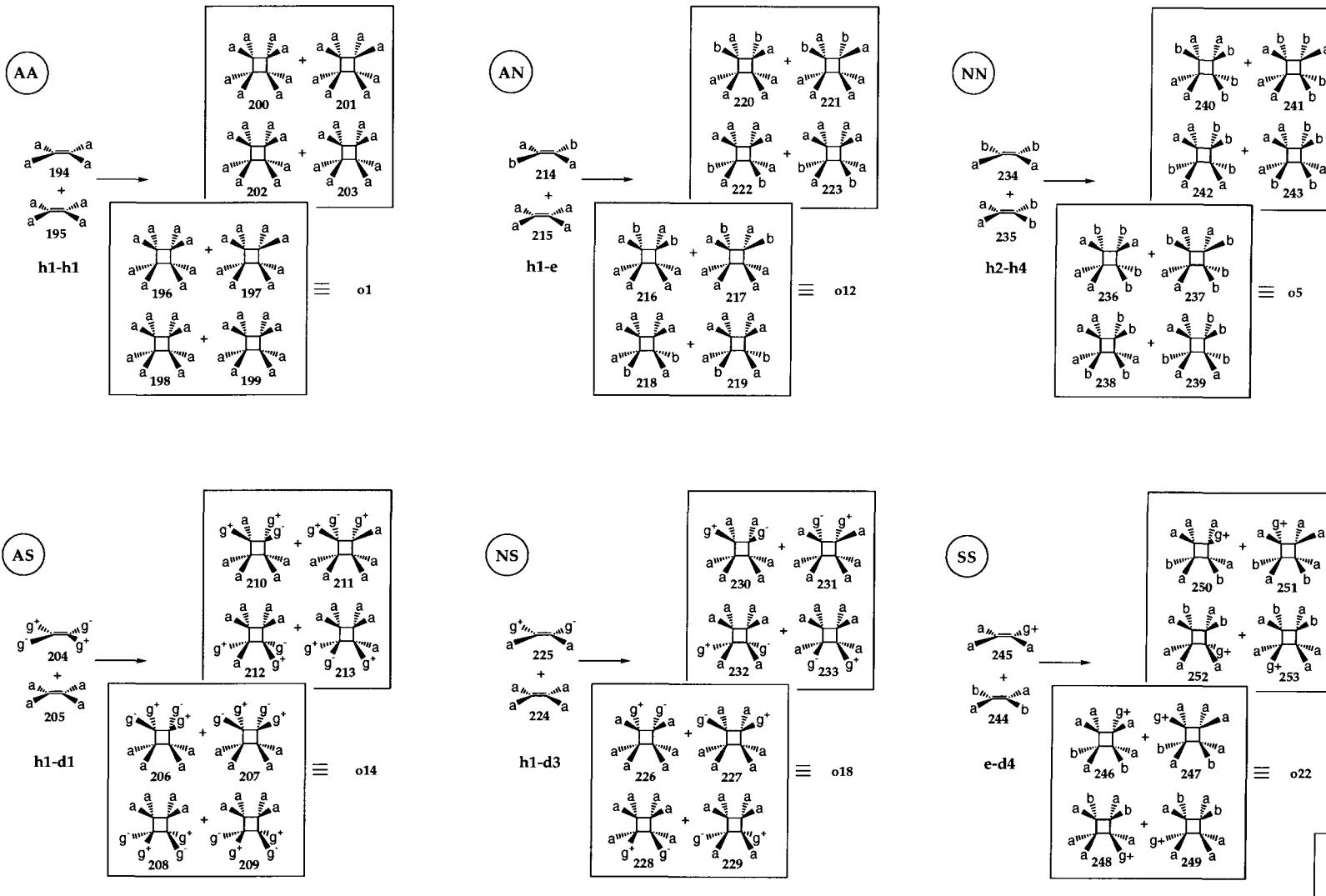


Figure 12.15. Examples of Difaciocselectivity AA, AN, NN, AS, NS, and SS

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"Language - human language - after all, is but little better than the croak and cackle of fowls, and other utterances of brute nature - sometimes not so adequate."

Nathaniel Hawthorn, *Passages from the American Notebooks*, 1868.

# 13

## Vectoselectivity

In 1968, Hassner coined the term *regiospecificity* (*regio*, L., direction) to denote directional preference of bond formation in a variety of reactions, such as addition reactions, eliminations, ring openings and cycloadditions.<sup>140</sup> The term has gained universal acceptance, received the blessings of IUPAC, and has been subjected to modified definitions. Trost has defined *regioselectivity* as "selective addition of an unsymmetrical reagent to an unsymmetrical functional group,"<sup>141</sup> and *regiocontrol*, as "orientational control in the reaction of an unsymmetrical functional group *and/or* an unsymmetrical reagent"<sup>142</sup> or "orientational control of two reacting partners".<sup>143</sup> Further, Goering has redefined regioselectivity to mean predominant formation of one of two possible products arising in the reaction of isomeric reactants.<sup>144</sup> It is now clear that the term *regioselectivity* embodies two conceptually distinct connotations - "Markovnikov/anti-Markovnikov-type" selectivity, on the one hand, and, situselectivity on the other. Trost's definition fits the former, and, in effect refers to the preference in the relative alignment of two dissymmetric reactants, whereas Goering's definition fits the latter to indicate selectivity between reacting sites (atom, bond, molecular face, molecular fragment). In the chemical literature, one finds the term is indiscriminately used in these two distinct contexts. It is perhaps due to this confusion that even authoritative books on stereochemistry avoid the term regioselectivity completely.<sup>145</sup>

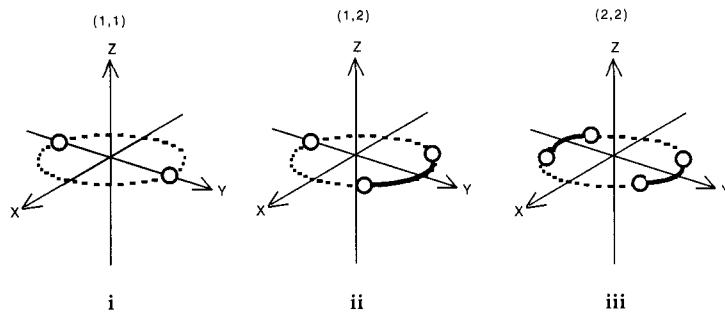
We defined situselectivity in Chapter 10; we now delve into regioselectivity, and demonstrate that not only is it distinct from situselectivity, but that it is also a special case of a much broader concept, which we term *vectoselectivity*. The latter concept encompasses a comprehensive and wider range of orientational possibilities, and is one that is applicable to reactions involving three or more (rather than two) reactants, and is applied to (1,1)-, (1,2)-, (2,2)-, (1,1,2)-, (1,2,2)-, and (2,2,2)-junctive processes.

### I. The Junctive Loop

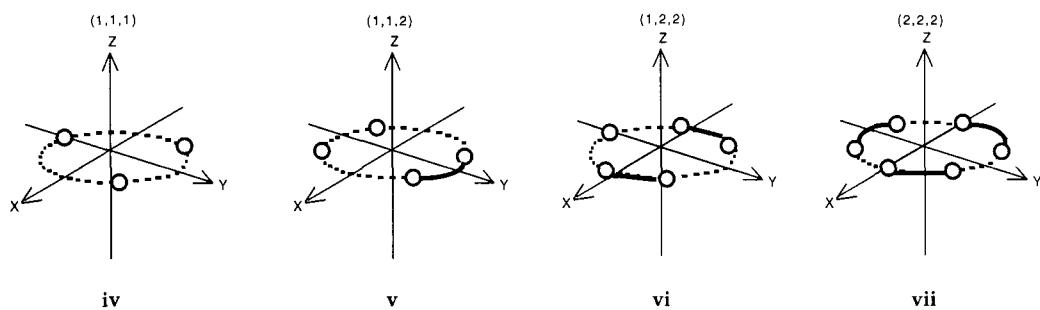
We have shown previously how a wide variety of chemical transformations may be represented as junctive/ligogenic processes (*cf.* Volume 2, Chapters 8 and 9). Figure 13.1 depicts the most common types (i-vii) of such processes in organic chemistry. The first three of these represent (1,1)-, (1,2)-, and (2,2)-junctive processes, and involve interactions between two junctive simplexes; the

remaining four (iv-vii) involve the interaction of *three* junctive simplexes and represent (1,1,1)-, (1,1,2)-, (1,2,2)-, and (2,2,2)-junctive processes. In each of these ligogenic processes the junctive atoms define a topological *junctive loop* (Figure 13.1) - a flattened, idealized circle in the XY-reference plane; this is the formal plane in which the different  $\sigma$  (full or partial) bonds (shown in dashed lines) are formed (*vide infra*). The vectorial sense (if any; *vide infra*) of each simplex is specified with reference to this loop. This enables one to specify the *relative* alignment of *all* the vectorial simplexes taking part in a given process (with due consideration to any non-vectorial simplexes). We will apply this type of vectorial analysis to transformations involving two simplexes, as well as those involving three (or more) simplexes.

### Two Junctive Simplexes



### Three Junctive Simplexes

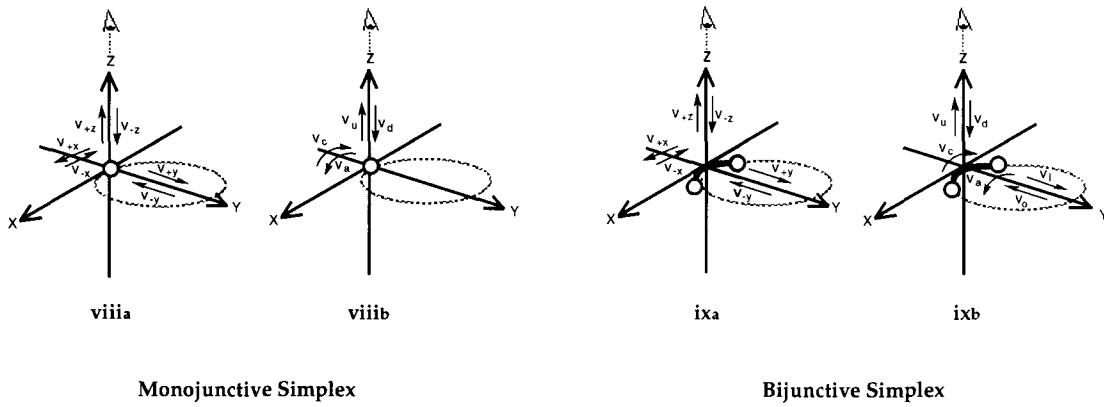


**Figure 13.1. The Junctive Loop in Junctive Processes**

## II. Vectoplexes and the Junctive Loop

A given simplex may or may not have an effective vectorial sense. Within the concept of vectoselectivity discussed in this chapter, a junctive simplex that does have a vectorial sense is represented by a vector  $v_v$  (*vide infra*), and is termed a *vectogenic* junctive simplex (*vectoplex*); a junctive simplex that has no vectorial properties is an *avectogenic* junctive simplex (*avectoplex*) (there is no vector  $v_v$  associated with it). For a vectoplex, vector  $v_v$  either lies in the XY-plane ( $v_v = v_{+x}, v_{-x}, v_{+y}, v_{-y}$ ), or is orthogonal to it ( $v_v = v_{+z}, v_{-z}$ ) (Figure 13.2). (The designations  $v_{+x}, v_{-x}, v_{+y}, v_{-y}, v_{+z}, v_{-z}$ , would, in principle, enable one to specify the *absolute* orientation of these vectors, within the XYZ frame (Figure 13.2, viia and ix). However, in the context of junctive and ligogenic processes, it is more useful to define the *relative* alignment of the vectors with reference to the junctive loop (in the XY-plane), *independent of the XYZ frame* (Figure 13.2, viib and ix). The junctive loop (*vide supra*) is, in effect, the locus of points defined by all the reacting junctive atoms taking part in the junctive process. For Observer 1 viewing from the top of the

+Z-axis, vectors  $v_{+x}$ ,  $v_{-x}$  are tangent to the loop, and may be replaced by "v<sub>clockwise</sub>" ( $v_c=c$ ) or "v<sub>anticlockwise</sub>" ( $v_a=a$ ) because they denote the in-XY-plane clocksense of the said tangent vectors. Vectors  $v_{+y}$  and  $v_{-y}$  also lie in the XY-plane, but they are *perpendicular* to the loop; these two vectors are termed "v<sub>in</sub>" ( $v_i=i$ ) and "v<sub>out</sub>" ( $v_o=o$ ) - pointing towards the center, or, away from the center of the circle, respectively. Finally, vectors,  $v_{+z}$ ,  $v_{-z}$ , are orthogonal to the loop *and* to the XY-plane; these vectors are referred to as "v<sub>up</sub>" ( $v_u=u$ ) and "v<sub>down</sub>" ( $v_d=d$ ) as they both are parallel to the Z-axis, and point up (towards the viewer) and down (away from the viewer), respectively.<sup>146</sup> Thus, for the observer viewing the junctive loop from the top of the +Z-axis, the designations  $v_c, v_a, v_i, v_o, v_u$  and  $v_d$  define, with reference to the junctive loop of the XY-plane, the relative orientations of the vectogenic simplexes involved in the junctive/ligogenic process. The orientation of a vector representing a given vectoplex depends on the specific molecular structure of the vectoplex (*vide infra*).



**Figure 13.2.** Absolute and Relative Orientations of Vectogenic Monojunctive and Bijunctive Simplexes

### III. Molecular Vectoplexes

We will now examine molecular vectogenic simplexes - molecular vectoplexes - and define vector  $v_v$  for various monojunctive and bijunctive molecular vectoplexes encountered in organic transformations.

#### A. Monojunctive Vectoplexes

The various types of typical monoatomic junctive moieties are depicted, along with the characteristic vectors  $v_v$  in their *relative* orientations, in Figure 13.3 below. In case 1, vector  $v_v$  is parallel to the only bond; in the case of 2-4 it is parallel to one of the three bonds at the junctive atom. In cases 5-6,  $v_v$  is parallel to the axis of the  $\pi$  bond. For cases 7-10, vector  $v_v$  is based on the two substituents of the junctive atom. In the case of 11-14, the effective vector  $v_v$  is parallel to the main axis of the  $\pi$  system. In each of cases 1-14, the *absolute* sense (i.e.  $v_a$  vs.  $v_c$ , or  $v_i$  vs.  $v_o$ , or  $v_u$  vs.  $v_d$ ) of each vector is determined on the basis of the actual substituents (Figure 13.4, *vide infra*).

- 1: For monojunctive simplex m-X (1a/1b), vector  $v_v$  is defined by atoms X and m, in the XY-plane;  $v_v$  originates at atom X or m, whichever is of lower priority (Sequence Rule), and terminates at the atom of higher priority;  $v_v = v_o$  in 1a ( $X > m$ ),  $v_v = v_i$  in 1b ( $X < m$ ).

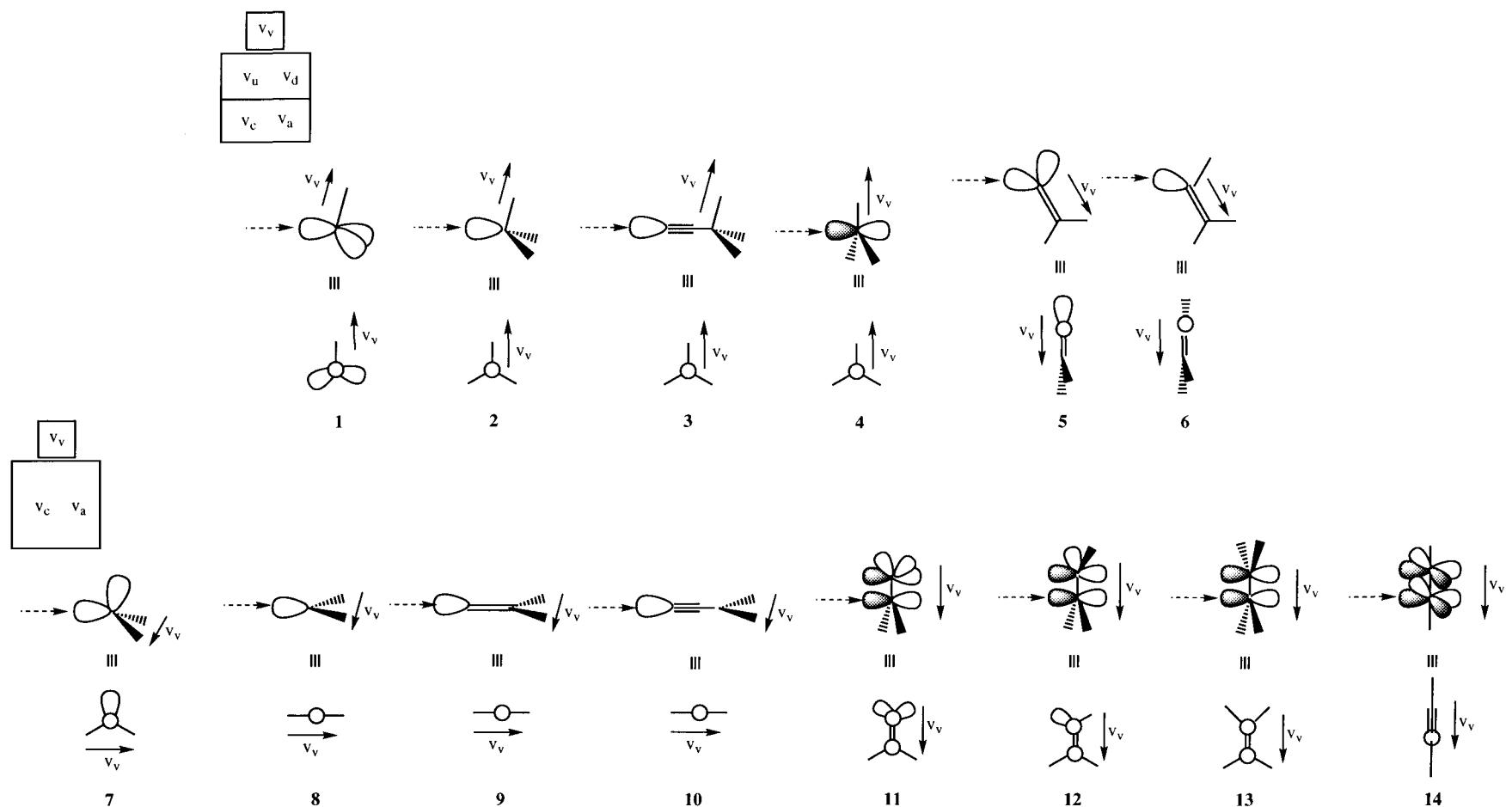


Figure 13.3. Monoatomic Junctive Moieties

**2,3:** A given *tricoordinate pyramidal* monojunctive simplex  $Xmnp$  (**2a,2b**; also applicable to **3a,3b**) is defined on the basis of the projection of vector  $v_v$  onto the  $XZ$ -plane (this is equivalent to flattening of the pyramidal  $mnpX$  onto the  $XZ$ -plane); further, one specifies the angle between the projected vector and the  $XY$  plane. In sum,  $v_v = v_c$  (**2a-1/-180°, 2b-3/0°**),  $v_v = v_a$  (**2a-3/0°, 2b-1/-180°**),  $v_v = v_u$  (**2a-2/-90°, 2b-4/+90°**),  $v_v = v_d$  (**2a-4/+90°, 2b-2/-90°**). Here too, the specification of the angle distinguishes between **2a-1** and **2b-3**, (and also **2a-3/2b-1, 2a-1/2b-4**, and **2a-4/2b-2**).

**4:** A given *tricoordinate planar* monojunctive simplex  $mnpX$  (**4a** and **4b**) is defined on the basis of the junctive atom  $X$  and ligand  $m$  (ligand  $m>n,p$ ) attached directly to  $X$ ; the vector originates at the atom of lower priority (Sequence Rule) and terminates at the atom of higher priority. One need also specify the angle between the vector and Observer 2 viewing the  $XZ$ -plane from the end of the  $-Y$  axis; the angle is between the  $X-m$  vector and the  $XY$ -plane. The angle is  $0^\circ$  for **4a-3** and **4b-3**; it is  $+90^\circ$  for **4a-4** and **4b-2**,  $\pm 180^\circ$  for **4a-1** and **4b-1**, and  $-90^\circ$  for **4a-2** and **4b-4**. In sum,  $v_v = v_c$  (**4a-1/-180°, 4b-3/0°**),  $v_v = v_a$  (**4a-3/0°, 4b-1/-180°**),  $v_v = v_u$  (**4a-2/-90°, 4b-4/+90°**),  $v_v = v_d$  (**4a-4/+90°, 4b-2/-90°**). For cases where there is a linear spacer between the junctive atom and the rest of the structure, the same vectors are defined on the basis of the ligands themselves as shown in Figure 13.3. The specification of the angle between vector  $v_v$  and the  $XY$  plane enables one to distinguish between **4a-1** and **4b-3**, (and also **4a-3/4b-1, 4a-2/4b-4**, and **4a-4/4b-2**). The value of the angle is determined after vector  $+v_x$  travels in the  $XZ$ -plane to reach the position of the  $v_v$  vector.

For both planar and pyramidal  $mnpX$  systems, the letter subscript, in effect, defines the angle between the vector/projected vector and the  $XY$ -plane. For other orientations of  $v_v$ , one may replace the letter subscript with a numerical subscript for the value of the angle, e.g.  $v_{+45^\circ}$  is the orientation intermediate between **4a-3** and **4a-4**, and  $v_{-45^\circ}$  corresponds to the intermediate between **2b-3** and **2b-4**.

**5,6:** Here, vector  $v_v$  is determined by the  $m$ -to- $X$  bond; vector  $v_v$  originates at  $X$  (**5a,6a**,  $v_v = v_d$ ;  $X>m$ ) or  $m$  (**5b,6b**,  $v_v = v_u$ ;  $m>X$ ).

**7-10:** For monojunctional simplex  $mnX$  (**7a-10a, 7b-10b, 7c-10c, 7d-10d**), vector  $v_v$  is defined on the basis of the ligands  $m,n$  directly attached to the junctive atom  $X$ . (For **7a-10a, 7b-10b**, vector  $v_v$  is tangent to the loop, and originates at the substituent of lower priority (Sequence Rule) and terminates at the substituent of higher priority *viz.*  $v_c$  (**7a-10a, m>n**),  $v_a$  (**7b-10b, n>m**). For **7c-10c, 7d-10d** vector  $v_v$  is perpendicular to the plane of the loop;  $v_v = v_u$  (**7c-10c, m>n**) and  $v_v = v_d$  (**7d-10d, n>m**).

**11-14:** Unlike **5a,5b** and **6a,6b** where bonding is at  $m$ , in cases **11a-13a** and **11b-13b** bonding occurs at  $X$ . Here too, dipole  $X-M$  provides the basis for defining vector  $v_v$ . The latter vector is equivalent to  $v_d$ , (**11a-13a, 14a**) if  $X$  is higher priority relative to  $m$ . That same vector is equivalent to  $v_u$ , (**11b-13b, 14b**), if  $m$  is of higher priority relative to  $X$ .

Figure 13.5 depicts a few molecular monojunctional  $n$ -coordinate avectoplexes and vectoplexes. The examples are oriented for the junctive loop in Figure 13.1; the dashed arrow in each case denotes the direction of bonding. Avectoplexes **15, 20, 25, 30, 37-39, 46** and **50** have no characteristic vector  $v_v$ . In contrast, monocoordinate vectoplexes **16-19** are characterized by either  $v_o$  or  $v_i$ ; **16** and **17** are  $v_o$  and  $v_i$  respectively, while **18** and **19** are  $v_i$  and  $v_o$ , respectively. Pyramidal (**21-24, 26-29**) and planar vectoplexes (**31-34**) are designated by  $v_c/v_a$ , and  $v_u/v_d$ . The pyramidal tricoordinate systems **21-24, 26-29** are  $v_c, v_u, v_a, v_d$  respectively; similarly, the planar tricoordinate systems **31-34** are also  $v_c, v_u, v_a, v_d$  respectively. Vectoplexes **35-36** are either  $v_u$  or  $v_d$ ; **40-42** and **43-45** are  $v_c/v_a, v_u/v_d$ ; **47-49** and **51-54** are  $v_u$  and  $v_d$ .

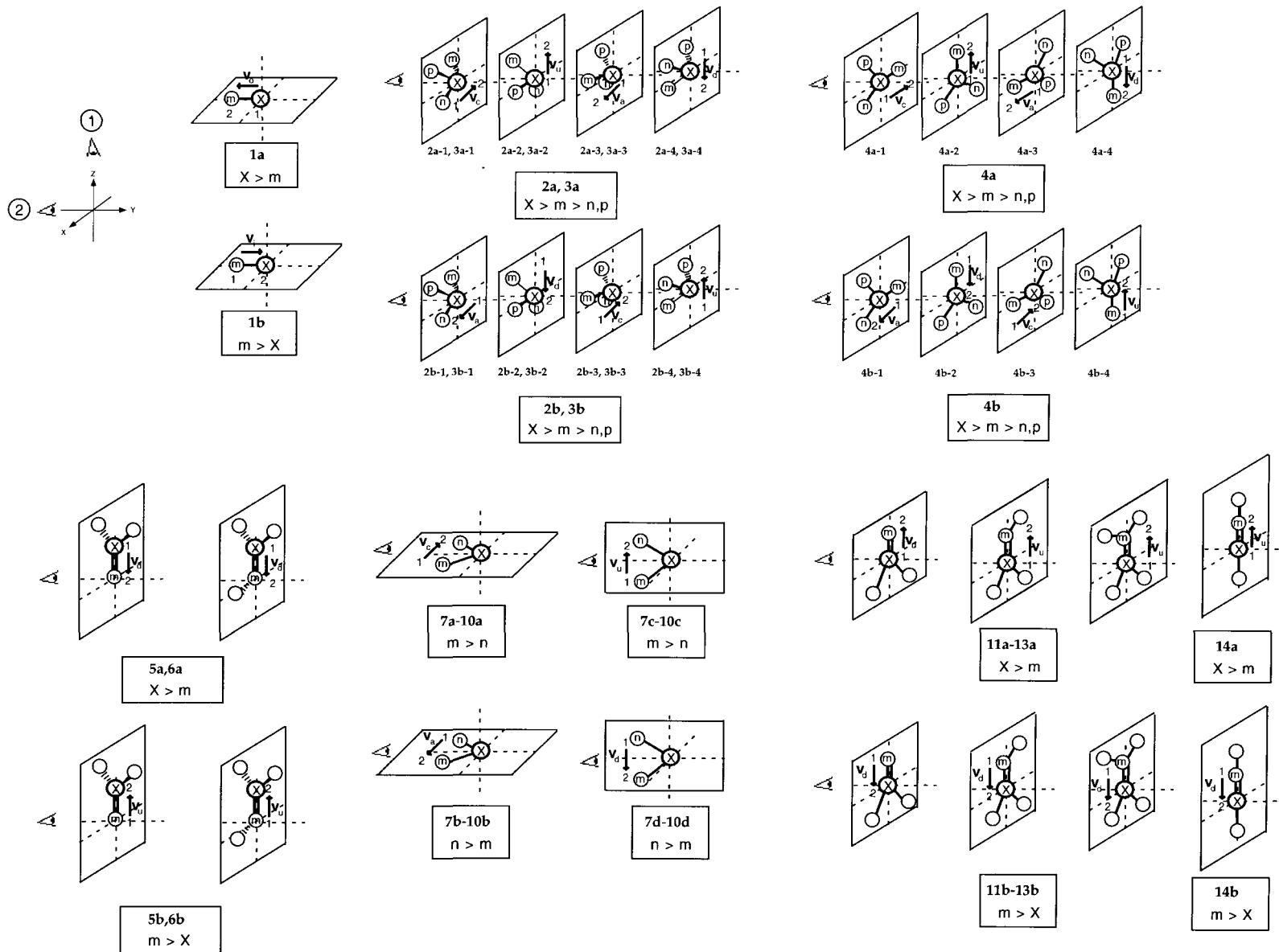
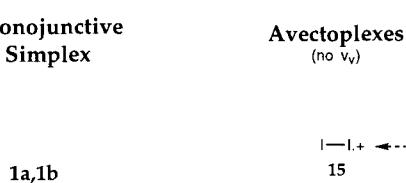
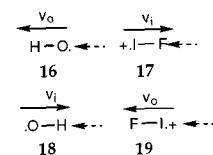


Figure 13.4. Defining Absolute Sense of Vectorial Monojunction Simplexes

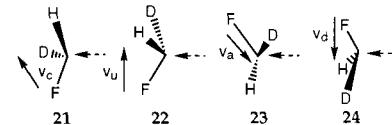
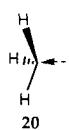
**Monojunctive  
Simplex**



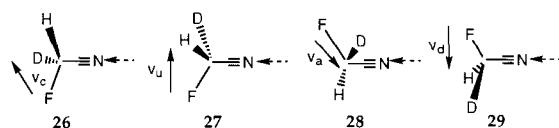
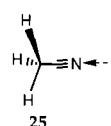
**Vectoplexes**



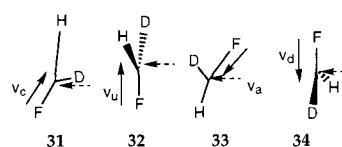
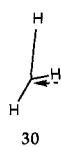
**2a,2b**



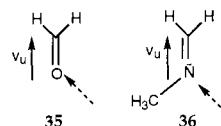
**3a,3b**



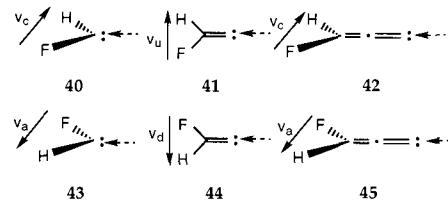
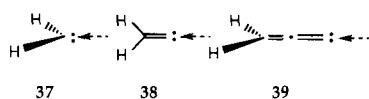
**4a,4b**



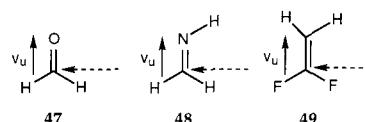
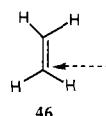
**5a,5b,6a,6b**



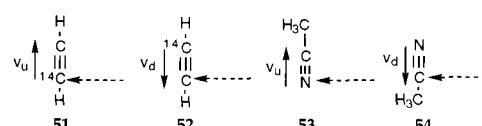
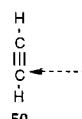
**7a,7b - 10a,10b**



**11a,11b - 13a,13b**



**14a,14b**



**Figure 13.5.** Examples of Monojunctive n-Coordinate Avectoplexes and Vectoplexes

### B. Bijunctive Vectoplexes

Figure 13.6 illustrates how  $v_v$  is defined in relation to the junctive loop, for a wide range of molecular vectogenic bijunctive simplexes (55a-63):

**X-Y:** For the simplest bijunctive case X-Y (e.g. H-Br, I-F, etc.), vector  $v_v$  is based on atoms X,Y and is directed from the atom of higher priority to lower (55a, Y>X; Sequence Rule).

**mX=Yn:** In the case of triply-bonded system m-X=Y-N,  $v_v$  is also based on atoms X and Y (56a, Y>X); should X=Y, then one resorts to ligands m and n (CIP priority).

**mnX=Y:** Case 57a is the prototype (Y>X) of a multitude of compounds with X=Y functionalities e.g. C=O, C=S, C=Se, and C=Te, and here  $v_v$  points from the heteroatom to C.

**mqX=Ynp:** For 58a-c, the examination is carried out sequentially on X/Y >> m/n > p/q in planes K (58a), L<sub>1</sub> (58b), and then L<sub>2</sub> (58c), respectively; this sequence of pairwise comparisons is followed until the degeneracy is broken.

**mpX-Yut-Znq:** In the case of dipolar systems 59a and 60a, for simplicity one could let  $v_v$  point from the negative pole to the positive pole, regardless of the identity of the X/Z atoms. However, for the sake of uniformity, for those dipolar systems, and for ones with no dipoles (that is, with degenerate junctive termini), one explores sequentially the X/Y >> m/n > p/q pairs in planes K (61a), L<sub>1</sub> (61b), and L<sub>2</sub> (61c), respectively, again until the degeneracy is broken.

**mpX=Yt-Zu=Wnq:** In the case of *cisoid* dienes 62a-e, the sequential exploration follows the order X/W > Y/Z > m/n > p/q > t/u in planes K<sub>1</sub> (62a), K<sub>2</sub> (62b), L<sub>1</sub> (62c), L<sub>2</sub> (62d), L<sub>3</sub> (62e) respectively.

**mrX=Xp-Yt=Zu-W=Qns:** For 63a, the order of exploration is P/Q > X/W > Y/Z > m/n > r/s > p/q > t/u; one stops at the first break in the degeneracies, and defines  $v_v$  accordingly.

For all of the above bijunctive cases, the  $v_v$ 's are tangent to the loop and are therefore classified as either  $v_a$  or  $v_c$ .

Examples of molecules that constitute avectoplexes (no  $v_v$ ) and vectoplexes (characterized by  $v_v$ ) are shown in Figure 13.7. Thus, 64, 65, 75, 86, 87, 108, 109 have no vector  $v_v$  associated with them. In contrast, each of 66-74, 76-85, 88-107, 110-118 has a vector  $v_v$  associated with it. The vector  $v_v$ , when placed on the loop, becomes in effect  $v_a$  (anticlockwise) or  $v_c$  (clockwise) in relation to the loop. Figure 13.7 also depicts the vector for each reactive moiety, obtained using the rules stated above for single bonds, double bonds, triple bonds, dipolar systems, dienes and tetraenes.

## IV. Topological Vectoplexes

In the discussion of junctive simplexes (Chapter 8), we made a distinction between fundamental simplexes and topological simplexes. Here, we note the distinction between molecular and

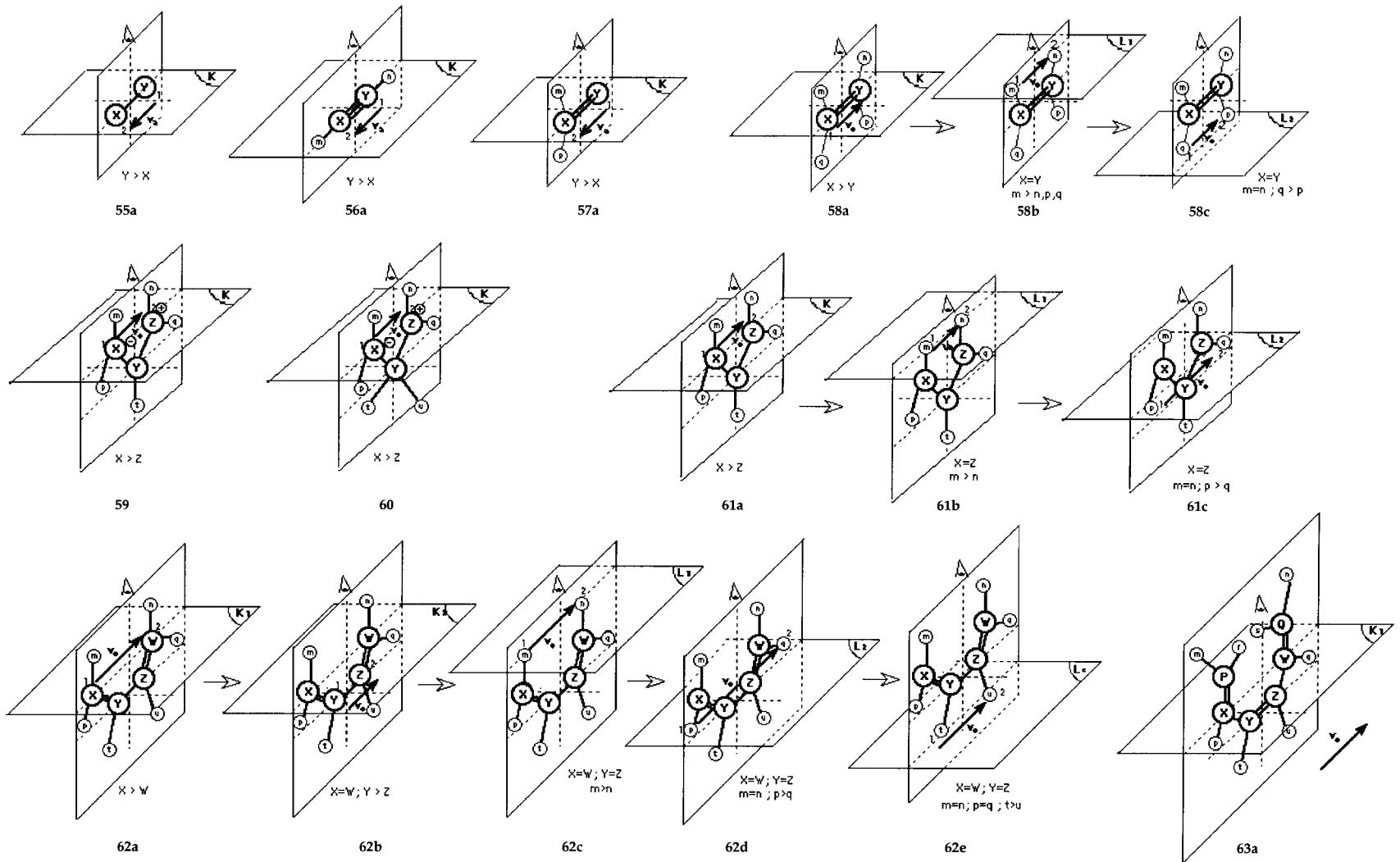
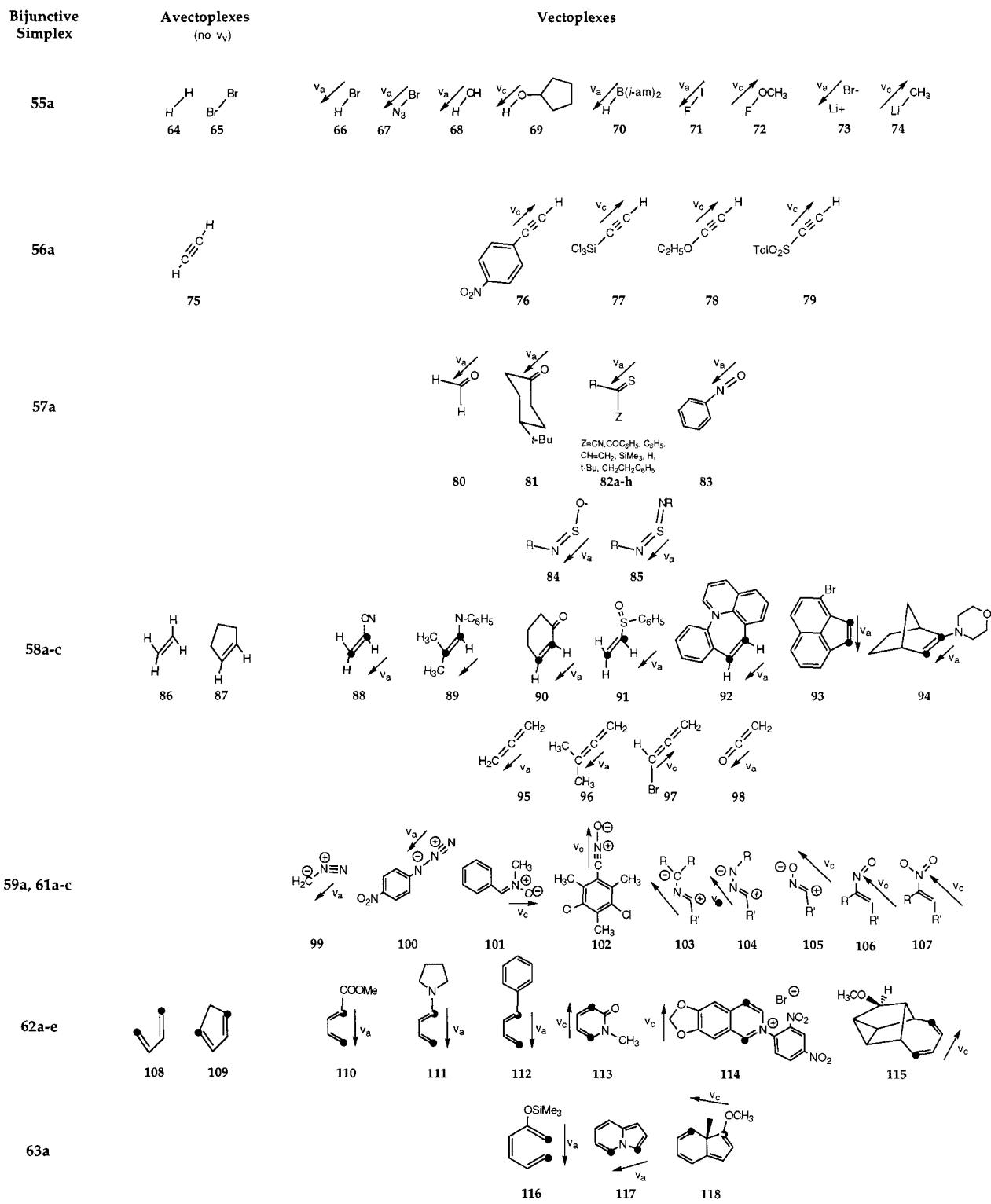
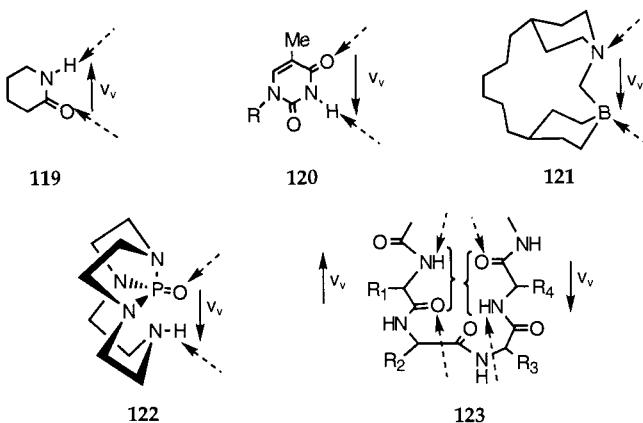


Figure 13.6. Vectorial Representations of Vectogenic Bijunctive Simplexes



**Figure 13.7.** Examples of Bijunctive Avectoplexes and Vectoplexes

topological vectoplexes. In effect, a bijunctive topological simplex is characterized by vectorial properties. A few examples are shown in Figure 13.8. In 119, 120, 122 and 123, vector  $v_v$  follows the Sequence Rule and goes from O to H. In bijunctive simplex 121,  $v_v$  is directed from N to B (N>B). In order to define these vectors  $v_v$ , we have arbitrarily picked the points of attachment/bonding (*vide infra*, for examples of junctivity).



**Figure 13.8.** Examples of Topological Bijunctive Vectoplexes

## V. Interactions of Junctive Vectoplexes/Avectoplexes

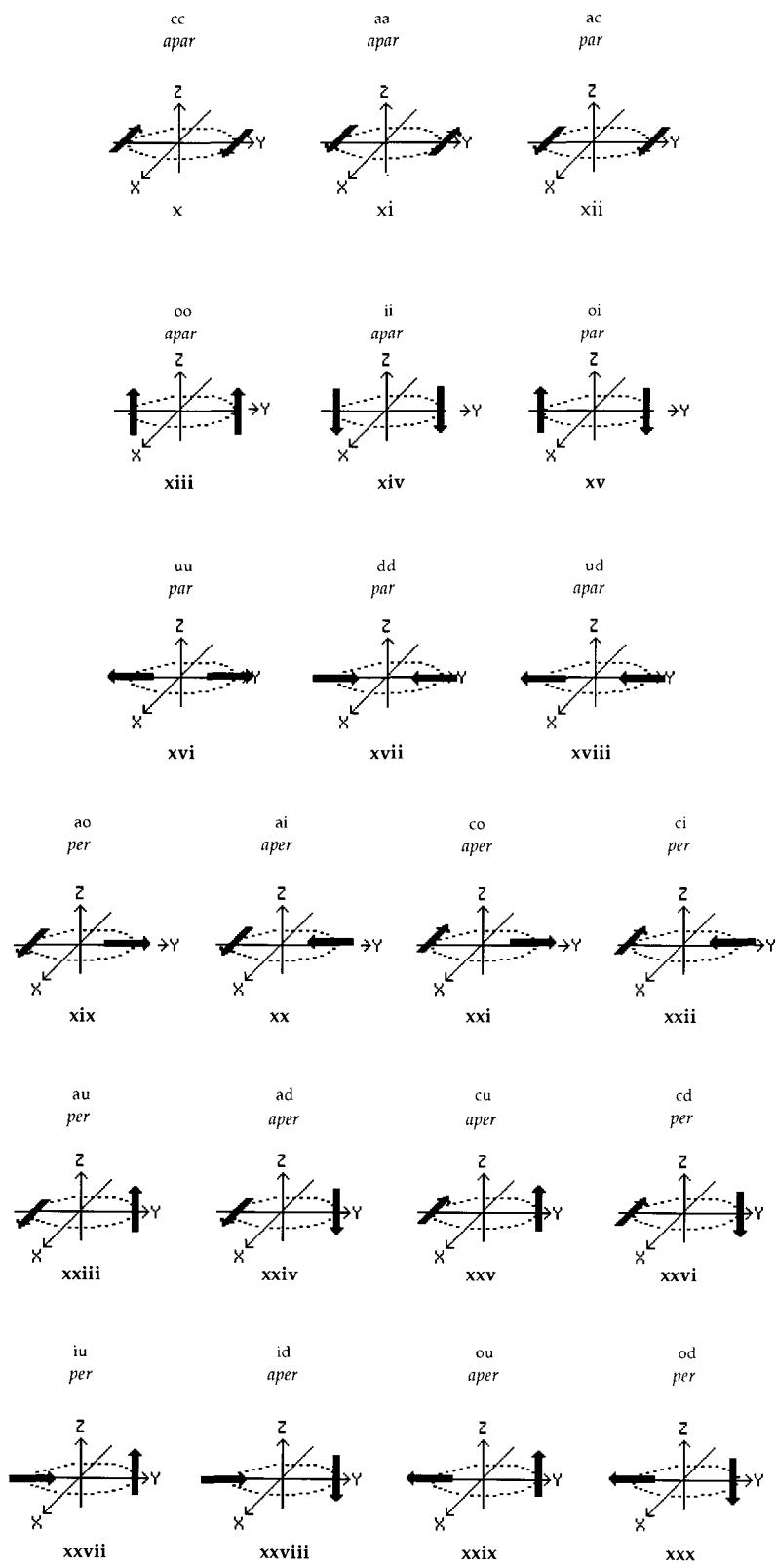
On the basis of the loop around which interacting moieties come together, we are now ready to describe the relative alignments of interacting vectoplexes and avectoplexes. A specific relative positioning of  $n$  vectoplexes (each with a characteristic  $v_v$ ) and  $m$  avectoplexes (with no characteristic  $v_v$  - represented by dashes) constitutes a *vectospecific alignment*. Geometric/vectorial reversal of at least one vector  $v_v$  in the set would transform such an alignment into a *reversovectospecific alignment* (clearly, no reversal is possible for avectoplexes). The original vectospecific and the newly generated reversovectospecific alignment may or may not be structurally identical (*vide infra*). A *vectospecific alignment* is characterized by a potential energy value  $E_s$ , and a *reversovectospecific alignment*, with characteristic potential energy  $E'_s$ ; they may ( $E_s = E'_s$ ) or may not be ( $E_s \neq E'_s$ ) equienergetic.

### A. Case of Two Junctive Elements

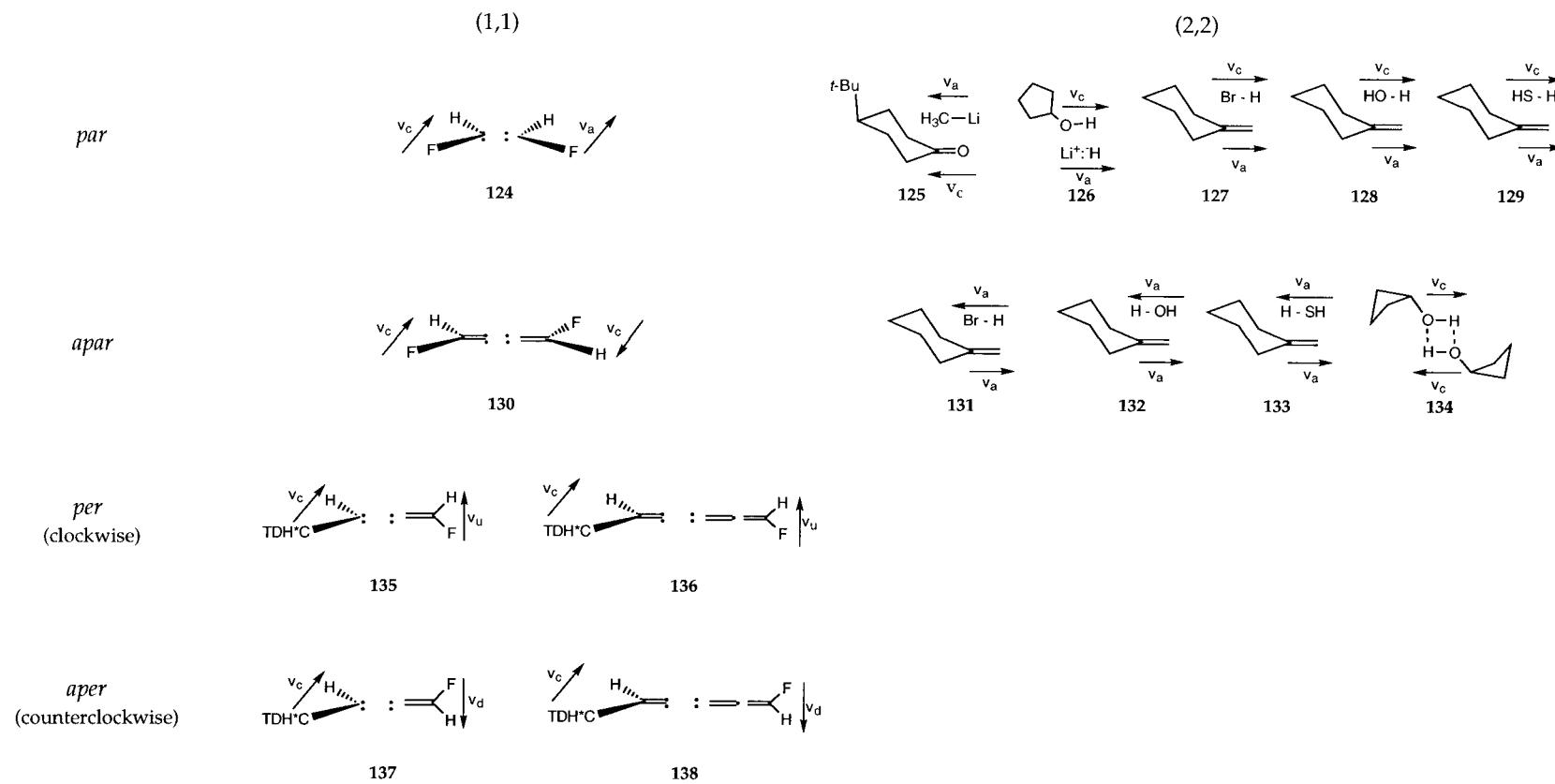
Figure 13.9 depicts the vectospecific and reversovectospecific cyclic alignments of two interacting vectoplexes. If one of the two junctive elements is avectogenic, then, a vectospecific and corresponding invertospecific alignments are degenerate and homomorphic.

The observer placed at the top of +Z axis, looking down at the loop in the XY-plane, discerns six types of vectors  $v_v$  (listed below along with their single-letter designations e.g. "a" for  $v_a$ , "u" for  $v_u$ , etc.):

- a : "anticlockwise" vector  $v_v = v_a$  (looked from the top of the +Z axis; tangent to the loop)
- c : "clockwise" vector  $v_v = v_c$  (looked from the top of the +Z axis; tangent to the loop)
- d : "down" vector  $v_v = v_d$  (pointing downwards, orthogonal to the loop)
- i : "in" vector  $v_v = v_i$  (pointing inwards, towards the center of the loop)
- o : "out" vector  $v_v = v_o$  (pointing outwards, away from the center of the loop)
- u : "up" vector  $v_v = v_u$  (pointing upwards, orthogonal to the loop)



**Figure 13.9.** Vectospecific Alignments of Two Bijunctive Vectoplexes



**Figure 13.10.** Examples of Interacting Bijunctive Vectoplexes

Examples of pairs of interacting vectors would be:

ac : "anticlockwise" vector  $v_a$  paired with "clockwise" vector  $v_c$   
oi : "in" vector  $v_i$  paired with "in" vector  $v_i$ , etc.

Each row in Figure 13.9 represents a set of three/four reversovectospecific alignments. All twenty one alignments (x-xxx) shown in Figure 13.9 actually reduce to four principal ones - *parallel (par)*, *antiparallel (apar)*, *perpendicular (per)*, and *antiperpendicular (aper)*:

*par* : ac, oi, uu, dd  
*apar* : cc, aa, oo, ii, ud  
*per* : ao, ci, au, cd, od, and iu  
*aper* : ai, co, ad, cu, ou.

These designations are independent of the nature of the ligogenic process; hence, the vectorial permutations shown apply equally well for (1,1)-, (1,2)-, and (2,2)- ligogenic processes. However, the two vectors here belong to a common plane (considered to be the reference plane). Molecular examples of the above-mentioned interacting bijunctive vectoplexes are shown in Figure 13.10.

The (1,1)-junctive coupling of fluorocarbenes (**124**) corresponds to a *par* alignment; so do the (2,2)-junctive addition of methylolithium to 4-*t*-butylcyclohexanone (**125**), neutralization of cyclopentanol with lithium hydride (**126**), the Markovnikov hydrobromination (**127**), hydration (**128**) and hydrosulfuration (**129**) of methylenecyclohexane. In contrast, the coupling of vinylidene fluorocarbenes shown (**130**) is *apar*; so are the peroxide-catalyzed hydrobromination (**132**), hydrosulfuration (**133**), and anti-Markovnikov hydration (by the hydroboration-oxidation sequence) of methylenecyclohexane (**132**). The dimerization of cyclobutanol follows an *apar* alignment. The coupling of the carbenes in **135** and **136** are shown in their *per* alignments; those of **137** and **138** are in *aper* alignments.

In Figure 13.11, we show the *apar* alignments of the topological simplexes in dimers **139**, **142**, **143**, the (2,2)-junctive association of adenine-thymine (**140**), and the peptide loop of **141**.

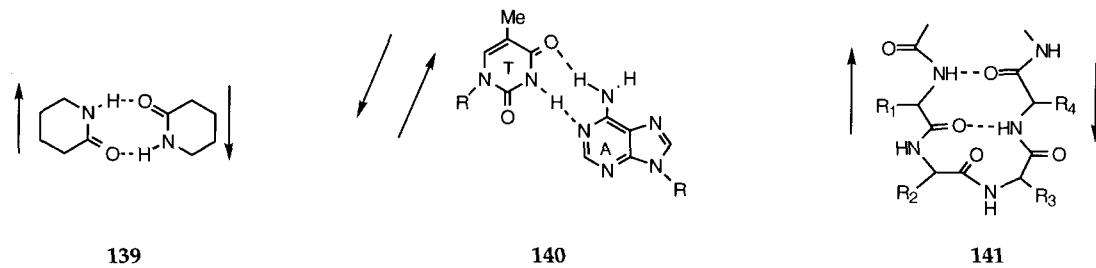
### B. Case of Three Junctive Elements

Processes involving three junctive elements are treated in a manner similar to those involving two junctive elements. This means we make reference to the junctive loop, and align the components around the loop. Vectogenic simplexes are again assigned vectors a,c,d,i,o,u (anticlockwise, clockwise, down, in, out, up, respectively). An avectogenic simplex, be it mono junctive or bijunctive, is denoted with a dash. Thus, in oo- or -ac, the third and first elements, respectively, are avectogenic.

There are two observers: the "+Z observer" (at the top of the +Z axis looking down onto the XY-plane) and the "-Z observer" (at the bottom of the -Z axis looking up towards the XY-plane). Each observer must pick the simplex of highest priority, proceed clockwise through the cycle of simplexes and come up with a designation for the process in conformity with the following priority sequences:

bijunctive > mono junctive  
vectogenic > nonvectogenic  
a > c > d > i > o > u

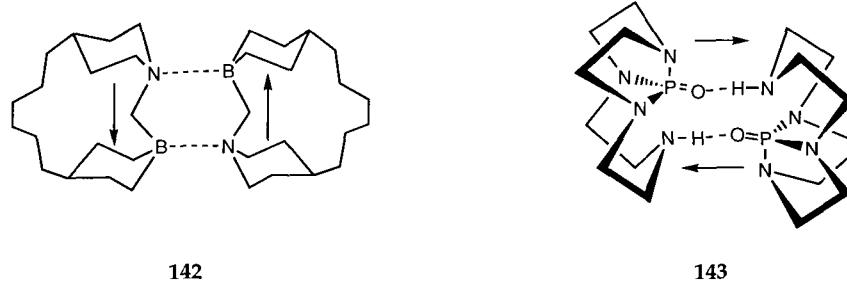
bijunctive (vectogenic a) > bijunctive (vectogenic c) > bijunctive (vectogenic d) > bijunctive (vectogenic i) >  
bijunctive (vectogenic o) > bijunctive (vectogenic u) >> bijunctive (nonvectogenic) >>  
mono junctive (vectogenic a) mono junctive (vectogenic c) > mono junctive (vectogenic d) >  
mono junctive (vectogenic i) > mono junctive (vectogenic o) > mono junctive (vectogenic u).



139

140

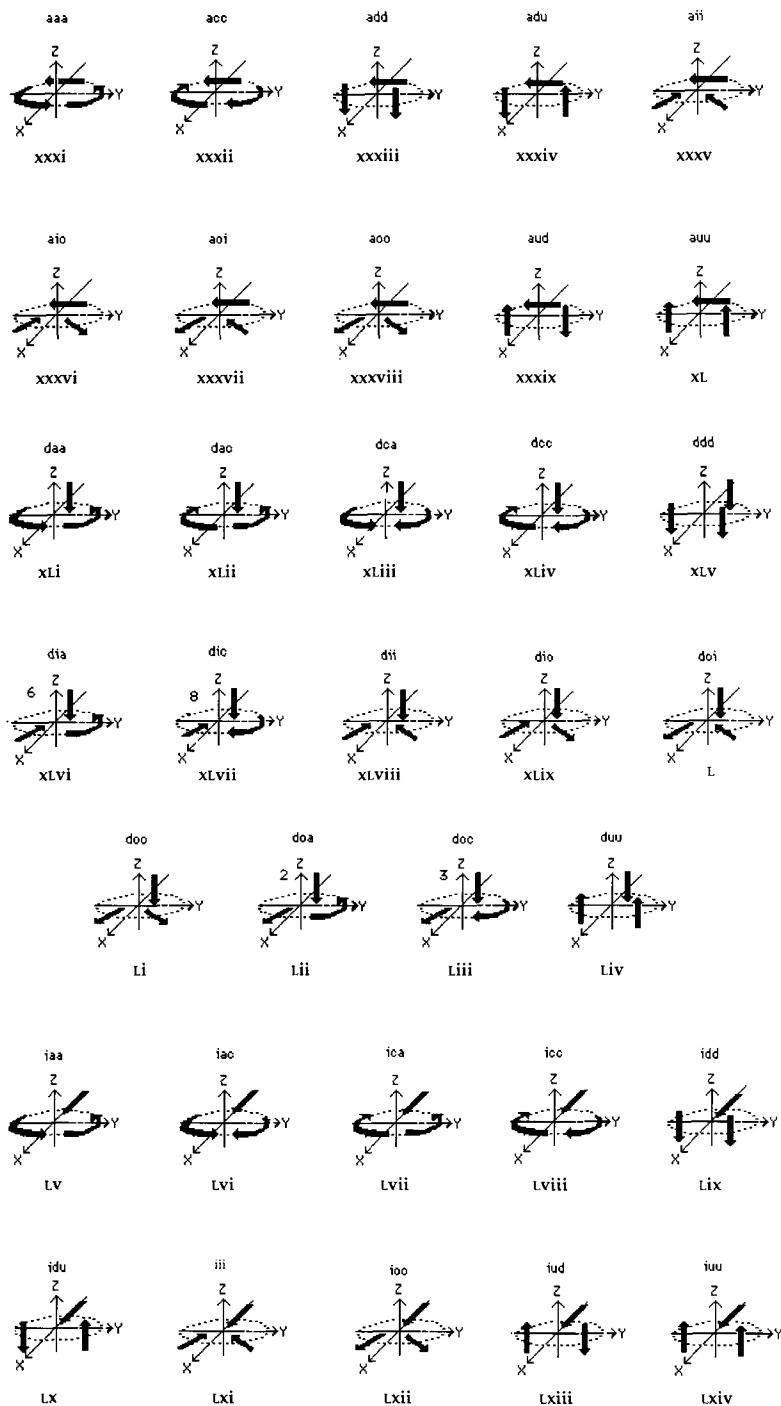
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142

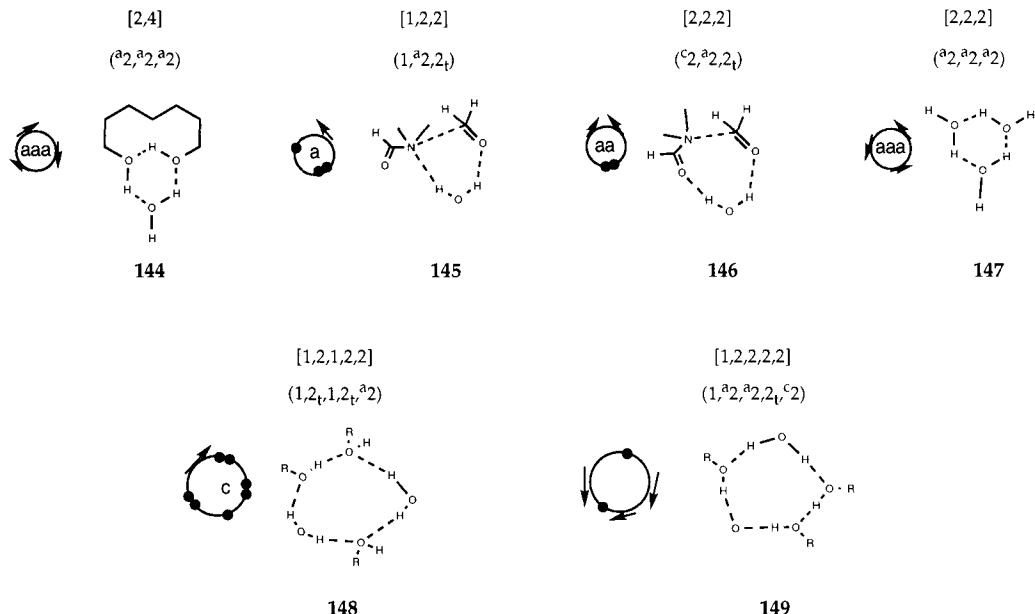
143

**Figure 13.11.** Examples of Interacting Topological *apar* (2,2)-Bijunctive Simplexes



**Figure 13.12.** Vectospecific Cyclic Alignments of Three Bijunctive Vectoplexes

In sum, (a) bijunctive precedes monojunctive, (b) vectogenic precedes nonvectogenic, and (c) the vectogenic ones follow the alphabetical order  $a > c > d > i > o > u$  (anticlockwise  $>$  clockwise  $>$  down  $>$  in  $>$  out  $>$  up). Of the two designations by the two observers, one opts for the alphabetically-preferred designation i.e.  $aac > cca$ ,  $acc > caa$ ,  $-ac > -ca$ ,  $duu > uud$ , etc. *irrespective* of the numerical designation of the junctive or ligogenic process. With these simple rules, the number of permutations reduces to  $3 \times 36 = 138$  (not counting those that involving avectogenic components). Figure 13.12 depicts 36 (**xxxi-Lxiv**) possible permutations of vectospecific cyclic alignments of three vectoplexes. Molecular examples involving cyclic alignments with two ore more molecular components are given in Figure 13.13 below.

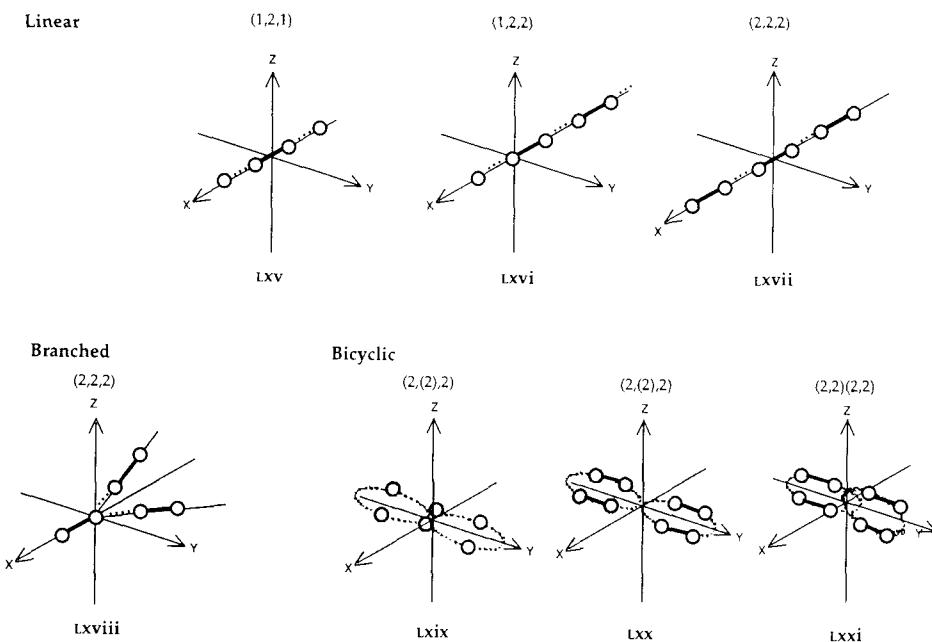


**Figure 13.13.** Examples of Multiple Interacting Vectoplexes

The hydrated diol **144** is an  $(^a2, ^a2, ^a2)$  system; the superscript  $a$  denotes the *anticlockwise* sense of the O-H bond, relative to the loop, for the observer who is looking down at the plane of the paper. The termolecular assembly **145** is a  $(1, ^a2, 2_t)$  entity with a nonvectogenic monojunctive element, an *anticlockwise* bijunctive element, and a nonvectogenic topological bijunctive element. Similarly,  $(^c2, ^a2, 2_t)$  for **146** represents a termolecular cyclic alignment of *clockwise* bijunctive element, an *anticlockwise* bijunctive element and a nonvectogenic topological bijunctive element. The trimer of water (**147**) is  $(^a2, ^a2, ^a2)$  with three *anticlockwise* bijunctive elements. Figure 13.13 also depicts two pentamolecular cyclic associative complexes **148** and **149** which are, respectively,  $(1, 2_t, 1, 2_t, ^a2)$  and  $(1, ^a2, ^a2, 2_t, ^c2)$ . The former system has one nonvectogenic monojunctive element, one nonvectogenic topological bijunctive element, another nonvectogenic bijunctive element, one more nonvectogenic monojunctive element, a nonvectogenic topological bijunctive element, and one *anticlockwise* bijunctive element. In contrast, **149** has a nonvectogenic monojunctive element, two *anticlockwise* bijunctive elements, one nonvectogenic topological bijunctive element, and a *clockwise* bijunctive element.

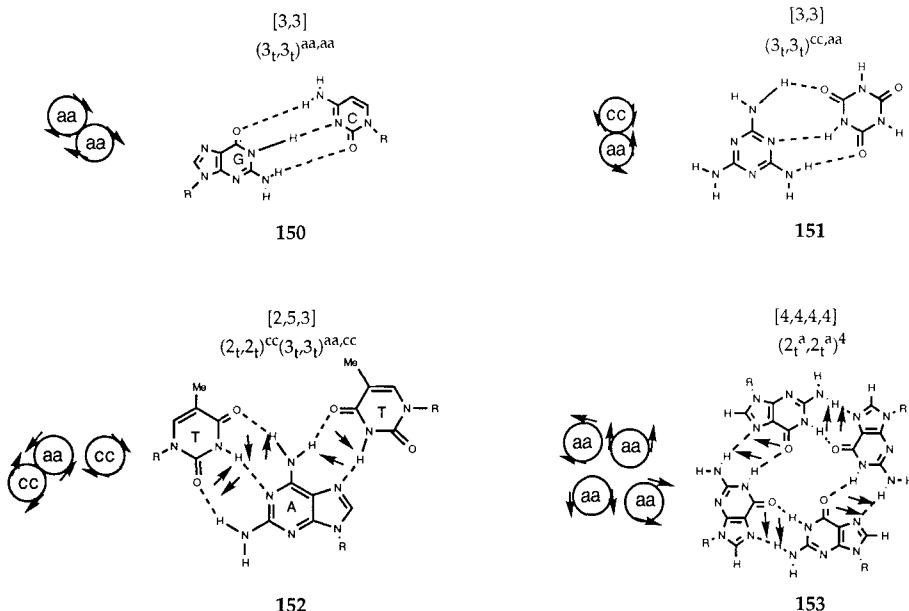
It should be pointed that, in addition to the topologically achiral cyclic (1,1)-, (1,2)-, (2,2)-, (1,1,2)-, (1,2,2)- and (2,2,2)-junctive processes discussed above, there are linear, branched, multiple-loop, and topologically chiral catenoidal associations, to mention a few. Figure 13.14 depicts the idealized representations of these associations.

### Three Junctive Simplexes



**Figure 13.14.** Examples of Multiple Complex Interacting Vectoplexes

Figure 13.15 shows a few typical molecular associations including two bicyclic ones, 150 and 151; a tricyclic case (152), and a tetracyclic case (153), all with denotations of their junctivities.



**Figure 13.15.** Examples of Multiple Interacting Vectoplexes

## VI. Modes of Vectoselectivity

### Vectoaselectivity, Vectononselectivity and Vectoselectivity

A molecular transformation involving two (or more) vectoplexes may proceed through competing parallel pathways each of which originates from a distinct vectospecific alignment. If two (or more) given distinct vectospecific arrangements (generated by vectorial reversal of a vectoplex) lead to structurally-distinct, and therefore nonisoenergetic transition states/intermediates/products, then there exist two (or more) competing *vectoselective* pathways. Selectivity resulting from the preference of one vectoselective pathway over another (or others) is termed *vectoselectivity*. The quantitative expression of vectoselectivity is given below. It should be stressed that the structural manifestation of vectoselectivity lies in the morphic relationship between the ensuing transition states, intermediates, and products. That is to say, these molecular states bear homomorphic, enantiomeric, diastereomeric, astereomeric, or nonequimorphic relationships; they should not be called "vectomers".

For a process involving the interaction of two or more vectoplexes/avectoplexes, three possible scenarios may arise: (1) vectospecific alignments are homomorphic (equienergetic) and the competing pathways are indistinguishable; in such a case, the process is said to be *avectoselective*; (2) vectorial reversal may lead to equienergetic but distinct (e.g. enantiomeric) alignments, in the total absence of chiral influence by the medium), in which case the process is *vectononselective*, and (3) vectorial reversal may lead to nonequienergetic (e.g. diastereomeric, astereomeric, or nonequimorphic) alignments in which case the process can be *vectoselective*. Examples of these three cases are portrayed in Figure 13.16.

Where zero (**154a/b**) or one vectoplex (**155a/b**) is involved, every point on one pathway has a homometric counterpart on the other; hence, the pathways are exactly superimposable and no selectivity is possible; these are cases of *vectoaselectivity*. On the other hand, for *per/aper* alignments such as those in **156a/b** and **157a/b**, every point on one pathway has an enantiometric counterpart on the other; in the absence of chiral influences, the pathways are isoenergetic, though obviously not superimposable, and while the resultant transition states/intermediates/products are enantiomeric, no vectoselectivity is expected - these are cases of *vectononselectivity*.

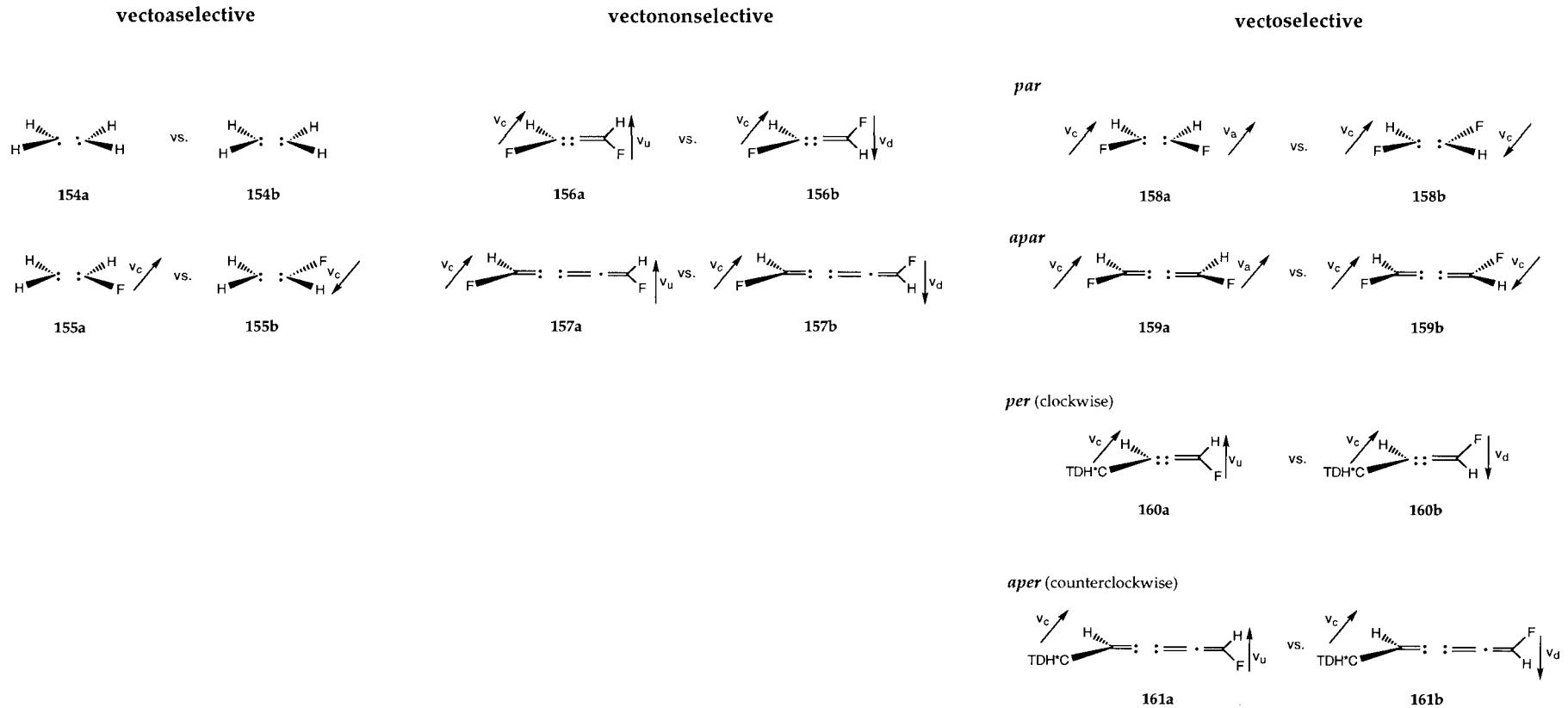
Finally, *par/apar* alignments of say **158a/b**, and **159a/b**, or *per/aper* alignments of **160a/b**, and **161a/b**, one finds corresponding diastereomeric counterparts on the two pathways. Barring accidental energetic equivalence, the pathways are distinct, and *vectoselectivity* is expected.

## VII. Vectoselectivity and Regioselectivity. Regioselectivity Revisited

In order to establish the relationship between vectoselectivity and regioselectivity, we consider the vectorial reversal of monojujective and bijunctive elements.

A vectorial alteration of an n-fold monojujective element, in ligogenic processes involving one or more monojujective element(s), *viz.* (1,1)-, (1,2)-, (1,1,1)-, (1,1,2)-, and (1,2,2)-ligogenic processes, may generally manifest itself as *vectostereoselectivity*, and not as *vectononstereoselectivity*; stereoconvergent processes are the exceptions. That is to say, selectivity resulting from the vectorial reversal of a *monojujective* simplex usually leads *only* to stereomeric transition states and/or products; the topology or connectivity is generally unaffected. For a two-coordinate monojujective element, there are two orientations, and therefore vectorial alteration is equivalent to vectorial reversal.

Vectorial reversal (accomplished by reversing any one of  $v_x$ ,  $v_y$ , or  $v_z$ ) in ligogenic processes involving either two bijunctive elements, *viz.* (2,2)-, (1,2,2)-, (2,2,2)-ligogenic processes, or, one



**Figure 13.16.** Examples of Vectoselective, Vectononselective and Vectoselective Processes

bijunctive and two monojunctive elements, *viz.* (1,1,2)-ligogenic processes, may manifest itself either as *vectostereoselectivity* (=stereoregioselectivity) or *vectorononstereoselectivity* (=regioselectivity). That is to say, selectivity resulting from the vectorial reversal of a vectogenic *bijunctive* element can lead to *either* nonstereomeric *or* stereomeric transition states/products. These molecular states bear homomorphic, enantiomorphic, diastereomeric, astereomeric, or nonequimorphic relationships; they should not be called "regiomers". Furthermore, their connectivities or constitutions may or may not be affected depending on the constitutions of the components. The ensuing vectorononstereoselectivity may be the result of *vectoastereoselectivity* or *vectoronequiselectivity*. For example, the (1,1)-process **162a+162b→163+164** which involves vectorial reversal of reactants, is expectedly vectostereoselective (here, vectodiastereoselective). The (1,2)-process **165+166→167+168** in which there occurs vectorial reversal of **165**, is also vectostereoselective (here, vectoenantioselective). In contradistinction, (2,2)-junctive processes are vectostereoselective - **169+170→171+172**, or vectorononstereoselective - **173+174→175+176** (here, vectoastereoselective) and **177+178→179+180** (here, vectoronequiselective). It should be noted that both vectostereoselectivity, and vectorononstereoselectivity may degenerate into vectorononstereoaselectivity or vectorononstereononselectivity

*We conclude that vectoselectivity is a universal concept that encompasses regioselectivity. Vectoselectivity is applicable to not just two-, but also to three- and more interacting junctive elements, such as those required in conjunctive states - be it transition states or products.*

### VIII. Vectoselectivity/Regioselectivity vs. Situselectivity

To emphasize the importance of distinguishing between vectoselectivity/regioselectivity and situselectivity, we consider examples (Figure 13.18, p. 128), in each of which we illustrate the need for both terms - situselectivity *and* regioselectivity.

The ring opening of **181** with conc. HCl<sup>147</sup> is situselective at bond "a" (as opposed to bonds "b" or "c"); in addition the opening is regioselective, since the H-Cl vector aligns *par* relative to bond "a" as in [182]. In contrast, the HCl-mediated opening of **184**<sup>148</sup> cleaves bond "b" (as opposed to bonds "a" or "c"). Clearly, the situselectivity (not regioselectivity!) has changed from bond "a" in **181** to bond "b" in **184**, but the regioselectivity has remained unchanged; it is *par* in both ring openings. The phenylselenide openings of **187**<sup>149</sup> and **190**<sup>150</sup> also show different situselectivities (cyclopropyl bond "b" in **187** vs. bond "d" in **190**), but similar regioselectivities - *apar* in both [188] and [191]. The net addition of the elements of hydrogen iodide to **193**<sup>151</sup> is regioselective with an *apar* alignment of iodo(trimethyl)silane relative to the alkene ([194]); the addition is concomitantly situselective – the reaction is at the alkenic bond as opposed to, say, the carbonyl group. Based on the perception that only the alkenic bond (as opposed to other bonds e.g. "b", "c", "d" or other bond) of **193** would react with iodo(trimethyl)silane, the situselectivity is taken for granted; nevertheless this is a situselective reaction since iodo(trimethyl)silane can potentially react with single C-C bonds (albeit in strained systems). Thus, hydroiodination of **196** is situselective at bond "a" (as opposed to bond "b") and regioselective in the *apar* sense ([197]). The situselectivities in the ring-openings of oxetane **199**<sup>152</sup> (=202<sup>153</sup>) with trimethylsilyl cyanide are remarkable. It is bond "b" that is severed normally; however, in the presence of diethylaluminum chloride it is bond "a" that cleaves. Despite the different situselectivities, the regioselectivities remain *par*. In the ruthenium-catalyzed coupling of allyltrimethylsilane with 2-methylacetophenone (**205**),<sup>154</sup> one observes that the addition of C-H bond "a" (as opposed to bonds "b", "c", or "d") to the double bond of the silane is situselective; the addition is also regioselective (*apar*). Finally, the [2+2] addition of 1,1-dimethylallene (**208**) with 1,1-dichloro-2,2-difluoroethane<sup>155</sup> is situselective since it is bond "a" (and not "b") that is involved in the reaction. The reaction is simultaneously regioselective, since it is the *apar* alignment [209] of the two reactants that leads to product **210**.

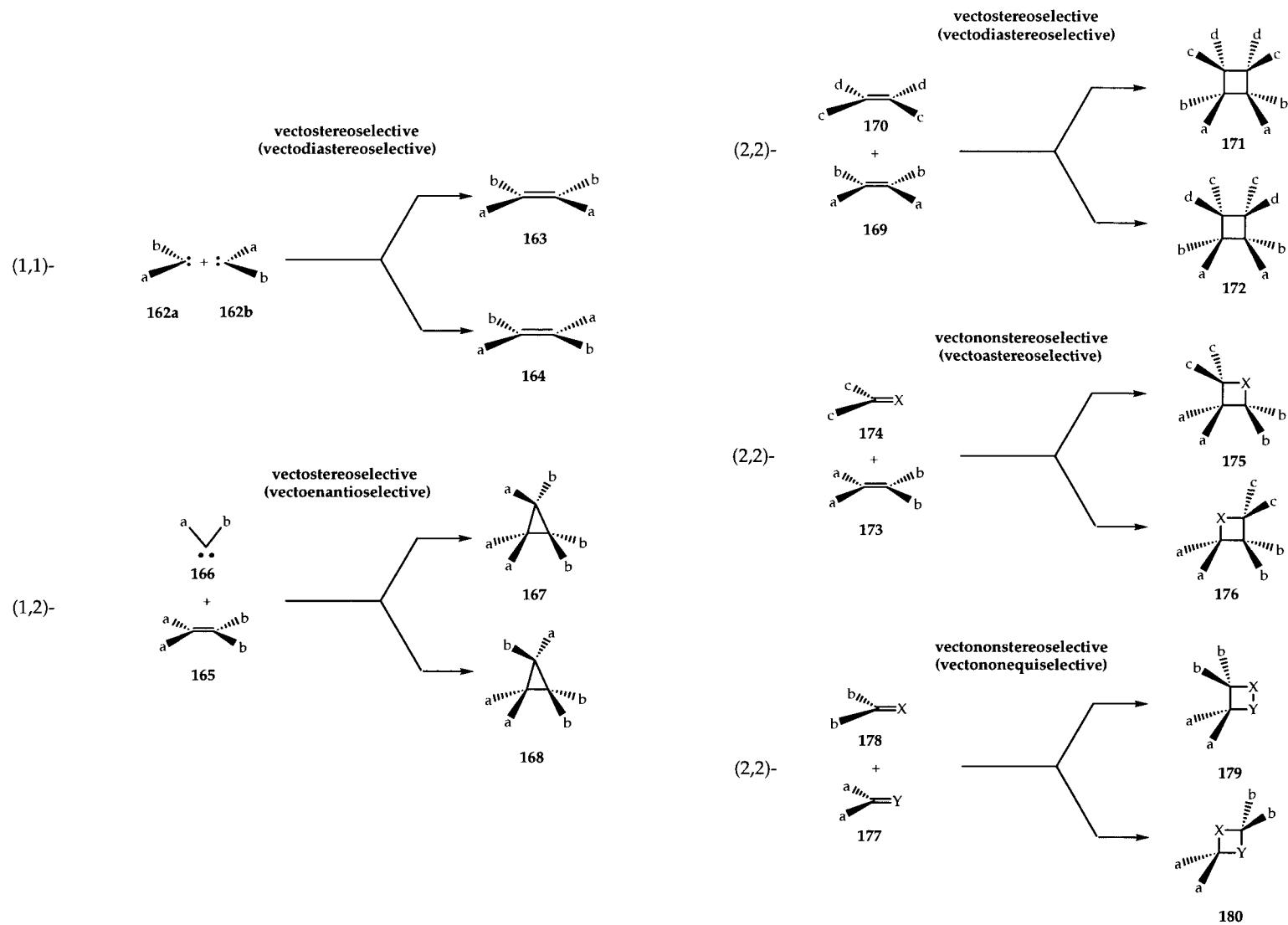


Figure 13.17. Examples of Vectostereoselective vs. Vectononstereoselective Processes

## IX. Classification and Specification of Vectoselectivity

Vectoselectivity is classified into *vectostereoselectivity* and *vectorononstereoselectivity*. Each of these selectivities may reduce into aselective or nonselective variants. Further, vectostereoselectivity is subclassified, in principle, into "*vectoenantioselectivity*" (*vide infra*) and *vectodiastereoselectivity*, while vectorononstereoselectivity is subclassified into *vectoastereoselectivity* and *vectoronequiselectivity*. Figure 13.19 depicts the overall classification of vectoselectivity.

### A. Case of Two Junctive Elements

For a vectoselective process leading to two structurally- distinct products  $P_1$  and  $P_2$ , vectoselectivity is defined by Equation 13.1:

$$\% \text{ vectoselectivity} = \% \Delta_{1/2} = | \% P_1 - \% P_2 |. \quad (13.1)$$

Vectoselectivity may be classified into vectostereoselectivity or vectorononstereoselectivity depending on whether the ensuing transition states/intermediates/products are stereomeric or nonstereomeric, respectively:

$$\% \text{ vectoselectivity} = \% \text{ vectostereoselectivity} = | \% P_S - \% P_{S'} | \quad (13.2)$$

$$\% \text{ vectoselectivity} = \% \text{ vectorononstereoselectivity} = | \% P_S - \% P_{S'} |. \quad (13.3)$$

In the case of vectostereoselectivity, if  $S,S' = E,I$  , (*vide infra*) then

$$\% \text{ vectostereoselectivity} = \% \text{ vectoenantioselectivity} = | \% P_E - \% P_I |, \quad (13.2a)$$

and if  $S,S' = D,F$ , then

$$\% \text{ vectostereoselectivity} = \% \text{ vectodiastereoselectivity} = | \% P_D - \% P_F |. \quad (13.2b)$$

In the case of vectorononstereoselectivity if  $S,S' = A,C$

$$\% \text{ vectoselectivity} = \% \text{ vectoastereoselectivity} = | \% P_A - \% P_C | \quad (13.3a)$$

and if  $S,S' = A,X$ , then

$$\% \text{ vectoselectivity} = \% \text{ vectoronequiselectivity} = | \% P_A - \% P_X |. \quad (13.3b)$$

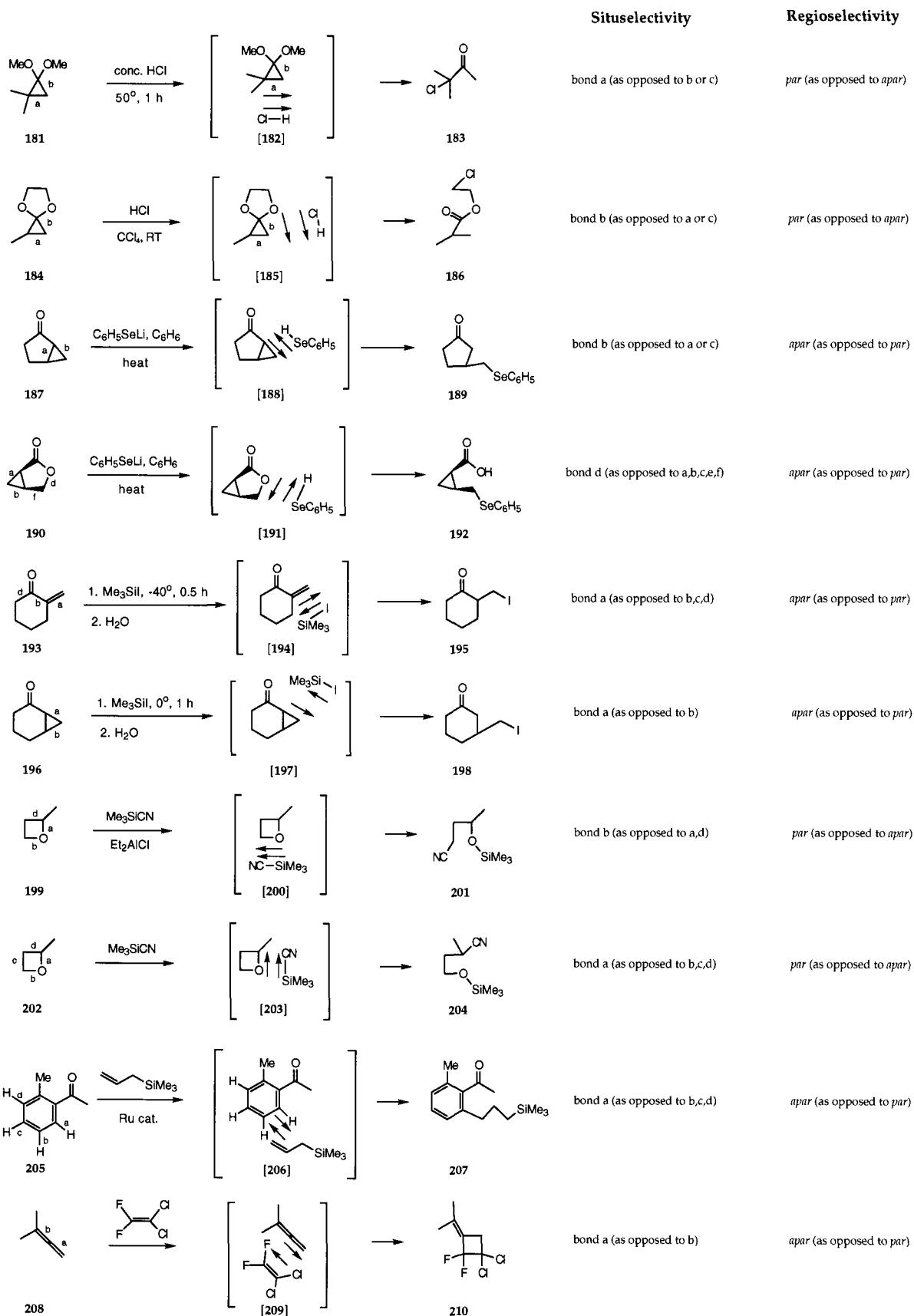
### B. Case of Three Junctive Elements

In order for vectoselectivity to be possible for three-component systems, at least two of the three elements must be vectogenic (*vide infra*).

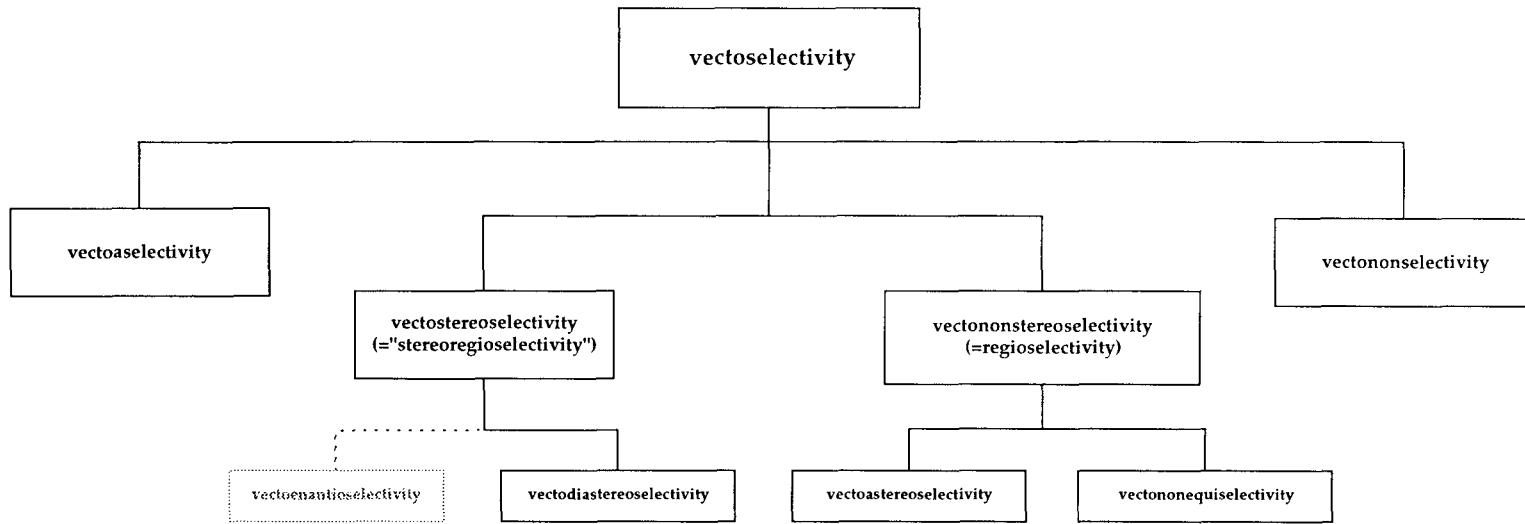
In a vectoselective process leading to  $n$  products  $P_1, P_2, P_3, \dots, P_N$ , through  $n$  competing vectoselective pathways, vectoselectivity may be defined for a specific pair of products, say  $P_{N-1}$  and  $P_N$ :

$$\% \text{ vectoselectivity} = \Delta_{N-1/N} = | \% P_{N-1} - \% P_N | \quad (13.4)$$

$$\% \text{ vectoselectivity} = \% \text{ vectostereoselectivity} = | \% P_{N-1} - \% P_N | = | \% P_S - \% P_{S'} | \quad (13.5a)$$



**Figure 13.18.** Examples of Situselective and Regioselective Reactions



**Figure 13.19.** Classification of Vectoselectivity

% vectoselectivity = % vectostereoselectivity = "% vectoenantioselectivity"

$$= | \%P_{N-1} - \%P_N | = | \%P_E - \%P_H | \quad (13.5b)$$

% vectoselectivity = % vectostereoselectivity = % vectodiastereoselectivity

$$= | \%P_{N-1} - \%P_N | = | \%P_D - \%P_F | \quad (13.5c)$$

% vectoselectivity = % vectononstereoselectivity = % vectoastereoselectivity

$$= | \%P_{N-1} - \%P_N | = | \%P_A - \%P_C | \quad (13.5d)$$

% vectoselectivity = % vectononstereoselectivity = % vectononequiselectivity

$$= | \%P_{N-1} - \%P_N | = | \%P_A - \%P_X | \quad (13.5e)$$

The usefulness of these equations lies in the ability to focus on a given pair of products and thus define the appropriate vectoselectivity arising from a *single* vectorial reversal. In Addendum A (Vol. 1, p. 143), we have discussed the quantitative treatment of 2-, 3-, and 4-component systems, and detailed how these individual pairwise differences can be used to described a given 3-, or 4-component system.

## X. Conjunctive States in Vectoselective Processes

The reaction at a paired set of molecular faces, in principle, may proceed through four pathways that lead to a quartet of conjunctive states  $m_1, m_1', m_2, m_2'$ . This was shown in the discussion on facioselectivity (Chapter 12).

The 45 quartets generated from the analysis of a wide variety of (1,2)-atom-face, (2,2)-bond-face (2,2)-face-face ligogenic reactions (Figure 12.5, p. 86), are regrouped in Figure 13.20 below on the basis of vectoaselectivity, vectononselectivity and vectoselectivity. This figure also shows the breakdown of vectoselectivity in terms of vectostereoselectivity (vectoenantioselectivity, vectodiastereoselectivity) and vectononstereoselectivity (vectoastereoselectivity, vectononequiselectivity).

For a given case, vectoselectivity is given by Equation 13.6:

$$\% \text{ vectoselectivity} = |(m_1 + m_1') - (m_2 + m_2')| \times 100 \quad (13.6)$$

Vectoselectivity may also be given as a ratio (see Volume 1, Addendum B, p. 149):

$$\% \text{ vectoselectivity} = |(m_1 + m_1') / (m_2 + m_2')| \times 100 \quad (13.7)$$

Quartets **q1,q2,q5,q22,q23,q30** typify avectoselective processes. Operationally, in an avectoselective transformation, the conjunctive state(s) obtained from a given orientational mode at a molecular face is(are) exactly identical (in structure and relative amounts) with that (those)

obtained from the corresponding reversoorientational mode. A *nonvectoselective* reaction is one in which (a) every orientational mode involved in the reaction at a face has an *isoenergetic* reversoorientational - reversovectospecific mode at that same face (the corresponding transition state pairs are either homomorphic or enantiomeric) and (b) at least one isoenergetic pair consists of *enantiomeric* transition states (the others being homomorphic). Quartets q3, q4 and q25 represent nonvectoselective transformations. In real terms, the conjunctive state(s) from a given mode will be formed in amounts identical with those from the reverse mode; if one of the conjunctive states (or the only state) from a given orientation is chiral, then an equivalent amount of the enantiomeric counterpart will result from the orientation, with one component reversed relative to the other. A reaction is said to be *vectoselective* if, with a given reagent, a vectospecific mode involves at least one conjunctive state that has *no* isoenergetic counterpart in the inversovectospecific mode; that is, there is at least one pair of corresponding stereomeric, astereomeric or nonequimorphic conjunctive states. Thus q6-q12,q24,q26-q29 are vectostereoselective, q13,q15,q17,q19,q20,q31,q33,q35,q37,q39,q41,q42,q44 are vectoastereoselective, and q14,q16,q18, q21,q32,q34,q36,q38,q40,q43,q45 are vectononequiselective.

The quantitative expressions for vectoselectivity for the five subclasses are as follows:

Vectoselectivity	Quartets Involved	% Vectoselectivity
vectoaselectivity	q1,q2,q5,q22,q23,q30	none possible ( $m_1 = m_2 = m_{1'} = m_{2'}$ )
vectoroneselectivity	q3,q4,q25	$ m_1 + m_2 - (m_{1'} + m_{2'})  = 0$
vectostereoselectivity	q6-q12,q24,q26-q29	$ m_1 + m_2 - (m_{1'} + m_{2'})  \neq 0$
vectoastereoselectivity	q13,q15,q17,q19,q20,q31, q33,q35,q37,q39,q41,q42,q44	$ m_1 + m_2 - (m_{1'} + m_{2'})  \neq 0$
vectoronequiselectivity	q14,q16,q18,q21,q32,q34,q36, q38,q40,q43,q45	$ m_1 + m_2 - (m_{1'} + m_{2'})  \neq 0$

## XI. Vectoselectivity at Stereotopic Molecular Faces

We now examine, in detail, aspects of vectoselectivity at the eleven fundamental stereotopic molecular faces.

### A. Homotopic Faces h1-h6

- Reactions of h1 and h4 are always avectoselective (q1,q2), with achiral or chiral reagents .
- Reactions of h2 and h5 with achiral or chiral reagents are avectoselective (q1,q2), vectostereoselective (q6,q7,q8,q9), vectoastereoselective (q13,q20) or vectononequiselective (q14,q16,21); h2, unlike h5, can display nonvectoselectivity (q3,q4), albeit with achiral reagents.
- Reactions of h3 and h6 with achiral and chiral reagents are avectoselective (q1,q2) or vectostereoselective (q6,q7,q8,q9); h3, unlike h6, can also be nonvectoselective (q3,q4) - with achiral reagents.

In sum, (a) all homotopic faces h1-h6 can be avectoselective (achiral and chiral reagents); (b) only h2,h3 can be nonvectoselective (achiral reagents); (c) only h2,h3,h5,h6 can be vectostereoselective (achiral and chiral reagents); (d) only h2 and h5 can be vectoastereoselective as well as vectoronequiselective (achiral and chiral reagents). It should be noted that a

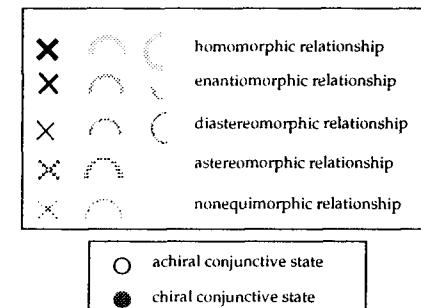
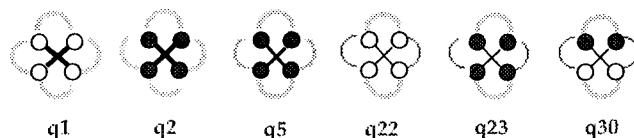
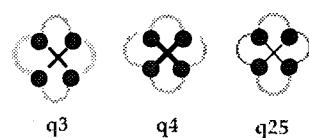
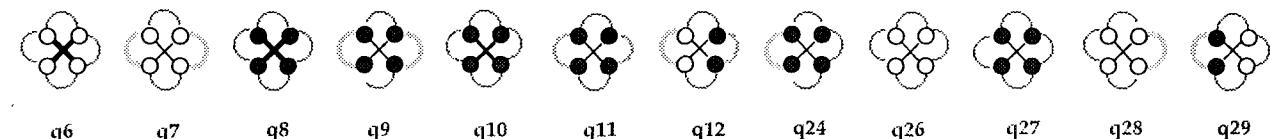
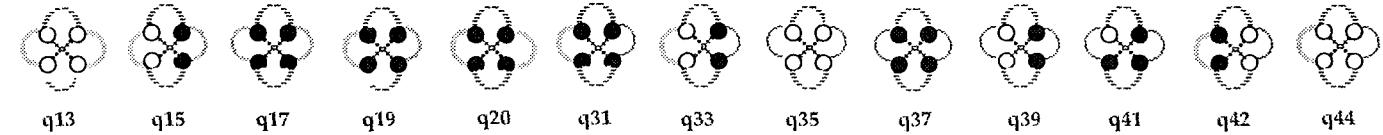
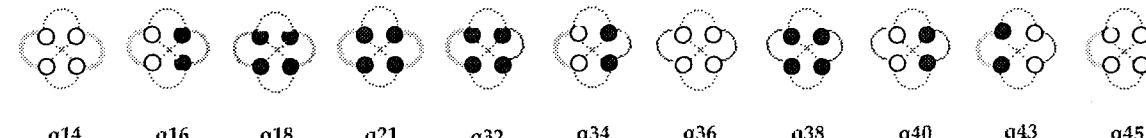
**Vectoaselective****Vectoronselective****Vectoselective****Vectostereoselective****Vectoronstereoselective****Vectoastereoselective****Vectoronequiselective**

Figure 13.20. Quartets q1-q45 and Vectoselectivity in Conjunctive States

vectostereoselective conjunctive transformation is necessarily vectodiastereoselective, since “vectoenantioselectivity” is tantamount to (vectostereo)nonselectivity.

### B. Enantiotopic Faces e

Reactions at enantiotopic faces are vectoaselective with achiral (q1,q5) or chiral reagents (q23). They are vectostereoselective (q10,q11,q12,q24,q27), vectoastereoselective (q15,q19,q37,q41) or vectononequiselective (q16,q18,q38) - with achiral or chiral reagents.

### C. Diastereotopic Faces d1-d4

Reactions at diastereotopic faces lead to the following generalizations:

1. Reactions at face d1 are always vectoaselective (q22,q23), with achiral or chiral reagents.
2. Reactions at face d2 can be vectoaselective (q1,q2,q22,q23), vectostereoselective (q24,q26-q28), vectoastereoselective (q31,q35,q37,q39,q42,q44), or vectononequiselective (q32,q36,q38,q40,q43,q45) with any reagent. They can also be vectononselective (q3,q25), with achiral reagents.
3. Reactions at face d3 can be vectoaselective (q1,q22,q23) (achiral or chiral reagents) or vectostereoselective (q9,q24,q26-q28) with achiral or chiral reagents. They can also be vectononselective (q25), with achiral reagents.
4. Reactions at face d4 can be avectoselective (q2,q22,q23), vectostereoselective (q24,q27,q29), vectoastereoselective (q17,q20,31,q35,q37,q39,q42,q44) and vectononequiselective (q21,q32,q45) with any reagent - achiral or chiral.

In effect, (a) d1-d4 can all be avectoselective (with achiral or chiral reagents); (b) only d2 and d3 can be nonvectoselective (achiral reagents); (c) only d2-d4 can be vectostereoselective (achiral and chiral reagents), and (d) only d2 and d4 can be vectoastereoselective or vectononequiselective (achiral and chiral reagents).

Table 13.1 (p. 134) summarizes the five modes of vectoselectivity at all homotopic (h1-h6), enantiotopic (e), and diastereotopic (d1-d4) faces. In Figures 13.22-13.24 are shown examples of vectoaselective, vectononselective and vectoselective transformations of molecules with homotopic, enantiotopic and diastereotopic faces, respectively.

The terms “regiomers” and “vectomers” are not useful and should be abandoned, since two given “regiomers”/“vectomers” can be homomers, enantiomers, diastereomers, astereomers, or nonequimers.

It is to be noted that prefixes *enantio-* and *diastereo-* in *enantiofacioselectivity* and *diastereofaciocoselectivity* refer to the type of molecular face in the *reactant* substrate. In the case of vectoselectivity, the term *stereovectoselectivity* is always a case of *diastereovectoselectivity*, and the latter term refers to the conjunctive *product* state (transition state or actual product).

## XII. Facioselectivity and Vectoselectivity - Reaction Paths - Quartets

The joint consideration of stereofaciocoselectivity and vectoselectivity for the 11 types of stereofaces (paired faces) leads to 12 facioselectivity-vectoselectivity modes - Aa, An, Na, Nn,

Quartet Mode	Vectoselectivity	Quartets	h1		h2		h3		h4		h5		h6		e		d1		d2		d3		d4	
			ac	c																				
a	Vectoaselectivity	q1,q2,q5,q22,q23,q30	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
n	Vectoroneselectivity	q3,q4,q25			+		+													+		+		
s	Vectostereoselectivity	q6-q12,q24,q26-q29			+	+	+	+			+	+	+	+	+	+			+	+	+	+	+	+
as	Vectoastereoselectivity	q13,q15,q17,q19,q20,q31, q33,q35,q37,q39,q41,q42, q44			+	+					+	+			+	+			+	+			+	+
ne	Vectoronequiselectivity	q14,q16,q18,q21,q32,q34. q36,q38,q40,q43,q45			+	+					+	+			+	+			+	+			+	+

 ac : achiral reagent  
 c : chiral reagent

**Table 13.1.** The Five Modes of Vectoselectivity in Conjunctive Processes

Ns, Nas, Nne, Sa, Sn, Ss, Sas, and Sne. These 12 composite modes are tabulated in Table 13.2 (p. 139).

In the said designations, the first letter - in upper case - indicates facioselectivity:

A	:	stereofacioAselectivity
N	:	stereofacioNonselectivity
S	:	stereofacioSelectivity.

The second letter (in lower case) refers to vectoselectivity:

a	:	vecto <del>a</del> selectivity
n	:	vectoron <del>n</del> selectivity
s	:	vectostereoselectivity
a	s:	vecto <del>a</del> stereoselectivity
n	e:	vectoronequiselectivity.

Quartets q1-q3 are stereofacioselective; q1 and q2 are vectoaselective, whereas quartet q3 is vectoronnonselective.

Quartets q4-q21 are stereofaciononselective. In this group of quartets, q5 is vectoaselective, q4 is vectoronnonselective, q6-q12 are vectostereoselective, q13,q15,q17,q19,q20 are vectoastereoselective, and q14,q16,q18 and q21 are vectorononequiselective.

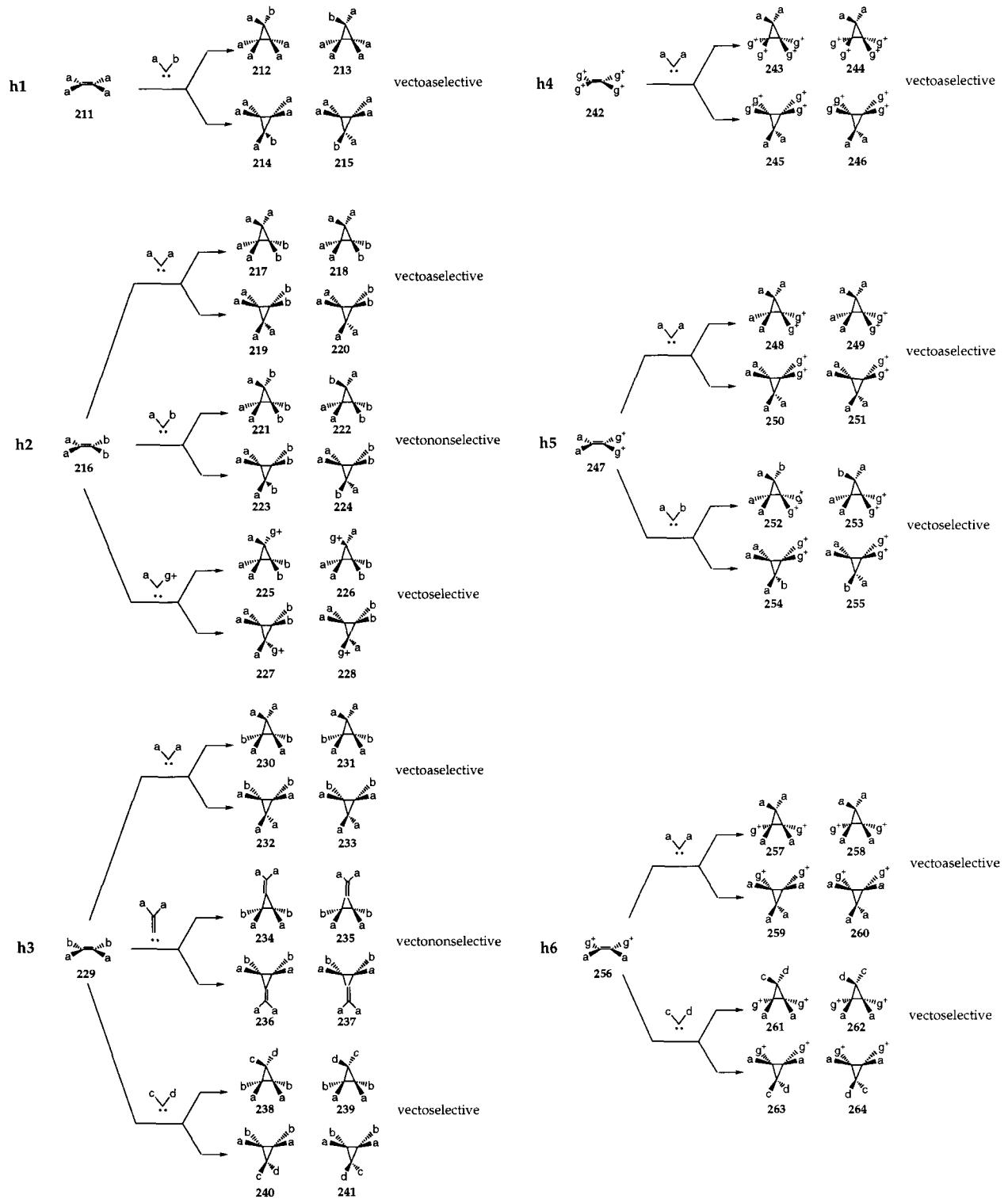
All the remaining quartets - q22,q23,q25,q30-q45 are faciostereoselective. In this set of quartets, q22,q23,q30 are vectoaselective, q25 is vectoronnonselective, q31,q33,q35,q37,q39,q41,q42,q44 are vectoastereoselective, whereas q32,q34,q36,q38,q40,q43, and q45 are vectorononequiselective.

A systematic examination of the eleven types of paired stereotopic faces, in relation to the twelve composite modes above, enables one to derive the correlations shown in Table 13.3 (p. 140). In comparison with the correlations noted for facioselectivity (Table 12.3, p. 92) and vectoselectivity (Table 13.1, p. 134), the new correlations, using the joint criteria of facioselectivity/vectoselectivity, reveal the distinct characteristics of each of the molecular face types. The results for h1 and h4 are, not unexpectedly, identical, owing to the similarities in their symmetries. It should be noted that when vectoselectivity comes into play, enantiofacioselectivity may manifest itself in the formation of all of the product mixtures shown below:

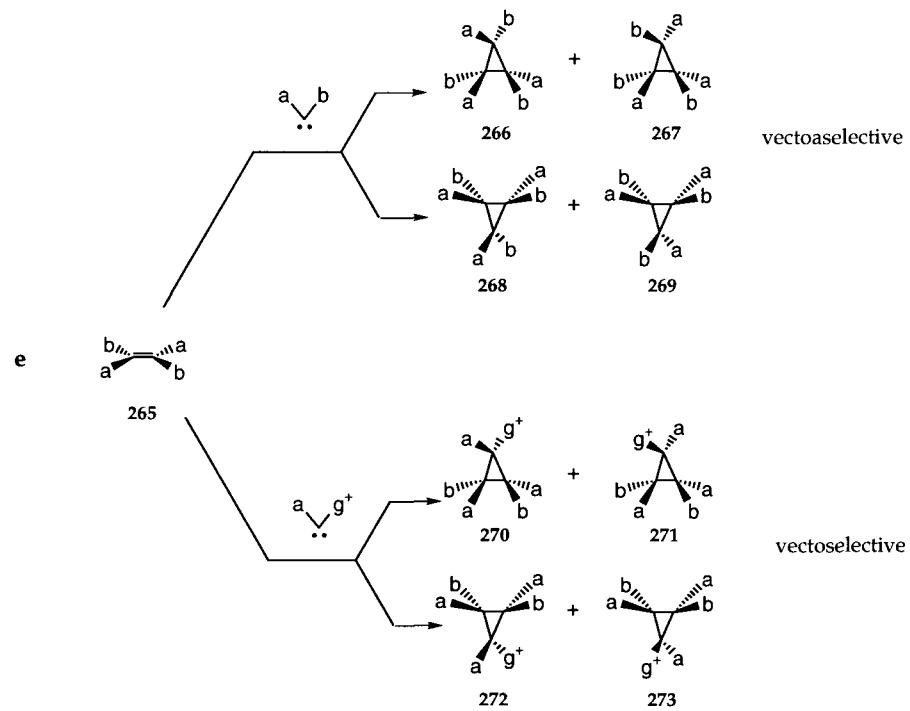
q23	D*,F*	2 chiral diastereomers
q24	D*,F*,G*	3 chiral diastereomers
q27	D*,F*,G*,J*	4 chiral diastereomers
q37	D*,F*,M*,N*	2 astereomeric chiral diastereomeric pairs
q38	D*,F*,X*,Y*	2 nonequimERIC chiral diastereomeric pairs
q41	D*,F*,M*,N	2 astereomERIC diastereomeric pairs (1 pair chiral, 1 pair mixed achiral/chiral)

Similarly, diastereofacioselectivity of a substrate in a reaction, where there is a definite role for vectoselectivity, one obtains the following product mixtures:

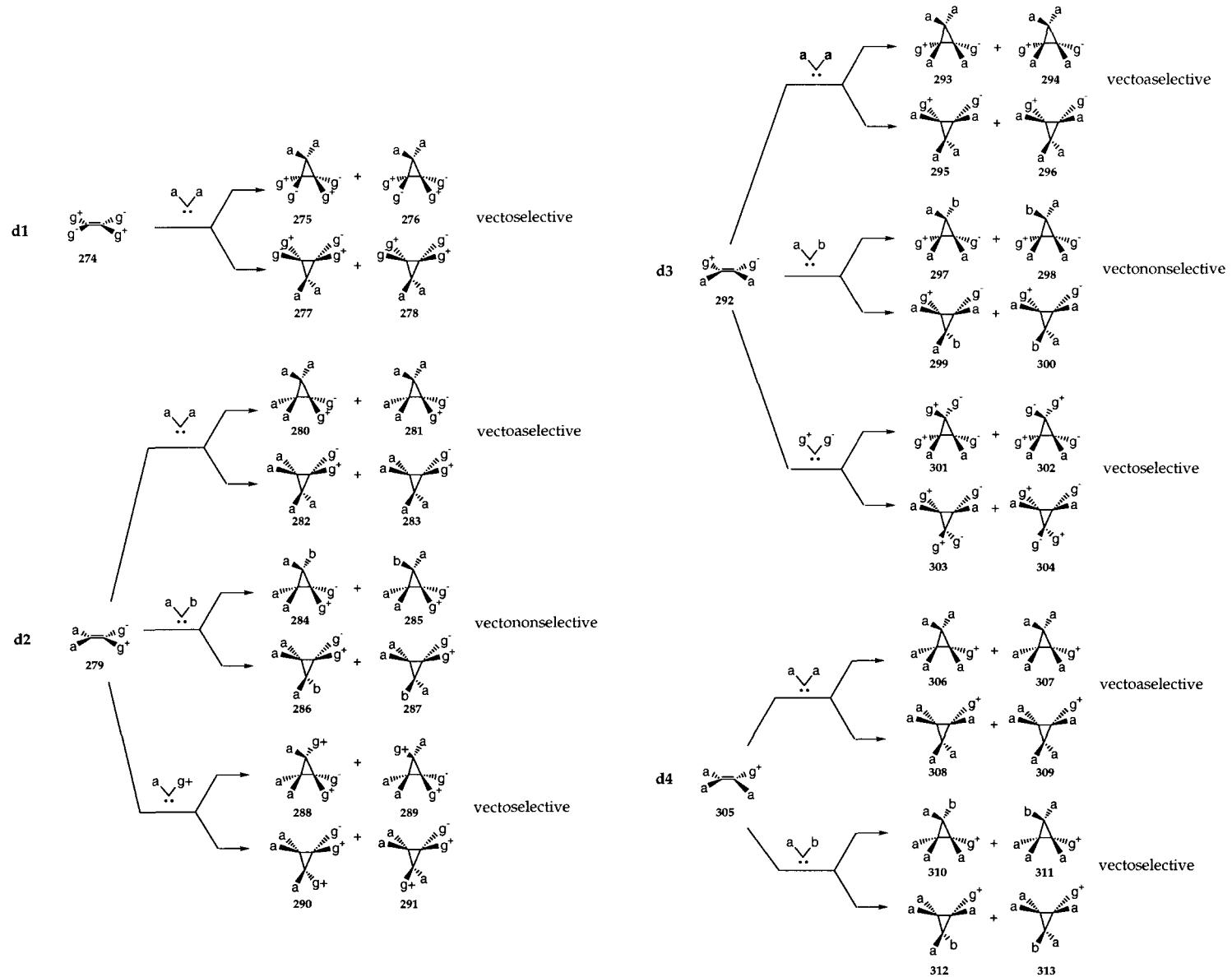
q22	D,F	2 achiral diastereomers
q23	D*,F*	2 chiral diastereomers
q24	D*,F*,G*	3 chiral diastereomers
q26	D,F,G,J	4 achiral diastereomers
q27	D*,F*,G*,J*	4 chiral diastereomers
q28	D,F,G	3 achiral diastereomers
q29	D*, F,G	3 diastereomers (1 chiral, 2 achiral)



**Figure 13.21.** Examples of Vectoaselectivity, Vectononselectivity and Vectoselectivity at Homotopic Faces



**Figure 13.22.** Examples of Vectoaselectivity, Vectononselectivity and Vectoselectivity at Enantiotopic Faces



**Figure 13.23.** Examples of Vectoaselectivity, Vectononselectivity and Vectoselectivity at Diastereotopic Faces

Quartet Mode	Quartets	Facioselectivity of M <sub>A</sub>			Vectoselectivity			
		Facioselectivity	Faciononselectivity	Faciostereoselectivity	Vectoselectivity	Vectorononselectivity	Vectostereoselectivity	Vectoastereoselectivity
Aa	q <sub>1</sub> , q <sub>2</sub>	+			+			
An	q <sub>3</sub>	+				+		
Na	q <sub>5</sub>		+		+			
Nn	q <sub>4</sub>		+			+		
Ns	q <sub>6</sub> -q <sub>12</sub>		+				+	
Nas	q <sub>13</sub> , q <sub>15</sub> , q <sub>17</sub> , q <sub>19</sub> , q <sub>20</sub>		+					+
Nne	q <sub>14</sub> , q <sub>16</sub> , q <sub>18</sub> , q <sub>21</sub>		+					+
Sa	q <sub>22</sub> , q <sub>23</sub> , q <sub>30</sub>			+	+			
Sn	q <sub>25</sub>			+		+		
Ss	q <sub>24</sub> , q <sub>26</sub> -q <sub>29</sub>			+			+	
Sas	q <sub>31</sub> , q <sub>33</sub> , q <sub>35</sub> , q <sub>37</sub> , q <sub>39</sub> , q <sub>41</sub> , q <sub>42</sub> , q <sub>44</sub>			+				+
Sne	q <sub>32</sub> , q <sub>34</sub> , q <sub>36</sub> , q <sub>38</sub> , q <sub>40</sub> , q <sub>43</sub> , q <sub>45</sub>			+				+

**Table 13.2.** The Twelve Modes of Facioselectivity-Vectoselectivity in Conjunctive Processes

Quartet Mode	Quartets	h1		h2		h3		h4		h5		h6		e		d1		d2		d3		d4	
		ac	c																				
Aa	q1, q2	+	+	+	+	+	+	+	+	+	+	+	+					+	+	+		+	+
An	q3			+		+													+				
Na	q5																	+					
Nn	q4			+		+																	
Ns	q6-q12			+	+	+	+					+	+	+	+	+						+	
Nas	q13, q15, q17, q19, q20			+	+							+	+			+						+	+
Nne	q14, q16, q18, q21			+	+							+	+			+						+	
Sa	q22, q23, q30																+	+	+	+	+	+	+
Sn	q25																		+		+		
Ss	q24, q26-q29																+		+	+	+	+	+
Nas	q31, q33, q35, q37, q39, q41, q42, q44															+		+	+			+	+
Nne	q32, q34, q36, q38, q40, q43, q45															+		+	+			+	+

ac : achiral reagent  
c : chiral reagent

Table 13.3. Vectoselectivity-Facioselectivity in Conjunctive Processes

q31	D*,F*,N*	2 chiral diastereomers and a common chiral astereomer
q32	D*,F*,X*	2 chiral diastereomers and a common chiral nonequimer
q35	D,F,M,N	2 astereomeric achiral diastereomeric pairs
q36	D,F,X,Y	2 nonequimERIC achiral diastereomeric pairs
q37	D*,F*,M*,N*	2 astereomERIC chiral diastereomeric pairs
q38	D*,F*,X*,Y*	2 nonequimERIC chiral diastereomeric pairs
q39	D*,F*,M,N	2 astereomERIC diastereomeric pairs (1 pair chiral, 1 pair achiral)
q40	D*,F*,X,Y	2 nonequimERIC chiral diastereomeric pairs (1 pair chiral, 1 pair achiral)
q42	D,F,N*	2 achiral diastereomers and a common chiral astereomer
q43	D,F,X*	2 achiral diastereomers and a common chiral nonequimer
q44	D,F,M,N	2 achiral diastereomers and 2 astereomERIC achiral diastereomers
q45	D,F,X,Y	2 achiral diastereomers and 2 nonequimERIC achiral diastereomers

Examples of enantiofacioselective and diastereofaciocoselective processes involving avecto-, vecto- and nonvecto- aspects are given in Figures 13.24 and 13.25.

### XIII. Difaciocoselectivity-Vectoselectivity

In the chapter on faciocoselectivity (Chapter 11) we examined (2,2)-face-face ligogenic processes involving four face-face combinations - 1-3, 2-3, 1-4, and 2-4. When vectoselectivity is also taken into account, such a process would lead to a maximum of eight conjunctive states (i)-(viii), and is portrayed as an octet (Figure 13.26, p. 144).

As discussed previously, moving from top to bottom defines faciocoselectivity at the two faces of M<sub>A</sub>:

$$\text{faciocoselectivity of } M_A \text{ (substrate)} = (m_1 + m_{1'} + m_3 + m_{3'}) / (m_2 + m_{2'} + m_4 + m_{4'})$$

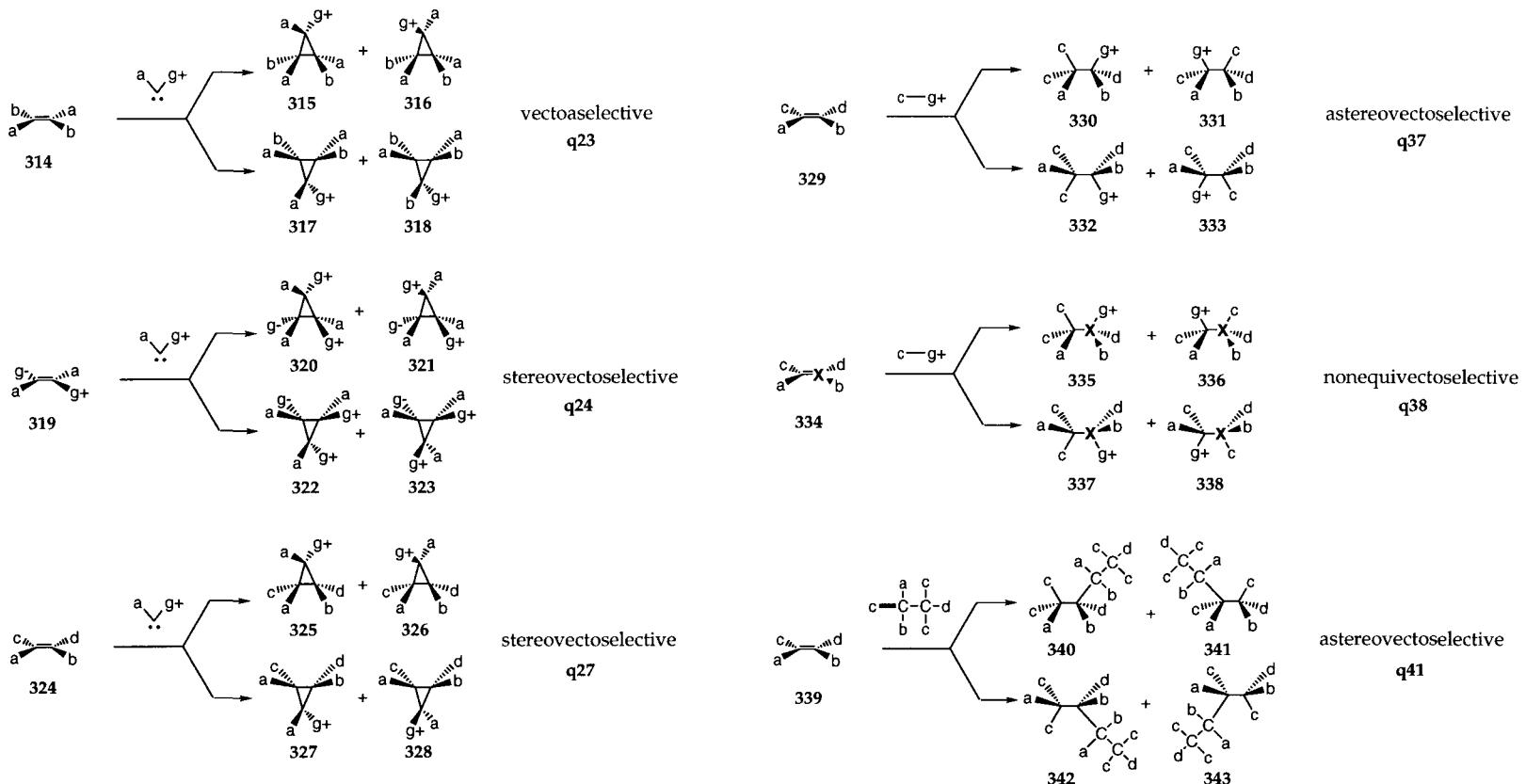
Moving from front to back defines faciocoselectivity at the two faces of M<sub>B</sub>:

$$\text{faciocoselectivity of } M_B \text{ (reagent)} = (m_1 + m_{1'} + m_2 + m_{2'}) / (m_3 + m_{3'} + m_4 + m_{4'})$$

Finally, moving from left to right defines vectoselectivity between M<sub>A</sub> and M<sub>B</sub>:

$$\text{toposelectivity} = (m_1 + m_2 + m_3 + m_4) / (m_{1'} + m_{2'} + m_{3'} + m_{4'}).$$

The 45 octets we have uncovered for various [2+2] and [2+4] cycloadditions, using a wide variety of alkenes and 1,3-dienes, are grouped in three main categories - vectoaselective, vectononselective and vectoselective (Figure 13.27, p. 145). In sum, octets o1-o3,o5,o15-o19,o21,o37,o38 are vectoaselective; octets o4,o6,o20,o22,o25 and o39 are vectononselective. Of the



**Figure 13.24.** Examples of Enantiofacioselective and Vectoselective, Stereovecto-/Astereovecto-/Nonequivectoselective Processes

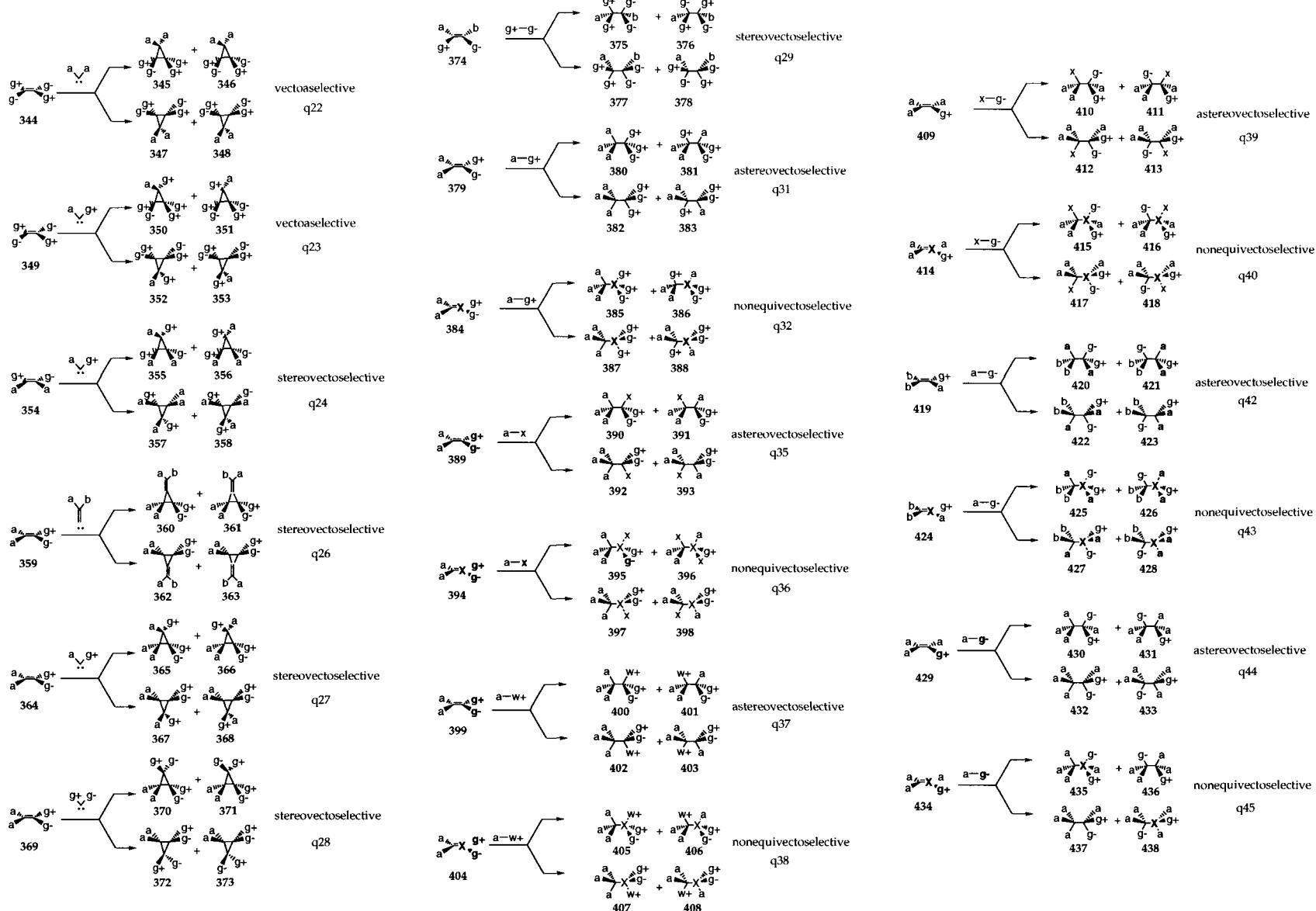
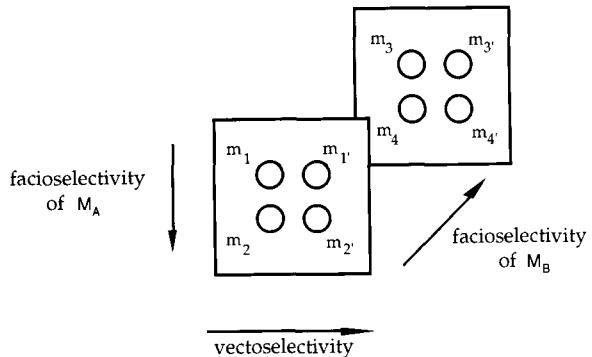


Figure 13.25. Examples of Diastereofaciocoselective and Vectoselective, Stereovecto-/Astereovecto-/Nonequivectoselective Processes



**Figure 13.26.** The Eight Conjunctive Permutations in (2,2)-Ligogenic Face-Face Processes

remaining octets, **o7-o10,o23,o24,o26-o28,o40,o41** are vectostereoselective, **o11,o12,o29-o32,o42,o43** are vectoastereoselective, whereas **o13,o14,o33-o36,o44** and **o45** are vectononequiselective.

The joint consideration of stereofaciocoselectivity (for both substrates A and B) *and* vectoselectivity leads to 18 facioselectivity-faciocoselectivity-vectoselectivity modes – Aaa, Ana, Asa, Nna, Nsa, Ssa, NNn, NSn, SSn, NNs, NSs, SSs, Nnas, Nsas, Ssas, Nnre, Nsne, and Ssne. The 18 composite modes are tabulated in Table 13.4 (p. 147).

In the said designations, the first letter - in upper case - indicates stereofaciocoselectivity of M<sub>A</sub>:

A	:	stereofacioAselectivity
N	:	stereofacioNonselectivity
S	:	stereofacioSelectivity.

The second letter - in upper case - indicates stereofaciocoselectivity of M<sub>B</sub>:

A	:	stereofacioAselectivity
N	:	stereofacioNonselectivity
S	:	stereofacioSelectivity.

The third letter (in lower case) indicates vectoselectivity:

a	:	vectoaselectivity
n	:	vectoroneselectivity
s	:	vectostereoselectivity
as	:	vectoastereoselectivity,
ne	:	vectononequiselectivity).

Octets **o1-o3,o15,o16,o5,o17,o18,o19,o21,o37** and **o38** are vectoaselective. Of these, **o1,o2,o3, o2,o15,o16** are facioselective with respect to M<sub>A</sub>, but with respect M<sub>B</sub>, they are facioselective (**o1,o2**), faciononselective (**o3**), or faciostereoselective (**o15,o16**). Octet **o5** is faciononselective with respect to both reactants, while **o17,o18,o19,o21** are faciononselective for M<sub>A</sub>, but faciostereoselective with respect to M<sub>B</sub>. Octets **o37,o38** are faciostereoselective with respect to both reactants.

Octets **o4,o6,o20,o22,o25,o39** are vectoroneselective. Octets **o4,o6** are faciononselective with respect to both substrates. Octets **o20,o22,o25** are faciononselective with respect to M<sub>A</sub>, but faciostereoselective with respect to M<sub>B</sub>. Octet **o39** is faciostereoselective with respect to both substrates.

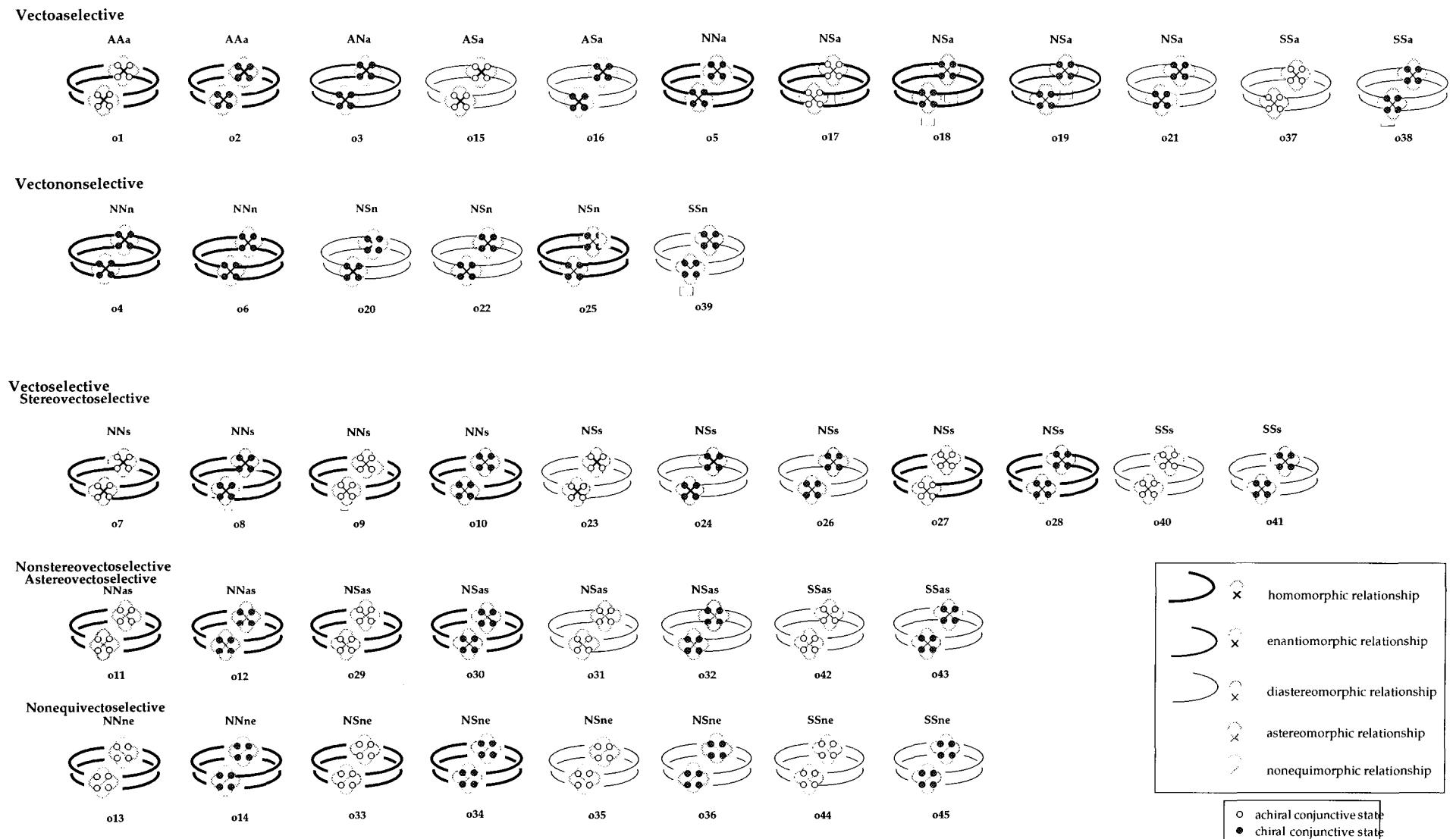


Figure 13.27. Vectoselectivity and the 45 Octets of Face-Face Conjunctive Processes

Octets **o7-o10,o23,o24,o26-o28,o40,o41** are vectostereoselective. Octets **o7-o10** are faciononselective with respect to both substrates. Octets **o23,o24,o26-o28** are faciononselective with respect to  $M_A$ , but faciostereoselective with respect to  $M_B$ . Octets **o40,o41** are faciostereoselective with respect to both substrates.

Octets **o11,o12,o29-o32,o42,o43** are vectoastereoselective. Octets **o11,o12** are faciononselective with respect to both substrates. Octets **o29-o32** are faciononselective with respect to  $M_A$ , but faciostereoselective with respect to  $M_B$ . Octets **o42,o43** are faciostereoselective with respect to both substrates.

Finally, octets **o13,o14,o33-o36,o44,o46** are vectoronequiselective. Octets **o13,o14** are faciononselective with respect to both substrates. Octets **o33-o36** are faciononselective with respect to  $M_A$ , but faciostereoselective with respect to  $M_B$ . Octets **o44,o45** are faciostereoselective with respect to both substrates.

In the analysis of face-face interactions between  $M_A$  and  $M_B$ , the eleven types of stereofaces of  $M_A$  are pitted against the eleven types of faces of  $M_B$ ; there emerges resultant vectoselectivity that is portrayed in Table 13.5 (p. 148).

#### A. Homotopic Faces h1-h6

Face  $h_1$  is vectoaselective with respect to  $h_1-h_6$ , and vectoselective with respect to  $d_1-d_4$ ; it can be vectoaselective or vectoselective with respect to  $e$ .

Face  $h_2$  is vectoronelective with respect to  $h_3, d_1$  and  $d_3$ ; it is vectoselective with respect to  $h_2, h_5, d_2$  and  $d_4$ ; it can be vectoaselective or vectoselective with respect to  $h_6$ , and it is vectoaselective or vectoronelective with respect to  $e$ .

Face  $h_3$  is vectoaselective with respect to  $h_4$ , vectoronelective with respect to  $h_5, h_6, d_1$ , and  $d_2$ ; it is vectoaselective or vectectononselective with respect to  $e$ ; it is vectoronelective or vectoselective with respect to  $h_3, d_3$  and  $d_4$ .

Face  $h_4$  is vectoaselective with respect to  $h_4, h_5, h_6$  and vectoronelective with respect to  $e, d_1, d_2, d_3$  and  $d_4$ .

Face  $h_5$  is vectoronelective with respect to  $e$  and  $d_1$ , vectoselective with respect to  $h_5, d_2, d_3$  and  $d_4$ ; it is vectoronelective or vectoselective with respect to  $h_6$ .

Face  $h_6$  is vectoronelective with respect to  $h_6, e$ , and  $d_1$ ; it is vectoronelective or vectoselective with respect to  $d_2, d_3$ , and  $d_4$ .

We note, parenthetically, that  $h_1$  and  $h_4$ , which had exhibited identical behavior in the vectoselectivity-facioselectivity correlations of Table 13.3 (p. 140), clearly show their differences in face-face selectivities (*vide supra*). With respect to face  $e$ ,  $h_1$  is avectoselective or vectoronelective;  $h_4$  can be only vectoronelective.

#### B. Enantiotopic Faces e

Face  $e$  is vectoronelective with respect to  $e, d_1, d_2, d_3$  and  $d_4$ .

#### C. Diastereotopic Faces d1-d4

Face  $d_1$  is also vectoselective with respect to  $d_1, d_2, d_3$  and  $d_4$ .

Face  $d_2$  is vectoronelective with respect to  $d_3$ , but vectoselective with respect to  $d_2$  and  $d_4$ . Face  $d_3$  is vectoselective with respect to  $d_3$  and  $d_4$ . Finally,  $d_4$  is vectoselective with respect to  $d_4$ .

Octet Mode	Octets	Facioselectivity of M <sub>A</sub>			Facioselectivity of M <sub>B</sub>			Vectoselectivity				
		Facioselectivity	Faciononselectivity	Faciostereoselectivity	Facioselectivity	Faciononselectivity	Faciostereoselectivity	Vectoselectivity	Vectononselectivity	Vectostereoselectivity	Vectoastereoselectivity	Vectononequiselectivity
AAa	o1,o2	+				+			+			
ANa	o3	+				+			+			
ASa	o15,o16	+					+	+				
NNa	o5		+			+			+			
NSa	o17,o18,o19,o21		+				+	+	+			
SSa	o37,o38			+			+	+	+			
NNn	o4,o6		+			+			+			
NSn	o20,o22,o25		+				+		+			
Sn	o39			+			+		+			
NNs	o7-o10		+			+				+		
NSs	o23,o24,o26-o28		+				+			+		
SSs	o40,o41			+			+			+		
NNas	o11,o12		+			+					+	
NSas	o29-o32		+				+				+	
SSAs	o42,o43			+			+			+		
NNne	o13,o14		+			+						+
NSne	o33-o36		+				+					+
SSne	o44,o45			+			+					+

**Table 13.4.** The Eighteen Modes of Difacioselectivity-Vectoselectivity in Conjunctive Processes

	h1	h2	h3	h4	h5	h6	e	d1	d2	d3	d4
h1											
h2											
h3											
h4											
h5											
h6											
e											
d1											
d2											
d3											
d4											

A VECTOSELECTIVE 

NONVECTOSELECTIVE 

VECTOSELECTIVE 

**Table 13.5 .** Vectoselectivity in Face-Face Conjunctive Processes

### **Summary**

The original definition of *regioselectivity* and the subsequent IUPAC recommendation of that term were reexamined and shown to encompass two conceptually distinct ideas. Where the focus of attention is on site selectivity, the correct term should be *siteselectivity/toposelectivity*; in this respect, the term *regioselectivity* is inapplicable and should be abandoned. On the other hand, where the effect of relative orientations of reactants is concerned and vectorial reversal is being considered, the term regioselectivity may still be used; however, one should realize that regioselectivity is indeed a specific manifestation of the wider concept of *vectoselectivity*, as defined in this chapter.

Finally, inasmuch as the relationships of products from (regio)vectoselective processes may be stereomeric or nonstereomeric, the term "regioisomer" fails to define the relationship between two substances and, thus, should be discontinued; the exact morphic relationship between *products* is given by the HEDAN system (Ch. 2, Volume 1). Any attribute of a *process* should be expressed in terms of junctivity (Ch. 8, Volume 2), ligogenicity (Ch. 9, Volume 2), facioselectivity (Ch. 12, Volume 2) and/or vectoselectivity/regioselectivity (Ch. 13, Volume 2); any attendant stereoselectivity may also be appended to the latter.

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"It is not how much we know that counts, but how much we know than nobody else knows."

Evan Esar, 20,000 Quips & Quotes, p. 455.

# 14

## Anguloselectivity

In ligogenic processes, the formation of  $\sigma$ -bonds involves hybridized ( $sp^3$ ,  $sp^2$ ,  $sp$ ) or simple atomic (s,p) orbitals (Figure 14.1).

The approach of the two reacting atoms may be represented in terms of two angles -  $\theta$  and  $\psi$  – relative to the trajectory of approach (dotted line) (Figure 14.2(a)). In the limit, when  $\theta$  and  $\psi$  are zero, the orbitals are colinear with the trajectory axis (Figure 14.2(b)).

As the sigma bond forms, the approach of the reacting moieties occurs along specific trajectories, and, through *vectospecific/nonvectospecific* alignments. If a given trajectory is preferred over other well-defined or feasible trajectories, the process is said to exhibit *trajectoselectivity*. For a given trajectory, a vectospecific mode is defined by a vectospecific alignment of two (or more) reactants that lead to a structurally-distinct product. A nonvectospecific mode involves a nonvectospecific alignment of reactants, and generally converges into a single product.

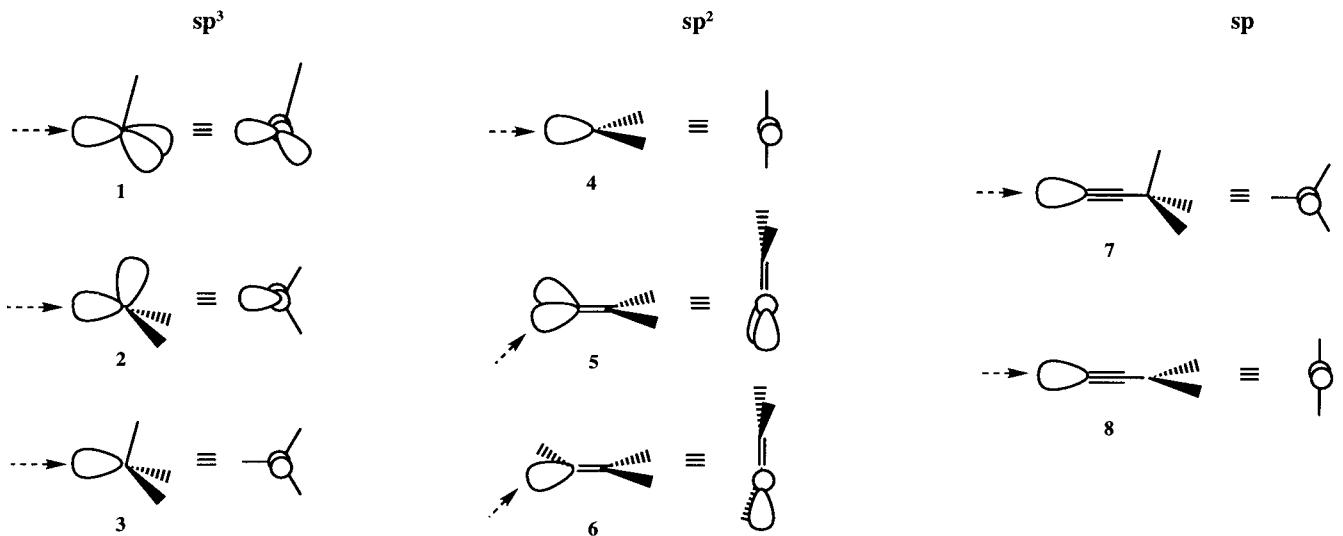
For a given vectospecific/nonvectospecific alignment, the exact positioning of the two moieties with respect to each other, at a given point in time, is termed an *angulospecific state*. For that given *vectospecific/nonvectospecific alignment*, there may be one or more angulospecific states. The preference for one angulospecific state over another (or others) is termed *anguloselectivity*. This preference may be expressed in terms of % anguloselectivity:

$$\% \text{ anguloselectivity} = \% \text{ angulospecific state 1} - \% \text{ angulospecific state 2} \quad (14.1)$$

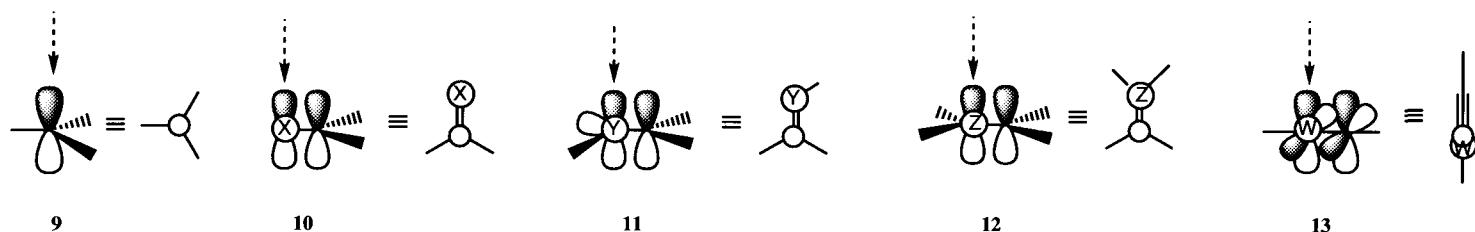
Preference of a given angulospecific state, to the exclusion of all other angulospecific states, would be characterized by 100% anguloselectivity; here, the term *angulospecificity*, to mean 100% anguloselectivity, is not desirable.

Angulospecific states refer to partially bonded entities as in transition states; they are not synonymous with conformational states, be it conformations or conformers. Where more than one  $\sigma$  bond is formed, the angulospecific state must define the alignment of the elements with respect to each and every  $\sigma$  bond that is being formed. We will next discuss the concept of anguloselectivity for (1,1)-, (1,2)- and (2,2)-ligogenic processes.

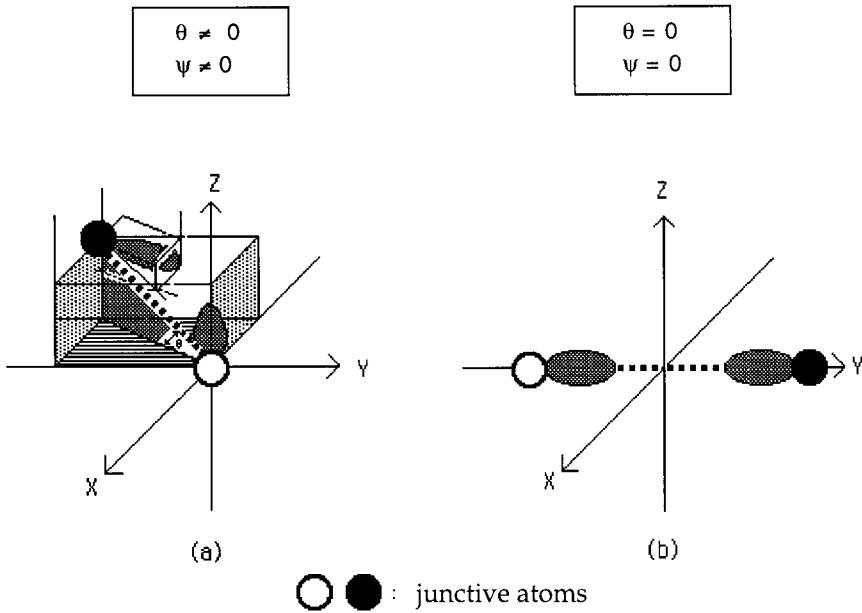
### Hybridized Atomic Orbitals



### Atomic p-Orbitals



**Figure 14.1.** Hybrid and Atomic Orbitals



**Figure 14.2.** Trajectories of (1,1)-Junctive Processes

### I. (1,1)-Ligogenic Processes

The various permutations for couplings in (1,1)-ligogenic processes using prototypes 1-13 (Figure 14.1) are portrayed in Figure 14.3 below; a particular angulospecific state is indicated by dihedral angle  $\theta$  – the angle between two fiducial groups on the two approaching moieties. The method of choosing the fiducial group in (1,1)-ligogenic processes is given in Appendix 14.A (p. 181). The couplings in (1,1)-ligogenic processes are as follows:

Rows 1-3:

$sp^3-sp^3$	:	14-16, 25, 26, 35
$sp^3-sp^2$	:	17-19, 27-29, 36-38
$sp^3-p$	:	20-24, 30-34, 39-43

Rows 4-6:

$sp^2-sp^2$	:	44-46, 52, 53, 59
$sp^2-p$	:	47-51, 54-58, 60-64

Row 7-10:

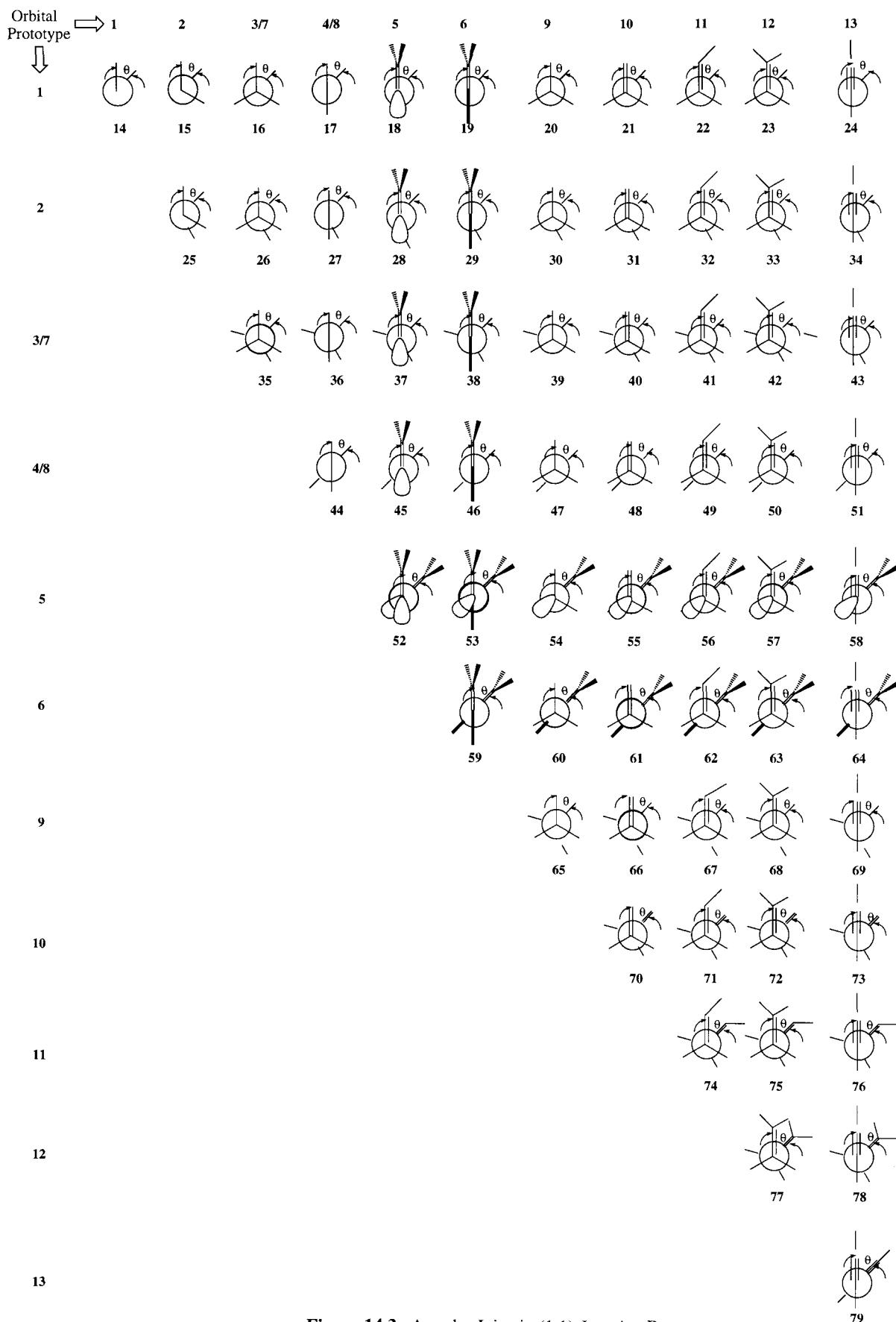
$p(sp^2)-p(sp^2)$	:	65-68, 70-72, 74, 75, 77
$p(sp^2)-p(sp)$	:	69, 73, 76, 78

Row 11:

$p(sp)-p(sp)$	:	79
---------------	---	----

It is noted that 3/7 (also 4/8) have identical Newman projections, since the difference consists of a linear ethynyl group.

In order to define  $\theta$  exactly, one needs to specify the vectospecific arrangements using the definitions given in Figure 14.3.



**Figure 14.3.** Angular Joins in (1,1)-Junctive Processes  
Between Atomic Orbital Prototypes 1-13

## II. (1,2)-Ligogenic Processes

The various permutations for coupling in (1,2)-ligogenic processes using prototypes 1-13 of Figure 14.1 are portrayed in Figure 14.4 below; a particular angulospecific state is indicated by dihedral angle  $\theta$  – that between the  $\pi$ -axis of the bijunctive substrate, and the fiducial group of the monojunctional moiety:

Row1:

monovalent $sp^3$ -( $sp^2-sp^2$ )	:	80-82
monovalent $sp^3$ -( $sp-sp$ )	:	83-85

Row 2:

divalent $sp^2$ -( $sp^2-sp^2$ )	:	86-88
divalent $sp^2$ -( $sp-sp$ )	:	89-91

Row 3:

divalent $sp^3$ -( $sp^2-sp^2$ )	:	92-94
divalent $sp^3$ -( $sp-sp$ )	:	95-97

Row 4:

trivalent $sp^3$ -( $sp^2-sp^2$ )	:	98-100
trivalent $sp^3$ -( $sp-sp$ )	:	100-103

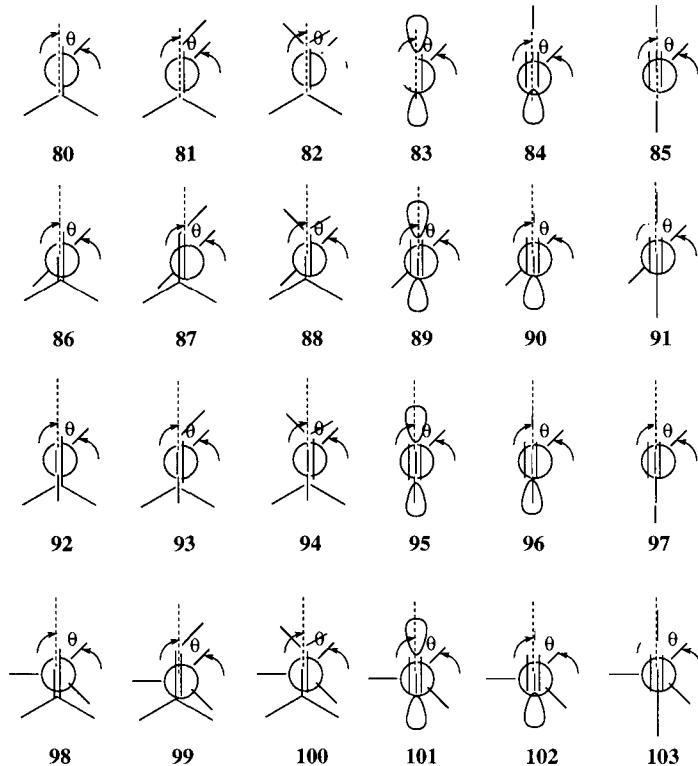


Figure 14.4. Angular Joins in (1,2)-Junctive Processes

### III. (2,2)-Ligogenic Processes

The various permutations for coupling in (1,2)-ligogenic are portrayed in Figure 14.5. A particular angulospecific state is indicated by dihedral angle  $\theta$  – that between the two  $\pi$ -axes of the approaching moieties:

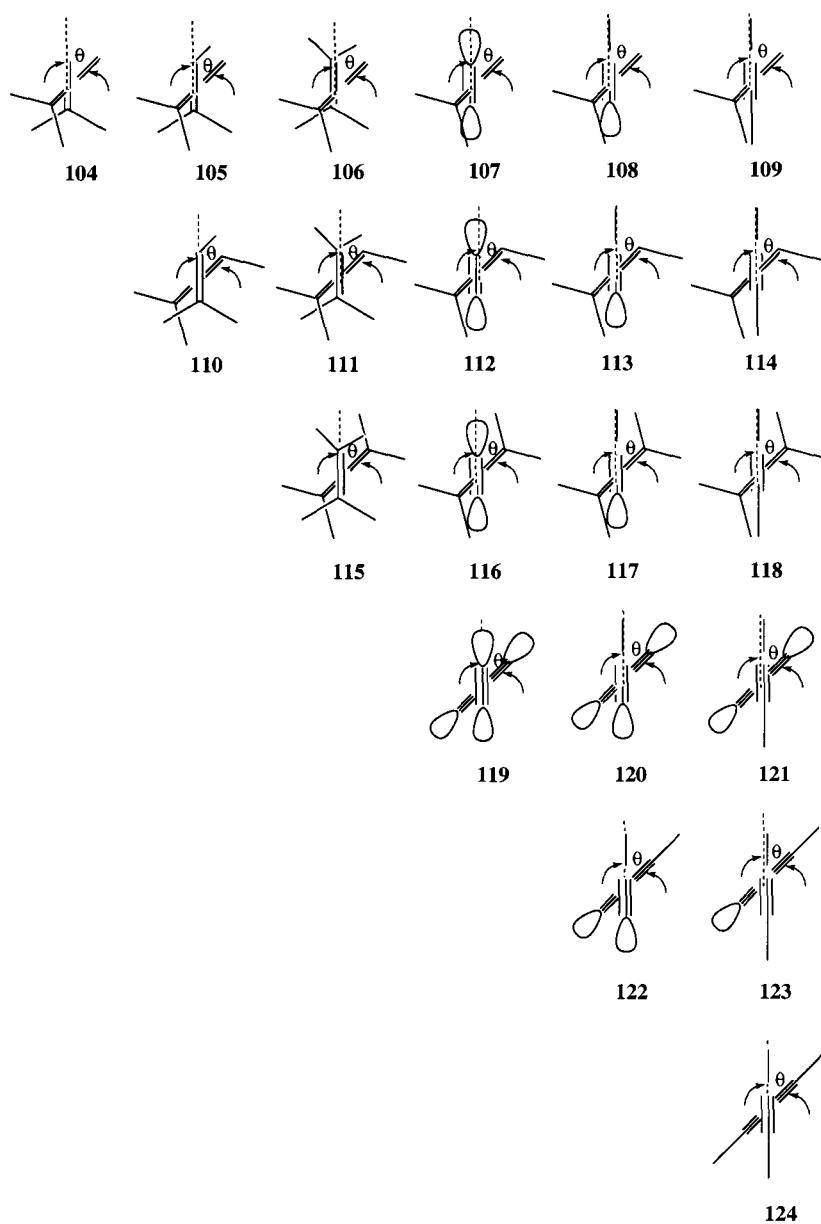
Row1:		
(sp <sup>2</sup> -sp <sup>2</sup> ) - (sp <sup>2</sup> -sp <sup>2</sup> )	:	<b>104-106</b>
(sp <sup>2</sup> -sp <sup>2</sup> ) - (sp-sp)	:	<b>107-109</b>
Row 2:		
(sp <sup>2</sup> -sp <sup>2</sup> ) - (sp <sup>2</sup> -sp <sup>2</sup> )	:	<b>110-111</b>
(sp <sup>2</sup> -sp <sup>2</sup> ) - (sp-sp)	:	<b>112-114</b>
Row 3:		
(sp <sup>2</sup> -sp <sup>2</sup> ) - (sp <sup>2</sup> -sp <sup>2</sup> )	:	<b>115</b>
(sp <sup>2</sup> -sp <sup>2</sup> ) - (sp-sp)	:	<b>116-118</b>
Rows 4-6:		
(sp-sp) - (sp-sp)	:	<b>116-124</b>

### IV. Vectoselectivity vs. Anguloselectivity

Vectoselectivity and anguloselectivity are conceptually distinct; indeed, anguloselectivity complements the concept of vectoselectivity. Vectoselectivity is based on (a) a competition between two (or more) pathways proceeding through distinct *vectospecific alignments* – alignments which are interrelated by vectorial reversal of a vectogenic component, and (b) the selective formation of a *structurally- distinct* – be it stereomeric or nonstereomeric – minimum-energy conjunctive state on the energy surface. Since vectoselectivity manifests itself in the preferential *connectivity* between the interacting moieties, it must be defined necessarily (Figure 13.9 (p. 116) and Figure 13.12 (p. 120)) in terms of *conjunctive states*.

In contrast, anguloselectivity, for a given vectoselective (*vectospecific*) mode is based on (a) a competition between two (or more) pathways proceeding through differing *angulospecific states*, and (b) the convergence of the two pathways to one and the same conjunctive, minimum-energy state. That is to say, anguloselectivity characterizes selectivity between angular states, at a given point along the specified trajectory, for processes proceeding through structurally-convergent transformations, en route to a single, minimum-energy state on the energy surface. In effect, anguloselectivity magnifies and clarifies the angular states of the reacting partners, en route to a specific, conjunctive state. Anguloselectivity may play a role even in the absence of vectoselectivity, as in the coupling between moieties with no vectorial properties. In any case, the specification of anguloselectivity requires a detailed knowledge of reaction paths (theoretical or actual),<sup>156</sup> and the operational assessment of anguloselectivity provides a considerable experimental challenge.

In general, anguloselective processes, in which components are vectogenic, may become *angulovectoselective* processes; if the components are avectogenic, one obtains *angulo-avectoselective* processes. Figure 14.6 shows the interrelationship between vectoselectivity and anguloselectivity. The latter figure is based on that given for vectoselectivity viz. Figure 13.19 (p. 129). Starting at the bottom of chart, it shows that processes are either nonanguloselective or anguloselective.



**Figure 14.5.** Angular Joins in (2,2)-Junctive Processes

Looking at the top of the chart, each type of vectoselectivity - vectoselectivity, vectostereoselectivity, vectorononstereoselectivity and vectorononselectivity - is subdivided into two subcategories - nonanguloselective and anguloselective. At the juncture of top and bottom, we find the hybrid subclasses. On the left side of the flow-chart, vectoaselectivity is subdivided into *angulovectoaselectivity* and *nonangulovectoaselectivity*. At the right end, vectorononselectivity is subdivided into *angulovectorononselectivity* and *nonangulovectorononselectivity*. In the middle left of the scheme, one sees that vectodiastereoselectivity is categorized into *angulo-* and *nonangulovectodiastereoselectivity*. We had noted before, that "*vectoenantioselectivity*" is nonexistent a subclass. Finally, in the middle right of the chart, vectoastereoselectivity and vectoronequiselectivity are subclassified into two categories - *angulo/nonangulovectoastereoselectivity*, and, *angulo-/nonangulovectoronequiselectivity*, respectively. Examples are given below.

For each type of anguloselectivity above - *angulovectoaselectivity*, *angulovectorononselectivity*, *angulovectodiastereoselectivity*, *angulovectoastereoselectivity*, and *angulovectoronequiselectivity*; % anguloselectivity is given by Equations 14.1a-e:

$$\% \text{ angulovectoaselectivity} = \% \text{ angulovectospecific state 1} - \% \text{ angulovectospecific state 2} \quad (14.1a)$$

$$\% \text{ angulovectorononselectivity} = \% \text{ angulovectospecific state 1} - \% \text{ angulovectospecific state 2} \quad (14.1b)$$

$$\% \text{ angulovectodiastereoselectivity} = \% \text{ angulovectospecific state 1} - \% \text{ angulovectospecific state 2} \quad (14.1c)$$

$$\% \text{ angulovectoastereoselectivity} = \% \text{ angulovectospecific state 1} - \% \text{ angulovectospecific state 2} \quad (14.1d)$$

$$\% \text{ angulovectoronequiselectivity} = \% \text{ angulovectospecific state 1} - \% \text{ angulovectospecific state 2} \quad (14.1e)$$

### A. (1,1)-Ligogenic Processes

We divide (1,1)-ligogenic examples into two categories - configurational and conformational.

#### 1. Configurational Cases

The configurational (1,1)-ligogenic cases are exemplified by the hypothetical coupling of two carbenes to form a carbon-to-carbon double bond (Figure 14.7).

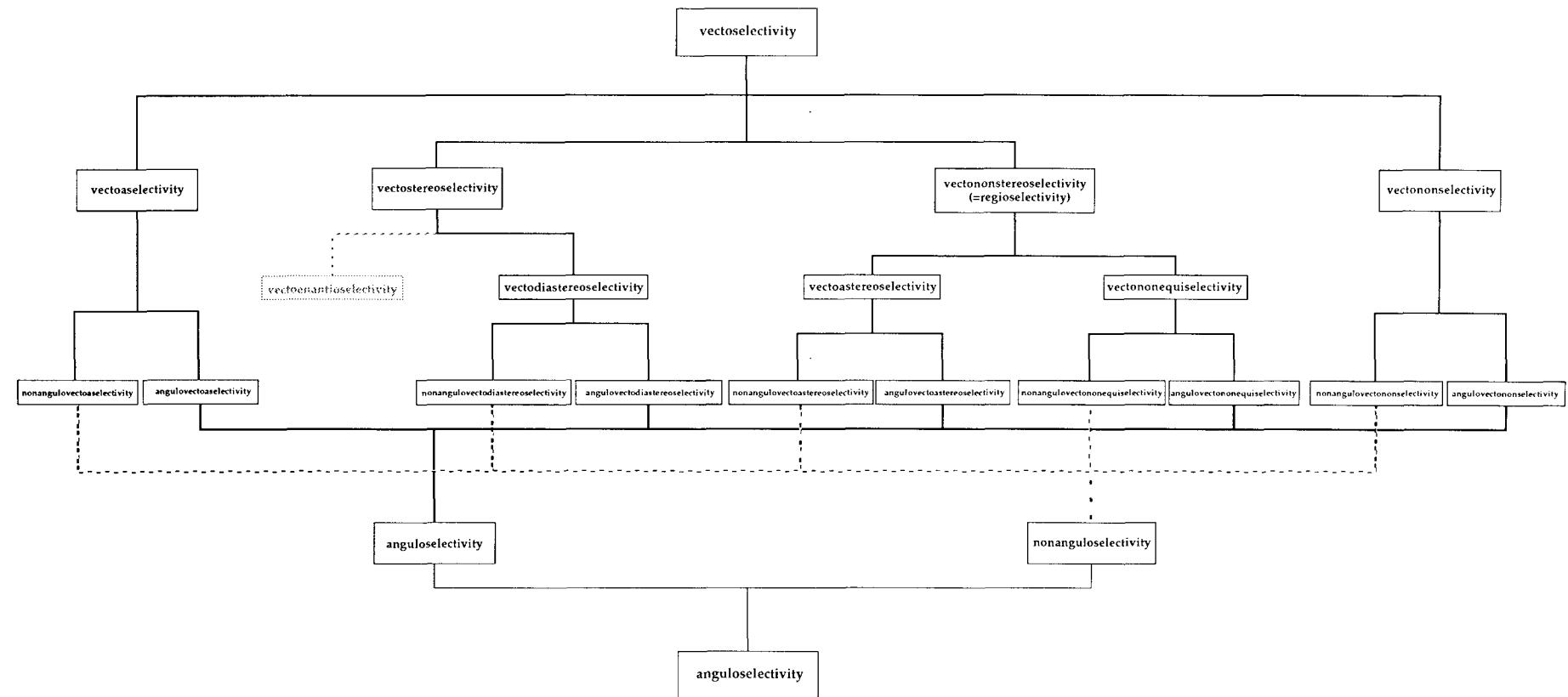
In case 1, the process is *vectoaselective* because parallel alignments 125 and 126 are identical. The process is also *nonanguloselective*, since 125a(=126a) and 125b(=126b) are enantiomeric and, therefore, isoenergetic with respect to each other.

In case 2, the process is also *vectoaselective* because parallel alignments 127 and 128 are identical. However, in this case the process is *anguloselective*, because 127a(=128a) and 127b(=128b) are diastereomeric and, hence, nonisoenergetic entities.

In case 3, the process is *vectorononselective* because alignments 129 and 130, while distinct, are hypothetically isoenergetic. The process, further, is *nonanguloselective* because angulospecific states 129a and 129b (and also 130a and 130b) are enantiomeric and isoenergetic with respect to each other.

In case 4, the process is *vectorononselective*, as in case 3 above. However here, the process would be *anguloselective*, if, one of two diastereomeric and necessarily-nonisoenergetic angulospecific states is favored over the other i.e. 131a > 131b and 132a > 132b.

Cases 5 and 6 represent *vectoselective* processes i.e. 133>134 and 135>136; 133,135 (*par; cisoid*) are preferred over the antiparallel ones - 134,136 (*apar; transoid*). However, the former process is *nonanguloselective* (133a and 133b are enantiomeric and, therefore, isoenergetic), while the latter process is *anguloselective* (135a and 135b are diastereomeric and nonisoenergetic).



**Figure 14.6.** Relationship of Vectoselectivity and Anguloselectivity

## 2. Conformational Cases

Conformational (1,1)-ligogenic processes are exemplified by the coupling of free radicals to form a single,  $\sigma$ -bonded, conformationally-labile, coupled product (Figure 14.8).

In case 1, the process is *vectoaselective*, because the parallel alignments (137) are identical. The process is also *nonanguloselective*, since 137a and 137b are enantiomeric and, therefore, isoenergetic with respect to each other.

In case 2, the process is also *vectoaselective*, because parallel alignments 138 and 139 are identical. However, the process is *anguloselective* because of the involvement of diastereomeric (nonisoenergetic) states 138a(=139a) and 138b(=139b).

In case 3, the process is *vectorononselective* because alignments 140 and 141, while distinct, are hypothetically assumed to be isoenergetic. The process, further, is *nonanguloselective* because angulospecific states 140a and 140b (and also 141a and 141b) are enantiomeric and isoenergetic.

In case 4, the process is also *vectorononselective*, as in case 3 above. However here, the process is *anguloselective*, if, among the diastereomeric/nonisoenergetic angulospecific states, 142a is favored over 142b, and 143a is favored over 143b.

Cases 5 and 6 represent *vectoselective* processes i.e. 144>145 and 146>147 (144, 146; *gauche*) are preferred over the antiparallel ones (145, 147; *anti*). However, whereas the former process is *nonanguloselective* (144a and 144b are enantiomeric/isoenergetic), the latter process is *anguloselective* (146a and 146b are diastereomeric/nonisoenergetic).

These examples of configurational and conformational (1,1)-ligogenic processes demonstrate that a process, whether vectosaelective, vectorononselective, or vectoselective, can be either nonanguloselective or anguloselective. Nonanguloselective processes result from homomeric or enantiomeric alignments, whereas anguloselective processes are derived from diastereomeric alignments.

Among the configurational cases of Figure 14.7, nonanguloselective cases 136a/b, 140a/b, 141a/b, 144a/b are characterized by enantiomeric alignments. In contrast, anguloselective cases 138a/b, 139a/b, 142a/b, 143a/b, 146a/b correspond to diastereomeric alignments.

In the case of conformational cases of Figure 14.8, nonanguloselective cases 125a/b, 126a/b, 129a/b, 130a/b, 133a/b are characterized by enantiomeric alignments. In contrast, anguloselective cases 127a/b, 128a/b, 131a/b, 132a/b, 135a/b correspond to diastereomeric pairs.

One should also note that there are no cases of vectoastereoselective or vectoronequiselective (1,1)-ligogenic processes. For the latter processes, vectoselectivity is aselective (125/126, 127/128; 136/137, 138/139), nonselective (129/130, 131/132; 140/141, 142/143) or diastereoselective (133/134, 135/136; 144/145, 146/147).

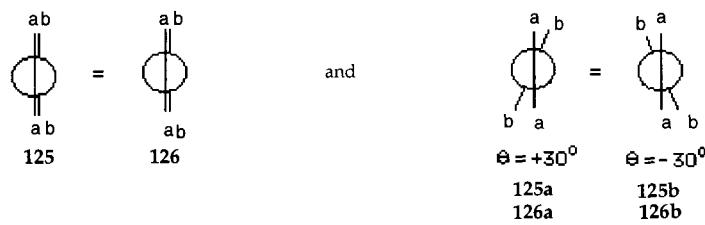
## B. (1,2)-Ligogenic Processes

(1,2)-Ligogenic processes are exemplified by the addition of a carbene to an alkene to form a cyclopropane ring (Figure 14.9, p. 164).

In case 1, the process is *vectoaselective*, because parallel alignments 148 and 149 are identical. The process is also *nonanguloselective*, since one is dealing with enantiomeric/isoenergetic states 148a(=149a) and 148b(=149b).

In case 2, the process is also *vectoaselective*, owing to identical parallel alignments 150 and 151. However, the process is *anguloselective* by virtue of diastereomeric/nonisoenergetic states 150a(=151a) and 150b(=151b).

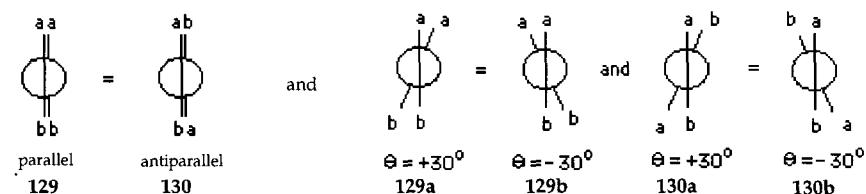
**Case 1 - nonangulovectoaselective (nonanguloselective and vectoaselective)**



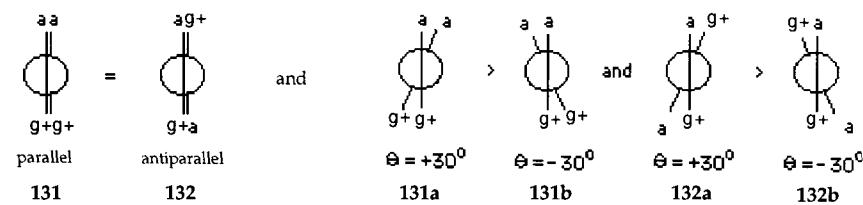
**Case 2 - angulovectoaselective (anguloselective and vectoaselective)**



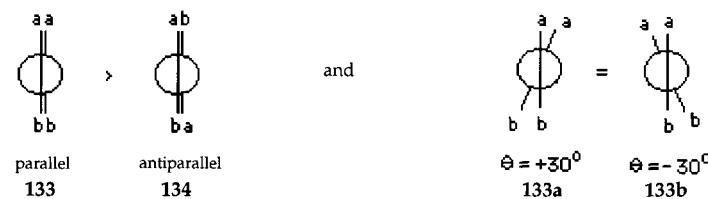
**Case 3 - nonangulovectononselective (nonanguloselective and vectononselective)**



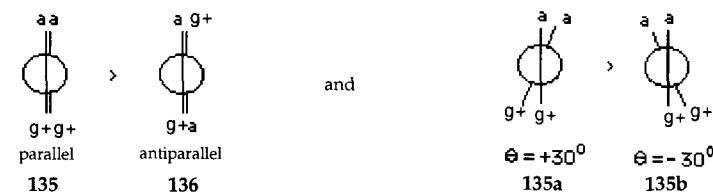
**Case 4 - angulovectononselective (anguloselective and vectononselective)**



**Case 5 - nonangulovectoselective (nonanguloselective and vectodiastereoselective)**

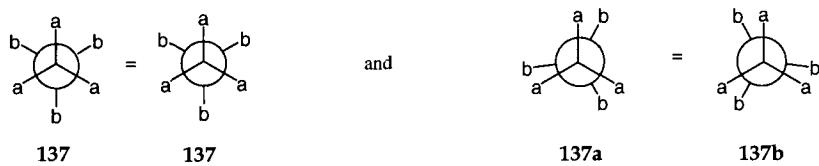


**Case 6 - angulovectoselective (anguloselective and vectodiastereoselective)**

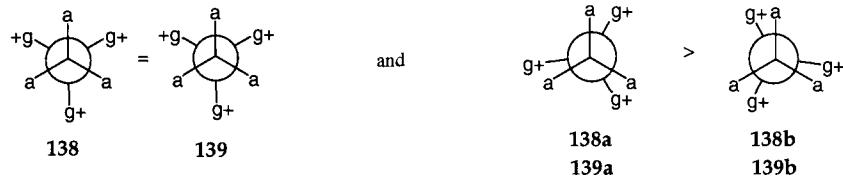


**Figure 14.7.** Vectoselectivity and Anguloselectivity in Configurational (1,1)-Ligogenic Processes

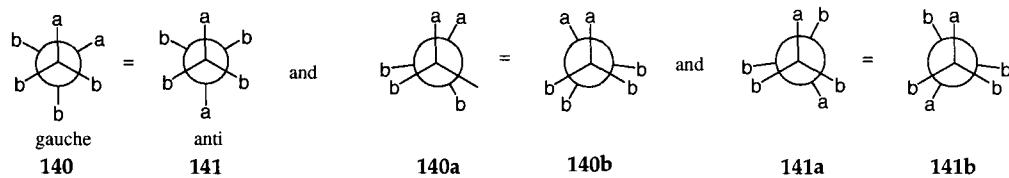
**Case 1 - nonangulovectoaselective (nonanguloselective and vectoaselective)**



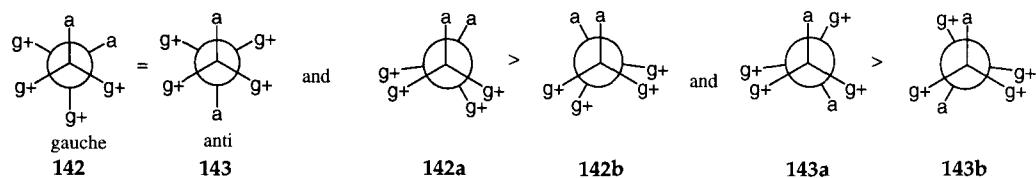
**Case 2 - angulovectoaselective (anguloselective and vectoaselective)**



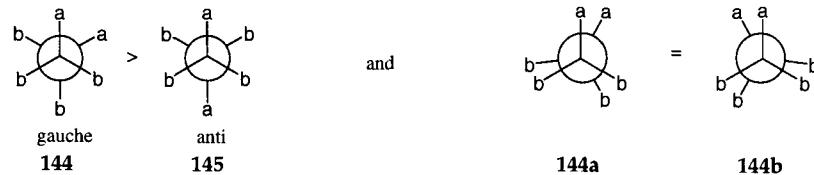
**Case 3 - nonangulovectononselective (nonanguloselective and vectononselective)**



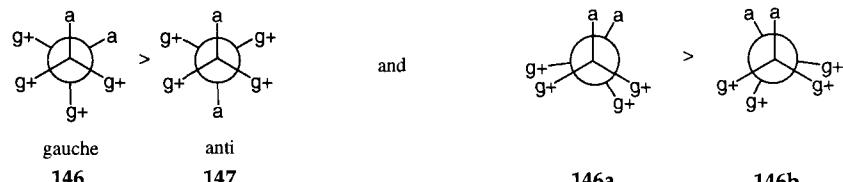
**Case 4 - angulovectononselective (anguloselective and vectononselective)**



**Case 5 - nonangulovectodiastereoselective (nonanguloselective and vectodiastereoselective)**



**Case 6 - angulovectodiastereoselective (anguloselective and vectodiastereoselective)**



**Figure 14.8.** Vectoselectivity and Anguloselectivity in Conformational (1,1)-Ligogenic Processes

In case 3, the process is *vectononselective* because alignments 152 and 153, while distinct, are hypothetically isoenergetic. The process, further, is *nonanguloselective* because angulospecific states 152a and 152b (and also 153a and 153b) are enantiomeric and, therefore, isoenergetic.

In case 4, the process is also *vectononselective*, as in case 3 above. However here, the process is *anguloselective*, if diastereomeric/nonisoenergetic angulospecific states 154a and 155a, are favored over their respective counterparts - 154b and 155b.

Cases 5 and 6 represent *vectoselective* processes i.e. 156>157 and 158>159 (*cisoid* 156,158 are preferred over *transoid* 157,159). However, whereas the former process is *nonanguloselective* (156a and 156b are enantiomeric/isoenergetic), the latter process is *anguloselective* (158a and 158b are diastereomeric/nonisoenergetic).

Here too, there are no cases of astereo- and nonequivectoselective processes, owing to identical connectivities in the 1,2-conjunctive states.

### C. (2,2)-Ligogenic Processes

(2,2)-Ligogenic processes are exemplified by the photochemical [2+2] cycloaddition to form cyclobutanes (Figure 14.10).

In case 1, the process is *vectoaselective* because identical parallel alignments 160 and 161 are involved. The process is concomitantly *nonanguloselective*, since 160a(=161a) and 160b(=161b) are enantiomeric/isoenergetic with respect to each other.

In case 2, the process is also *vectoaselective* because parallel alignments 162 and 163 are identical. However, the process is *anguloselective* owing to the involvement of diastereomeric/nonisoenergetic states 162a(=163a) and 162b(=163b).

In case 3, the process is *vectononselective* if one assumes, hypothetically, that distinct alignments 164 and 165 are isoenergetic. The process, further, is *nonanguloselective* because angulospecific states 164a and 164b (and also 165a and 165b) are enantiomeric/isoenergetic with respect to each other.

In case 4, the process is also *vectononselective*, as in case 3 above. However here, the process is *anguloselective*, if diastereomeric nonisoenergetic/angulospecific states 166a and 167a are favored over 166b and 167b.

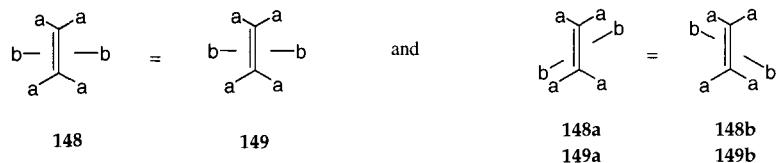
Cases 5 and 6 represent *stereovectoselective* processes i.e. 168>169 and 170>171 (*cisoid* 168,170 are preferred over *transoid* 169,171). However, whereas the former process is *nonanguloselective* (168a and 168b are enantiomeric/isoenergetic), the latter process is *anguloselective* (170a and 170b are diastereomeric/nonisoenergetic).

Cases 7 and 8 represent *astereovectoselective* processes i.e. 172>173 and 174>175 (*cisoid* 172,174 are preferred over *transoid* 173,175). However, whereas the former process is *nonanguloselective* (172a and 172b are enantiomeric/isoenergetic), the latter process may be *anguloselective* (174a and 174b are diastereomeric and therefore nonisoenergetic).

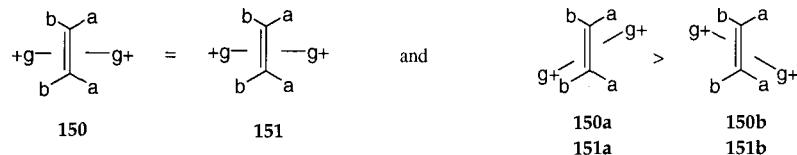
Cases 9 and 10 represent *nonequivectoselective* processes i.e. 176>177 and 178>179 (*cisoids* - are preferred over *transoids* (177,179)). However, whereas the former process is *nonanguloselective* (176a and 176b are enantiomeric/isoenergetic), the latter process is *anguloselective* (178a and 178b are diastereomeric/nonisoenergetic).

Note in the case (2,2)-ligogenic processes, unlike the (1,1)- and (1,2)-cases discussed above, one has cases of vectoastereoselectivity and vectononequiselectivity, in addition to vectoaselectivity, vectononselectivity and vectostereoselectivity.

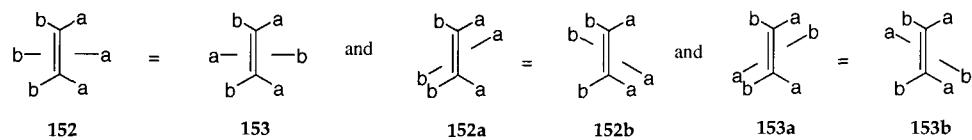
**Case 1 - nonangulovectoaselective (nonanguloselective and vectoaselective)**



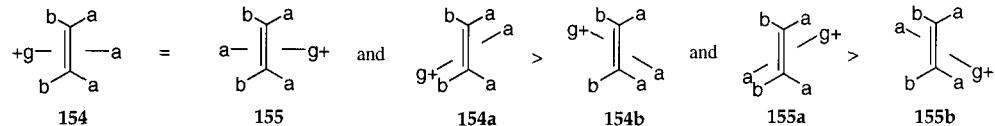
**Case 2 - angulovectoaselective (anguloselective and vectoaselective)**



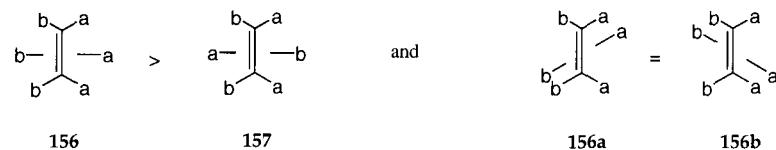
**Case 3 - nonangulovectononselective (nonanguloselective and vectononselective)**



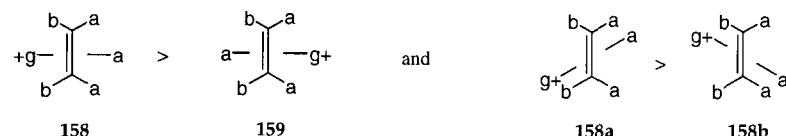
**Case 4 - angulovectononselective (anguloselective and vectononselective)**



**Case 5 - nonangulodiastereovectoselective (nonanguloselective and vectodiastereoselective)**

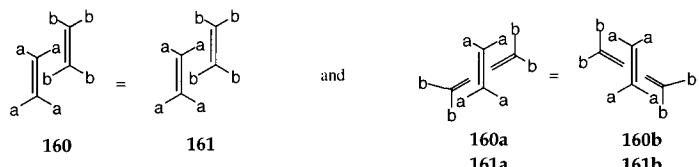


**Case 6 - angulodiastereovectoselective (anguloselective and vectodiastereoselective)**

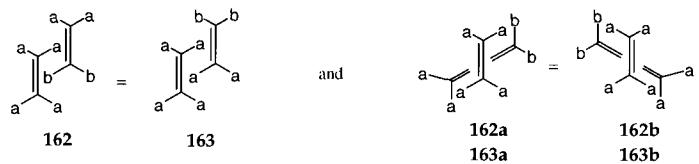


**Figure 14.9.** Vectoselectivity and Anguloselectivity in (1,2)-Ligogenic Processes

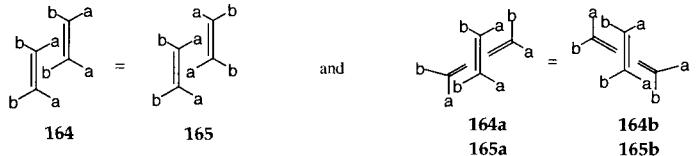
**Case 1 - nonangulovectoaselective (nonanguloselective and vectoaselective)**



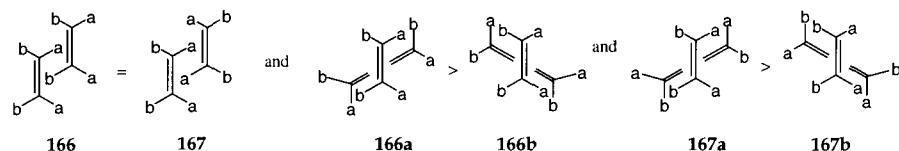
**Case 2 - angulovectoaselective (anguloselective and vectoaselective)**



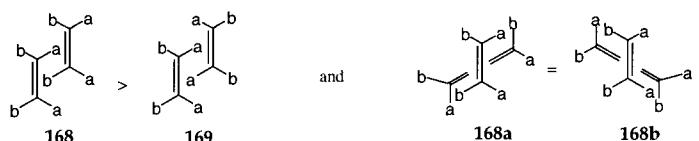
**Case 3 - nonangulovectononselective (nonanguloselective and vectononselective)**



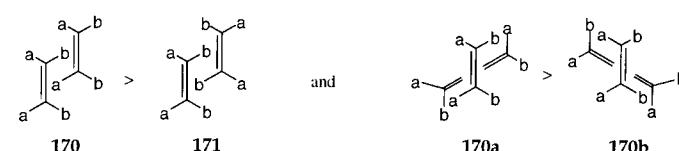
**Case 4 - angulovectononselective (anguloselective and vectononselective)**



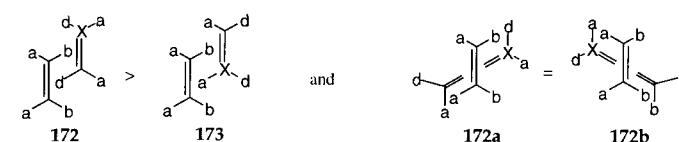
**Case 5 - nonangulodiastereovectoselective (nonanguloselective and diastereovectoselective)**



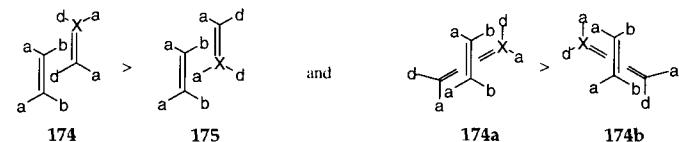
**Case 6 - angulodiastereovectoselective (anguloselective and diastereovectoselective)**



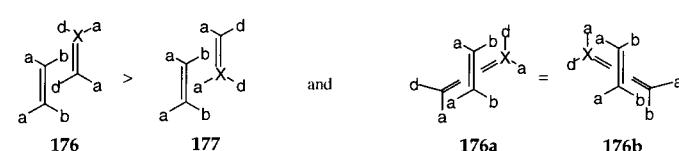
**Case 7 - nonangulostereovectoselective (nonanguloselective and astereovectoselective)**



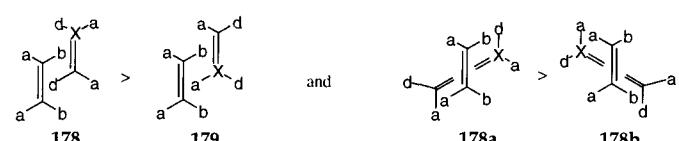
**Case 8 - angulostereovectoselective (anguloselective and astereovectoselective)**



**Case 9 - nonangulononequivectoselective (nonanguloselective and nonequivvectoselective)**



**Case 10 - angulononequivectoselective (anguloselective and nonequivvectoselective)**



**Figure 14.10.** Vectoselectivity and Anguloselectivity in (2,2)-Ligogenic Processes

## V. Facioselectivity, Vectoselectivity and Anguloselectivity at Stereotopic Molecular Faces

The complete description of processes taking place at stereotopic molecular faces involves three fundamental aspects - facioselectivity, vectoselectivity and anguloselectivity. In order to evaluate the interrelationships of the underlying three concepts above, we now consider (1,2)-ligogenic processes for all eleven types of molecular stereofaces.

Figures 14.11-14.16 depict hypothetical additions of divalent carbenes :Ca<sub>2</sub>, :Cab, :Cag<sup>+</sup>, and :Cg<sup>+</sup>g<sup>-</sup> to alkenes h1-h3, e and d1-d4 as prototypical (1,2)-ligogenic processes. In Figures 14.17-14.22 we examine the *hypothetical* (1,2)-ligogenic additions of trivalent species :Xa<sub>3</sub>, :Xa<sub>2</sub>b, :Xabc, :Xg<sub>3</sub><sup>+</sup>, :Xg<sub>2</sub><sup>+</sup>h<sup>+</sup>, and :Xg<sup>+</sup>h<sup>+</sup>i<sup>+</sup> to all eleven stereotopic faces.

We have seen that a given transformation may be *anguloselective* or *nonanguloselective* (Figure 14.6, p. 159). An anguloselective process, in turn, is angulovectoaselective, angulovectodiastereoselective (but not angulovectoenantioselective), angulovectoastereoselective, angulovectononequiselective, or angulovectononselective. Further, since enantiovectoangular arrangements are isoenergetic, there can be no vectoenantioselectivity; it follows that any *angulovectostereoselective* process has to be *angulovectodiastereoselective*. Angulodiastereoselective processes are possible not only in angulovectoselective transformations, but in anguloavectoselective and angulononvectoselective transformations as well.

### A. Homotopic Faces h1-h6

By way of example, we look at the addition of the divalent carbenes :Ca<sub>2</sub>, :Cab, :Cag<sup>+</sup>, and :Cg<sup>+</sup>g<sup>-</sup> to alkenes with h2 faces (Figure 14.11). The addition of :Ca<sub>2</sub> to a<sub>2</sub>C=Cb<sub>2</sub> is vectoaselective, facioselective and nonanguloselective. It is vectoaselective because 230 is identical with 231, and 232 is identical with 233. It is facioselective, because 230 is identical with 232, and 231 is identical with 233. The process is nonanguloselective because 234 and 235 are enantiomeric with respect to each other, as are 238 and 239, 236 and 237, and, 240 and 241. Since enantiomeric states are isoenergetic, the pathways are energetically congruent, and no anguloselectivity would ensue.

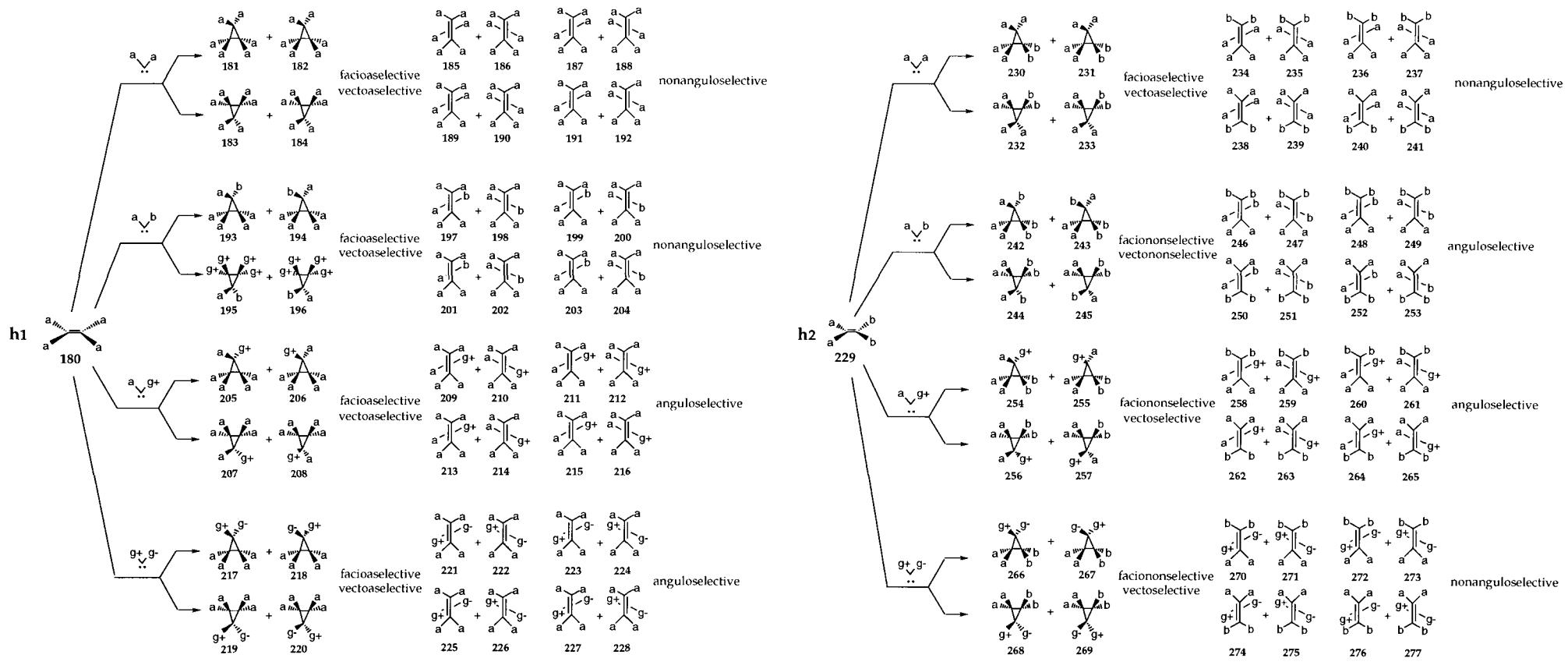
Consideration of all homotopic faces, with both sets of divalent and trivalent reactants listed above, leads to the following generalizations:

1. Nonanguloselective (enantioangular arrangements) processes are possible only at faces h1-h3 (found in achiral substrates); there is no nonanguloselectivity on faces h4-h6 (found in chiral substrates).
2. All nonanguloselective processes at faces h1-h3 occur with achiral reagents.
3. Anguloselective (diastereoangular arrangements) processes can occur on all faces – h1-h6; these encompass achiral as well as chiral substrates.
4. An anguloselective process on a given homotopic face (h1-h3 of achiral substrates, and faces h4-h6 of chiral substrates) may occur with either an achiral or chiral reagent.

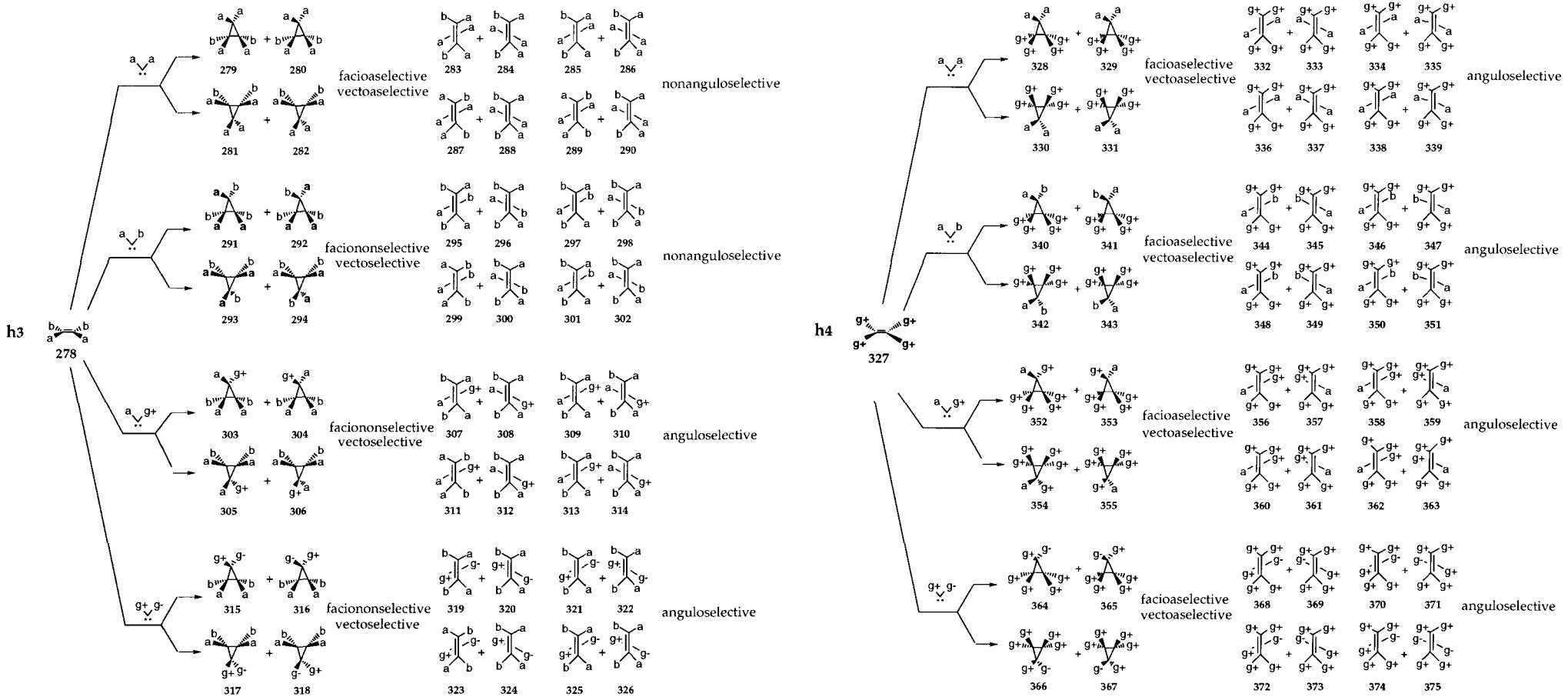
### B. Enantiotopic Faces e

On the basis of all the additions of divalent carbenes :Ca<sub>2</sub>, :Cab, :Cag<sup>+</sup>, and :Cg<sup>+</sup>g<sup>-</sup> (Figure 14.14, p. 170) and trivalent species :Xa<sub>3</sub>, :Xa<sub>2</sub>b, :Xabc, :Xg<sub>3</sub><sup>+</sup>, :Xg<sub>2</sub><sup>+</sup>h<sup>+</sup>, and :Xg<sup>+</sup>h<sup>+</sup>i<sup>+</sup> (Figure 14.20, p. 176) to alkenes with enantiotopic faces, one observes that:

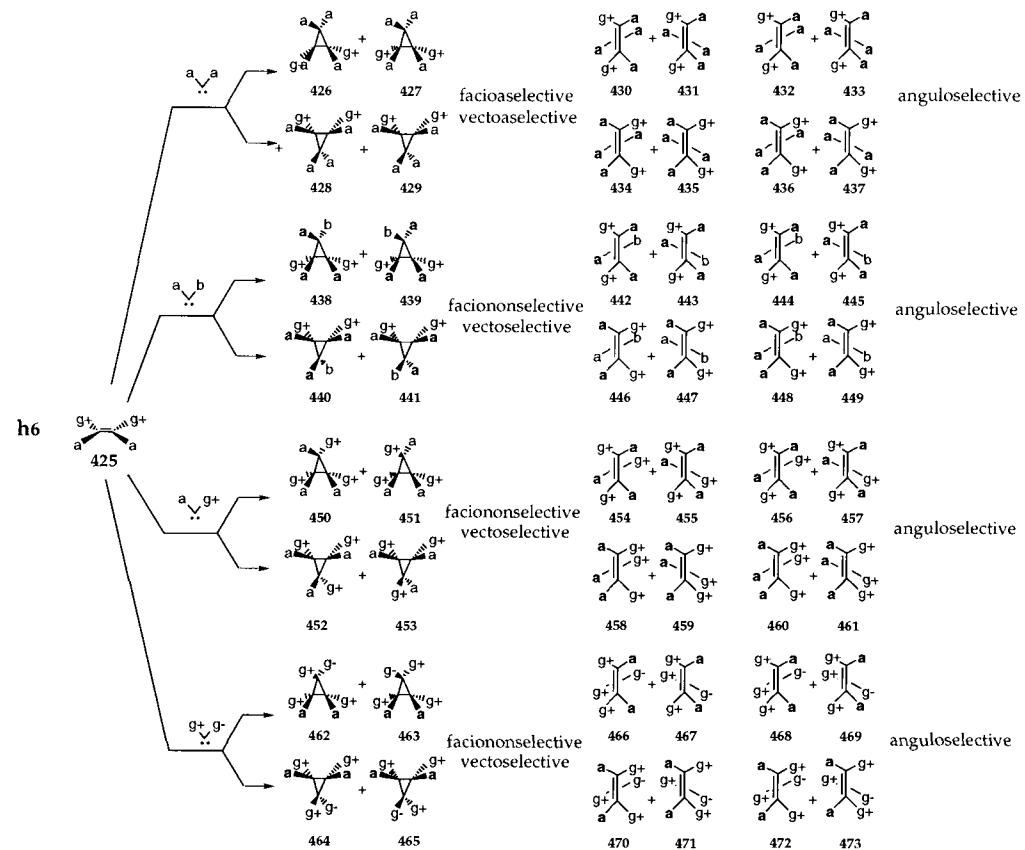
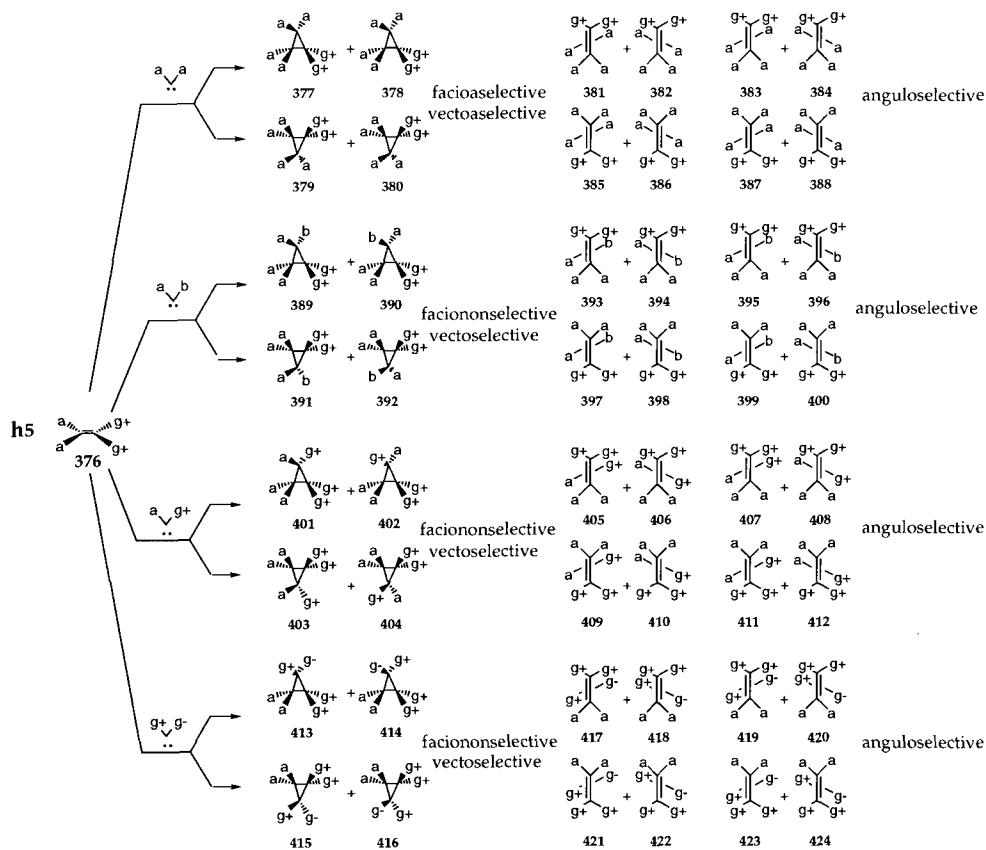
1. Nonanguloselective (enantioangular arrangements) processes are not possible at enantiotopic faces e (found only in achiral substrates).
2. Anguloselective (diastereoangular arrangements) processes can occur at enantiotopic faces e; these involve only achiral substrates.
3. Anguloselective processes at a given enantiotopic face may occur with either an achiral or chiral reagent.



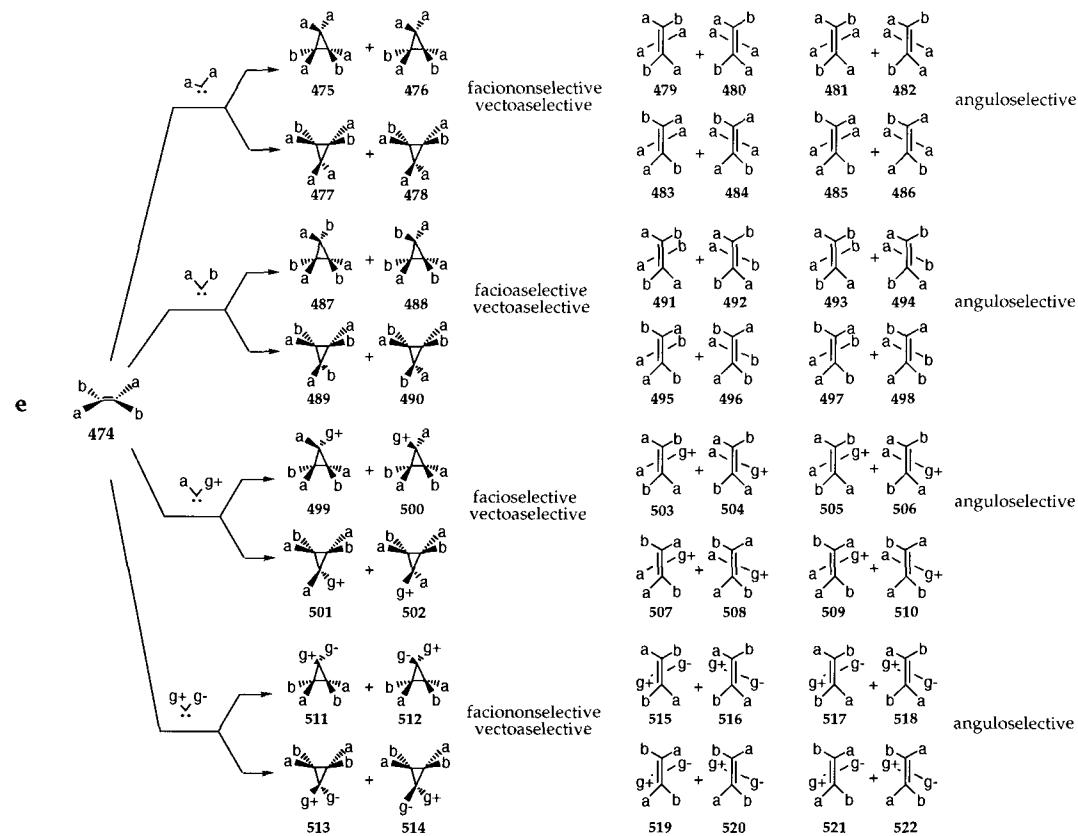
**Figure 14.11.** Relationship of Facioselectivity, Vectoselectivity and Anguloselectivity for 1,2-Ligogenic Processes at Homotopic Faces h1-h2



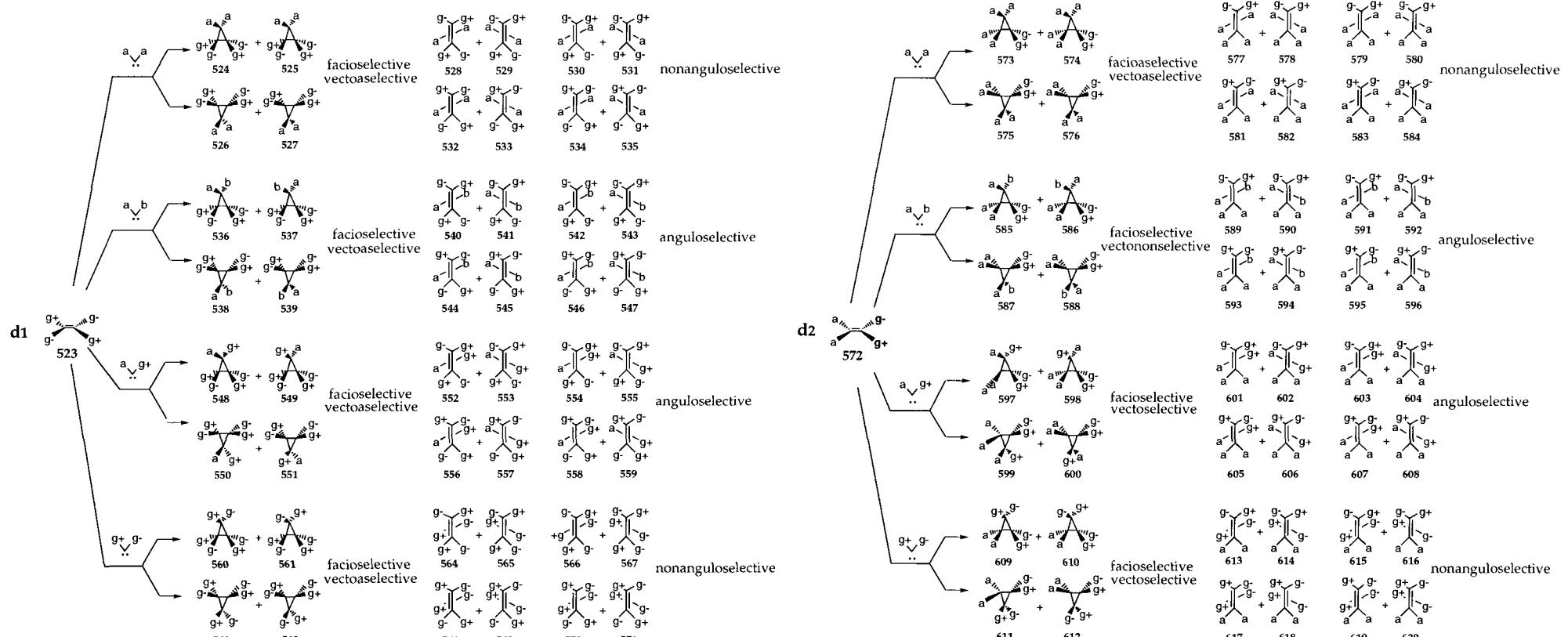
**Figure 14.12.** Relationship of Facioselectivity, Vectoselectivity and Anguloselectivity for 1,2-Ligogenic Processes at Homotopic Faces **h3-h4**



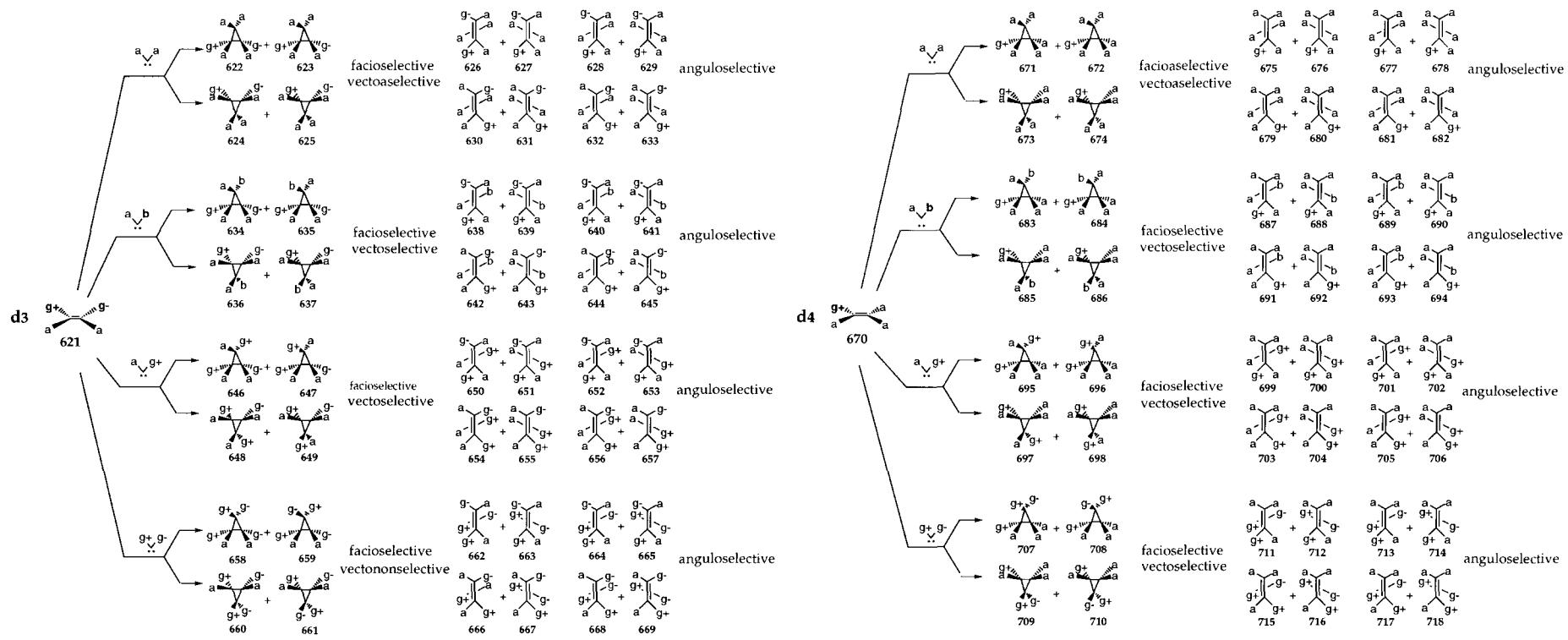
**Figure 14.13.** Relationship of Facioselectivity, Vectoselectivity and Anguloselectivity for 1,2-Ligogenic Processes at Homotopic Faces **h5-h6**



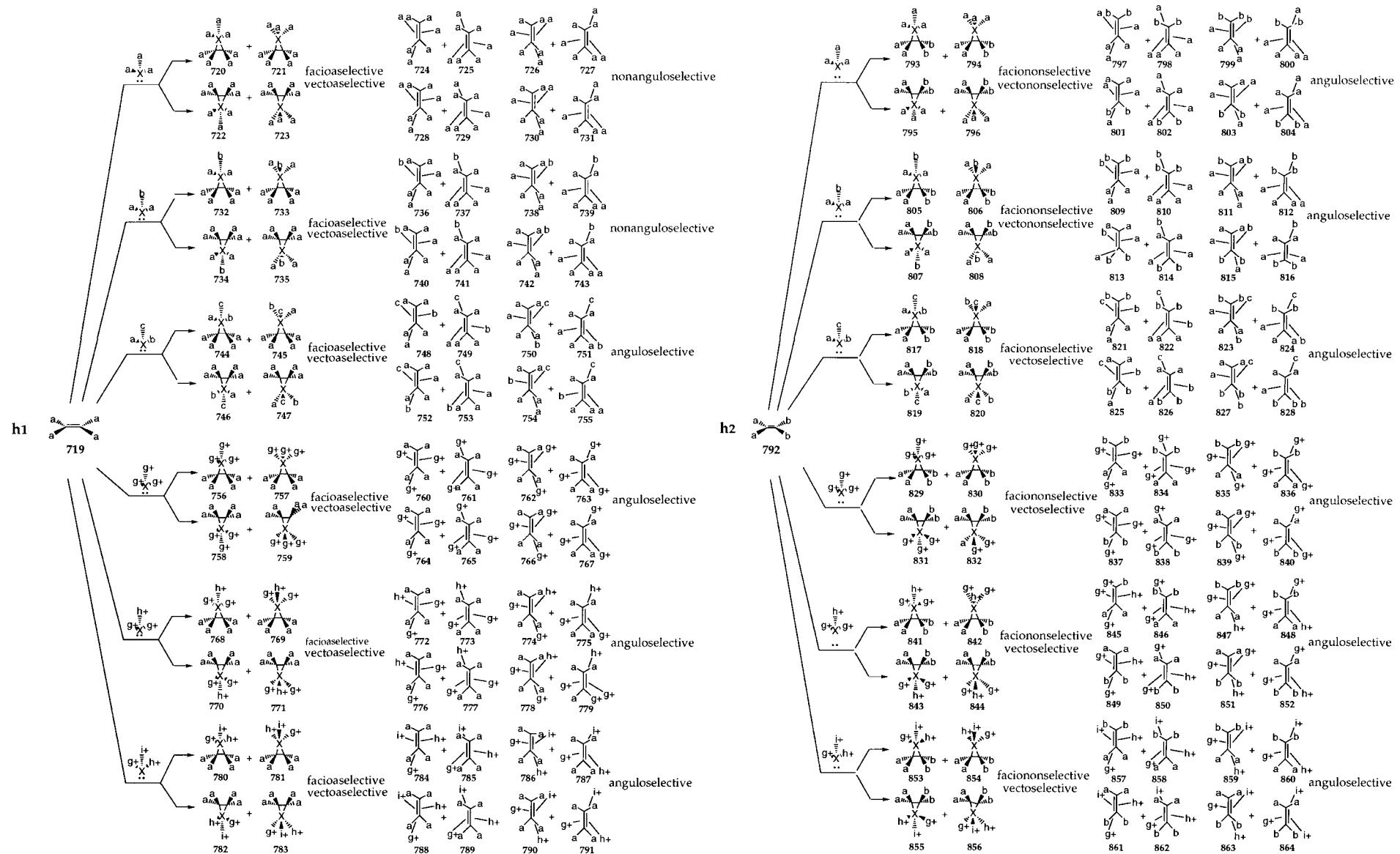
**Figure 14.14.** Relationship of Facioselectivity, Vectoselectivity and Anguloselectivity for 1,2-Ligogenic Processes at Enantiotopic Faces e



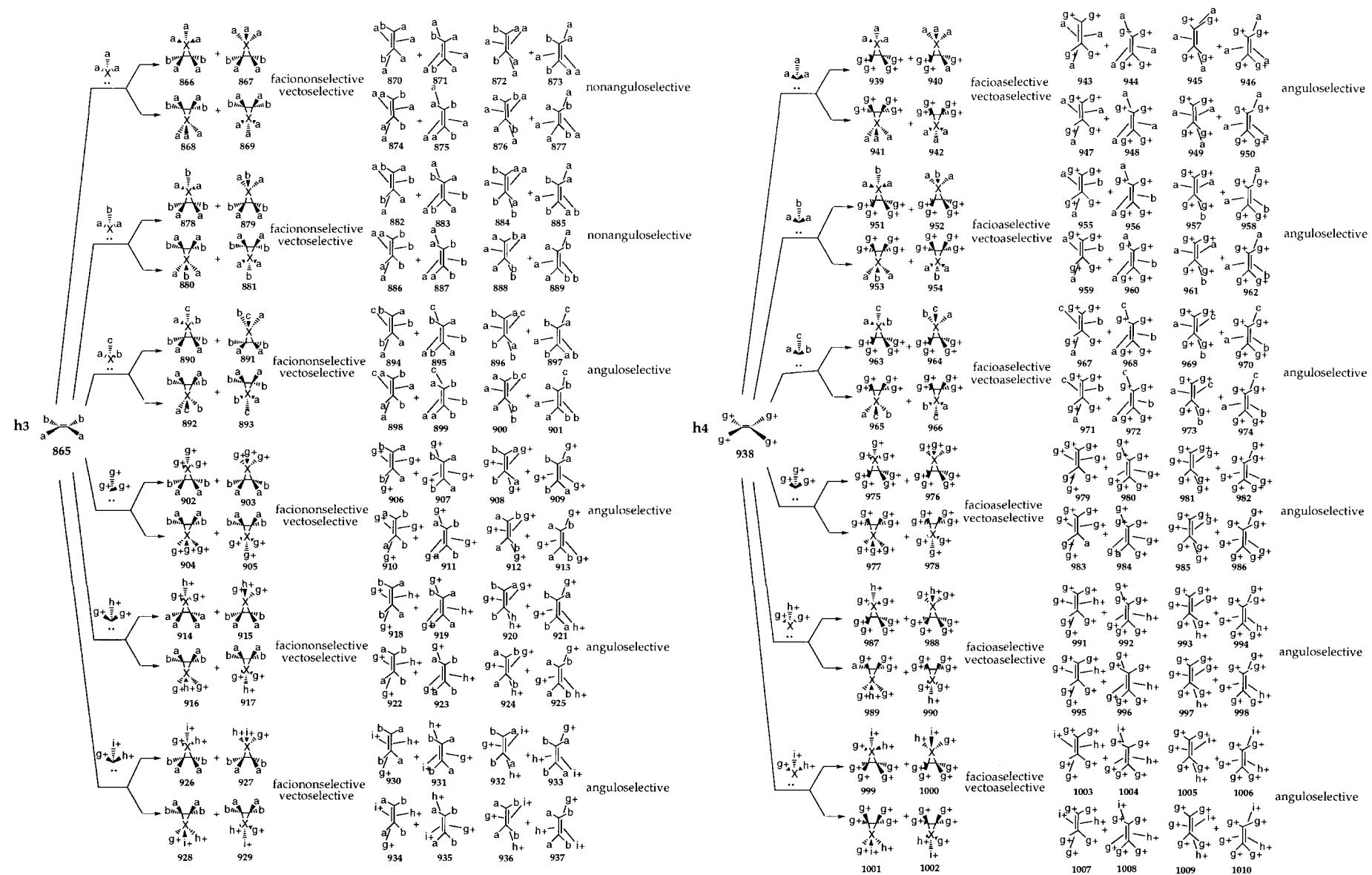
**Figure 14.15.** Relationship of Facioselectivity, Vectoselectivity and Anguloselectivity for 1,2-Ligogenic Processes at Diastereotopic Faces **d1-d2**



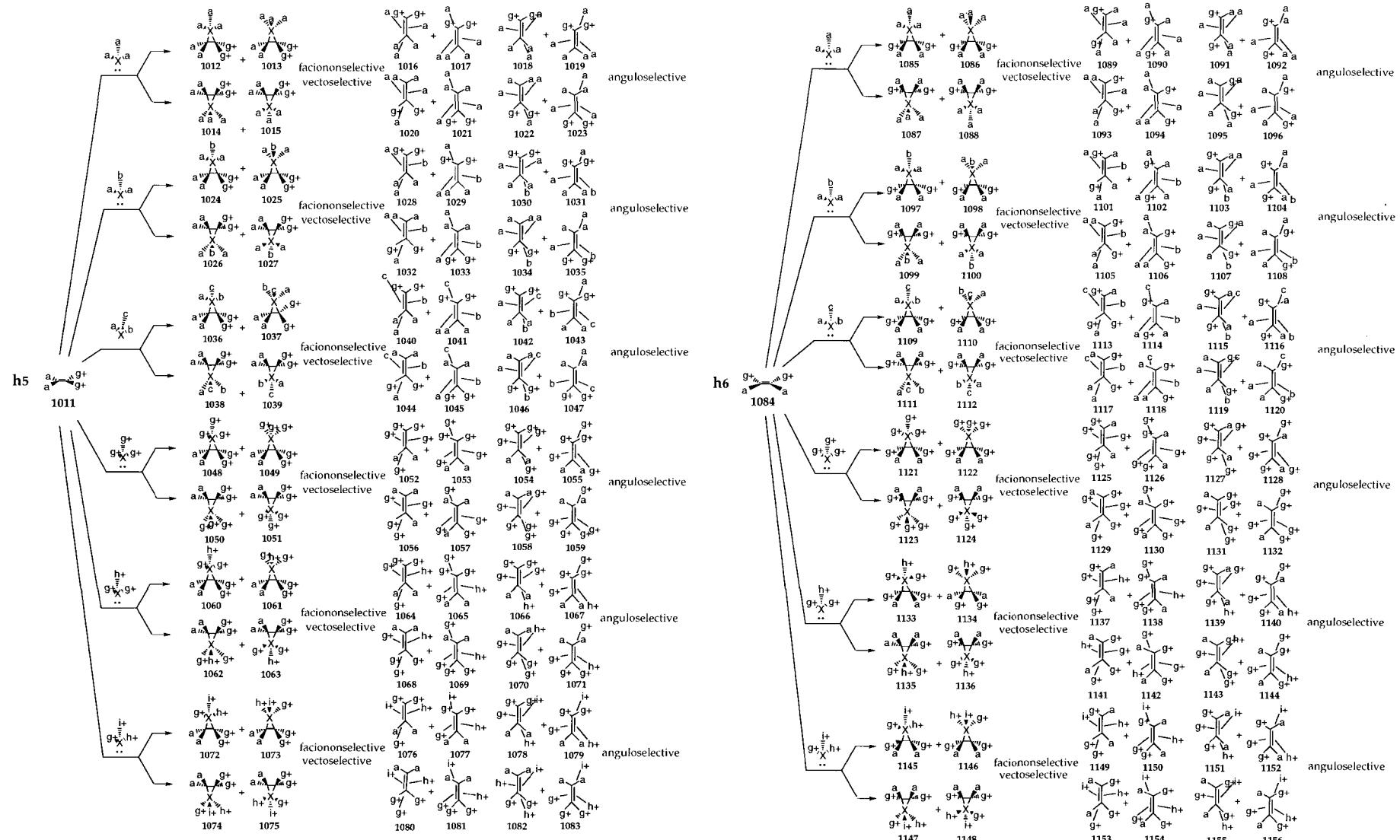
**Figure 14.16.** Relationship of Facioselectivity, Vectoselectivity and Anguloselectivity for 1,2-Ligogenic Processes at Diastereotopic Faces **d3-d4**



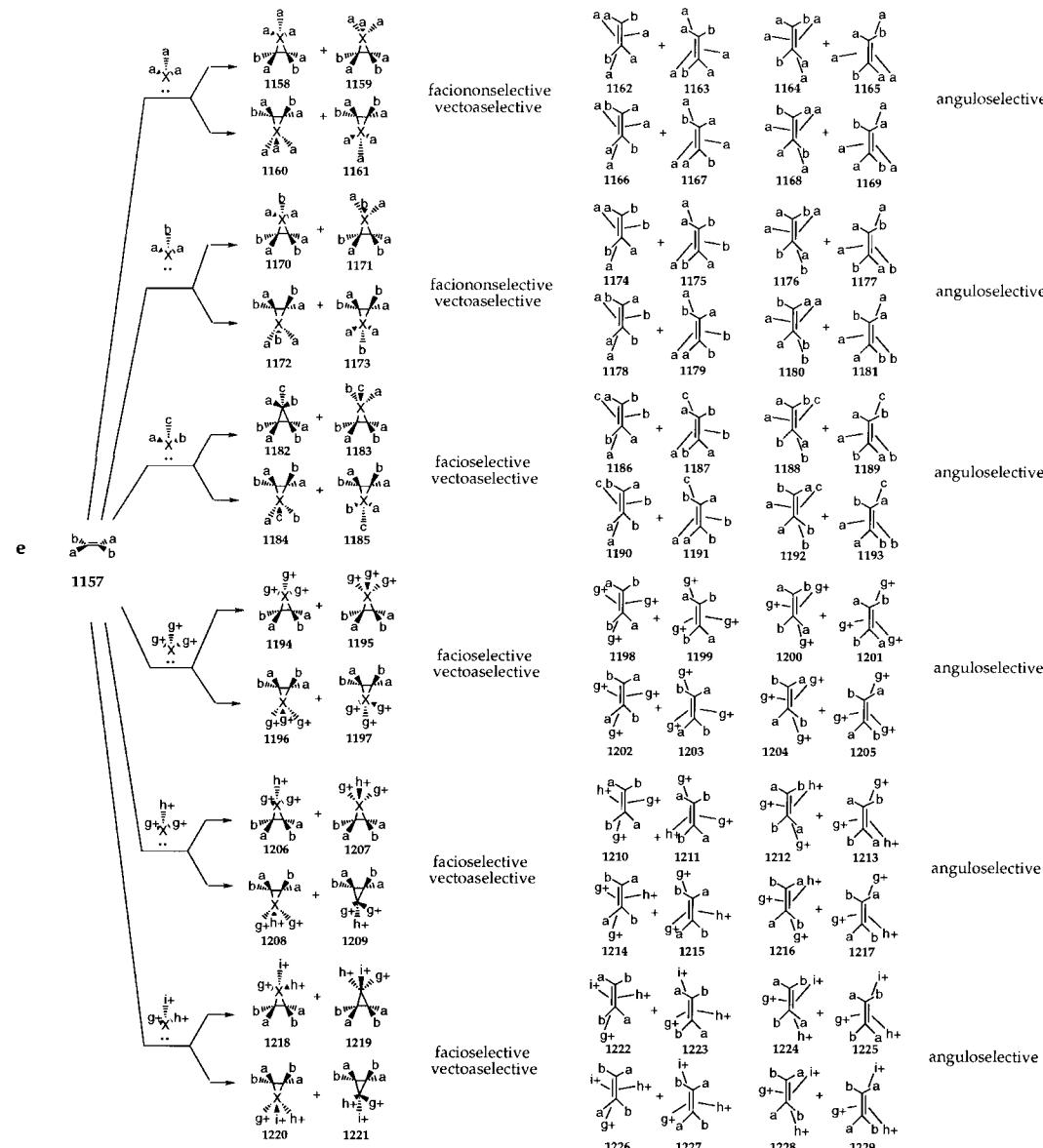
**Figure 14.17.** Relationship of Facioselectivity, Vectoselectivity and Anguloselectivity for 1,2-Ligogenic Processes at Homotopic Faces **h1-h2**



**Figure 14.18.** Relationship of Facioselectivity, Vectoselectivity and Anguloselectivity for 1,2-Ligogenic Processes at Homotopic Faces **h3-h4**



**Figure 14.19.** Relationship of Facioselectivity, Vectoselectivity and Anguloselectivity for 1,2-Ligogenic Processes at Homotopic Faces h5-h6



**Figure 14.20.** Relationship of Facioselectivity, Vectoselectivity and Anguloselectivity for 1,2-Ligogenic Processes at Enantiotopic Faces **e**

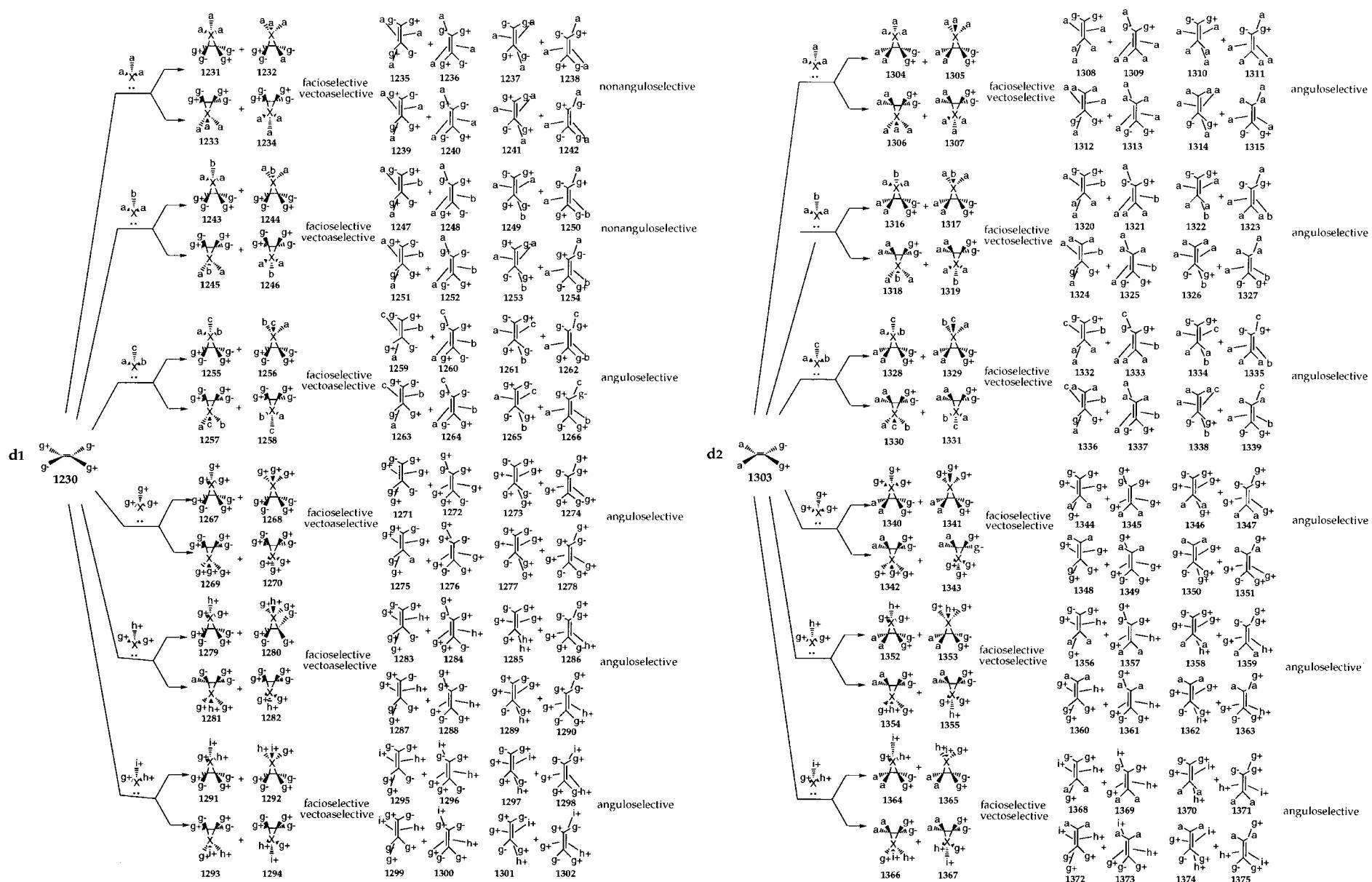
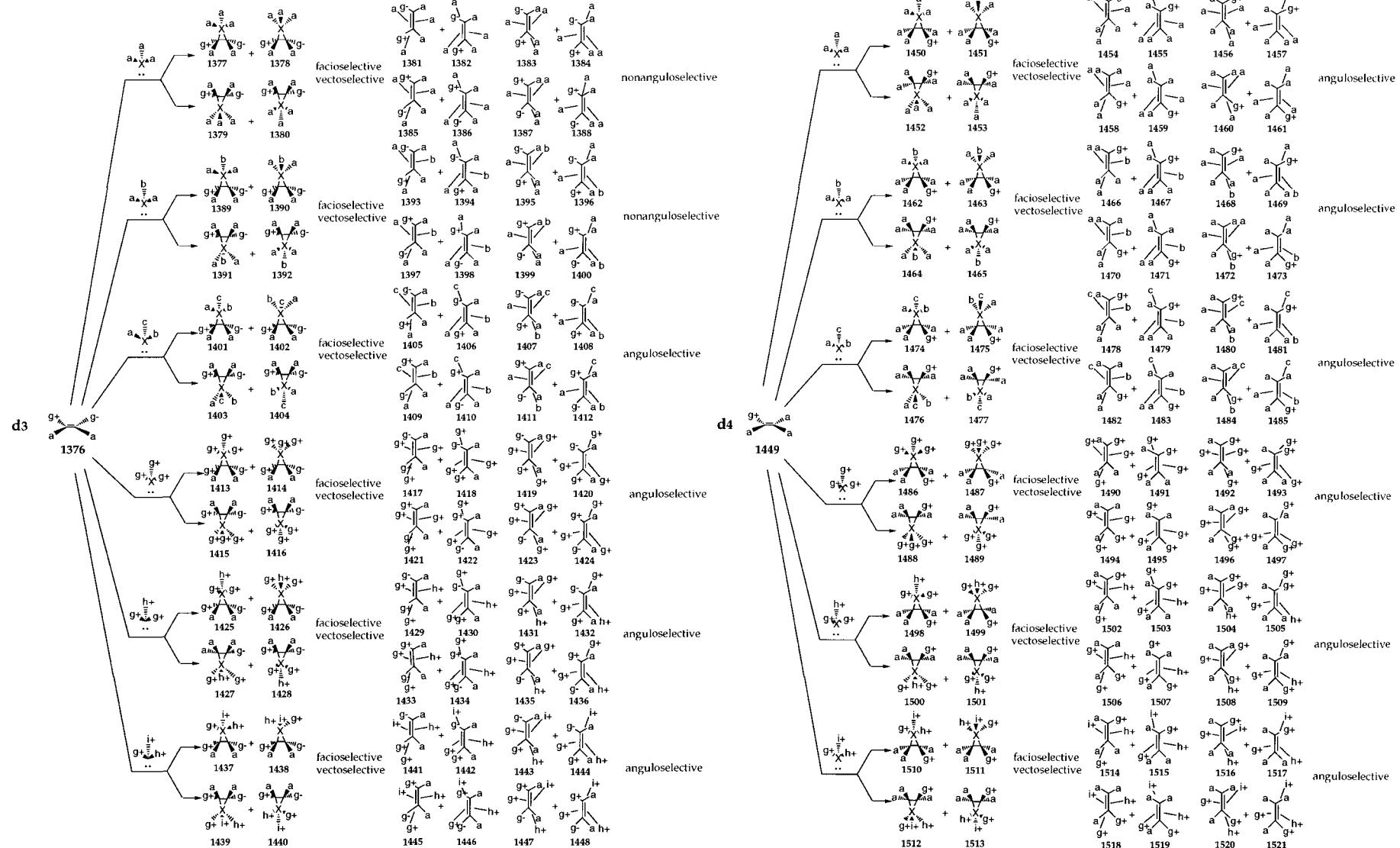


Figure 14.21. Relationship of Facioselectivity, Vectoselectivity and Anguloselectivity for 1,2-Ligogenic Processes at Diastereotopic Faces d1-d2



**Figure 14.22.** Relationship of Facioselectivity, Vectoselectivity and Anguloselectivity for 1,2-Ligogenic Processes at Diastereotopic Faces **d3-d4**

	h1		h2		h3		h4		h5		h6		e		d1		d2		d3		d4	
Quartet Mode	ac	c	ac	c	ac	c	ac	c	ac	c	ac	c	ac	c	ac	c	ac	c	ac	c	ac	c
Aa	± +	+	±		+		+	+	+		+		+			±				+		
An					+																	
Na													+									
Nn			+																			
Ns			±	+	± +	+			+	+	+	+										
Sa														+	± +	+			+			
Sn																+		+				
Ss																± +	+	± +	+	+	+	

±: nonanguloselective  
 +: anguloselective  
 ± +: nonanguloselective or anguloselective

ac : achiral reagent  
 c : chiral reagent

**Table 14.1.** Facioselectivity-Vectoselectivity-Anguloselectivity in Conjunctive Processes at Molecular Faces

### C. Diastereotopic Faces d1-d4

The additions of the divalent carbenes :Ca<sub>2</sub>, :Cab, :Cag<sup>+</sup>, and :Cg<sup>+</sup>g<sup>-</sup> (Figures 14.15-14.16, pp. 171-172) and trivalent species :Xa<sub>3</sub>, :Xa<sub>2</sub>b, :Xabc, :Xg<sub>3</sub><sup>+</sup>, :Xg<sub>2</sub><sup>+</sup>h<sup>+</sup>, and :Xg<sup>+</sup>h<sup>+</sup>i<sup>+</sup> (Figure 14.21-14.22, pp. 177-178) to alkenes with diastereotopic faces lead to the following generalizations:

1. Nonanguloselective (enantioangular arrangements) processes are possible only on faces d1-d3 (found in achiral substrates); there is no nonanguloselectivity on face d4 (found in chiral substrates).
2. All nonanguloselective processes on faces d1-d3 (found in achiral substrates) occur with achiral reagents.
3. Anguloselective (diastereoangular arrangements) processes can occur on faces d1-d4; these encompass achiral as well as chiral substrates.
4. An anguloselective process at a given diastereotopic face (d1-d3 of achiral substrates, and face d4 of chiral substrates) may occur with either an achiral or chiral reagent.

The results of the three-way correlations of facioselectivity, vectoselectivity and anguloselectivity, for all cases, are summarized in Table 14.1 (p. 179). The following generalizations emerge:

1. Nonanguloselective (enantioangular arrangements) processes are possible only on faces h1-h3, d1-d3 (all of which are found in achiral substrates); there is no nonanguloselectivity on enantiopic face e (achiral substrate) or faces h4-h6, and d4 (all of which are found in chiral substrates).
2. All nonanguloselective processes on faces h1-h3, d1-d3 (all found in achiral substrates) occur with achiral reagents.
3. Anguloselective (diastereoangular arrangements) processes can occur on all faces – h1-h6, e and d1-d4; these encompass achiral as well as chiral substrates.
4. An anguloselective processes on a given face (h1-h3, e, d1-d3 of achiral substrates, and faces h4-h6, d4 of chiral substrates) may occur with either an achiral or chiral reagent.
5. Nonanguloselective processes can accompany afacioselective, nonfacioselective or facioselective processes. Anguloselective processes can also go hand in hand with afacioselective, nonfacioselective or facioselective processes.
6. Nonanguloselective processes may characterize avectoselective, vectononselective or vectoselective processes. Anguloselectivity may also partake in avectoselective, vectononselective or vectoselective processes.

### Summary

We defined an *angulospecific state* as the exact alignment of two interacting moieties with respect to each other, at a given point in time, for a given vectospecific or nonvectospecific alignment. We discussed the novel concept of *anguloselectivity* – the preference for one angulospecific state over another (or others). We demonstrated that vectoselectivity and anguloselectivity are conceptually distinct, and indeed, anguloselectivity complements the concept of vectoselectivity.

Vectoselectivity is based on a competition between two (or more) pathways proceeding through *vectospecific alignments* which are interrelated by vectorial *alteration* or *reversal* of one vectogenic reactant. Hence, vectoselectivity characterizes the preferential *connectivity* between the interacting moieties.

In contrast, anguloselectivity is defined for a *specific vectoselective* (or *vectospecific*) mode, and manifests itself in the competition between two (or more) pathways proceeding through different *angulospecific states* en route to one and the same product.

**Choosing the Fiducial Group in (1,1)-Ligogenic Processes**

C Atomic Orbital	Monojunctive Element	Ligands	Fiducial Group
sp <sup>3</sup>	1	a	a
	2	a <sub>2</sub>	of the two a's the one that has the smaller $\theta (>0 \text{ or } <0)$
		ab	a (a>b)
	3	a <sub>3</sub>	of the three a's the one that has the smallest $\theta (>0 \text{ or } <0)$
		a <sub>2</sub> b	b
		abc	a (if a>b,c according to the Sequence Rule)
sp <sup>2</sup>	4	a <sub>2</sub>	of the two a's the one that has the smaller $\theta (>0 \text{ or } <0)$
		ab	a (a>b)
	5	electron pair	imaginary point along axis of orbital
	6	electron pair	imaginary point along axis of orbital
sp	7	a <sub>3</sub>	of the three a's the one that has the smallest $\theta (>0 \text{ or } <0)$
		a <sub>2</sub> b	b
		abc	a (if a>b,c according to the Sequence Rule)
p	8	a <sub>2</sub>	of the two a's the one that has the smaller $\theta (>0 \text{ or } <0)$
		ab	a (a>b)
	9	a <sub>3</sub>	of the three a's the one that has the smallest $\theta (>0 \text{ or } <0)$
		a <sub>2</sub> b	b
		abc	a (if a>b,c according to the Sequence Rule)
10-13			skeletal atom X,Y,Z,W (none of which is involved in the formation of the $\sigma$ bond)

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## ADDENDA

### Addendum C

#### On a Unified and General Specification of Paired Ligands and Molecular Faces

In the realm of intramolecular relationships, two ligands, two bonds, two molecular faces or two molecular segments are either stereotopic or nonstereotopic, *regardless* of the chirality or achirality of the molecular field. If stereotopic, such nuclei, bonds, faces or segments are homotopic, enantiotopic or diastereotopic. We hereby present a simple, unified, and general notation for the specification of paired (geminal) ligands (at tetrahedral and trigonal carbons) and paired molecular faces.

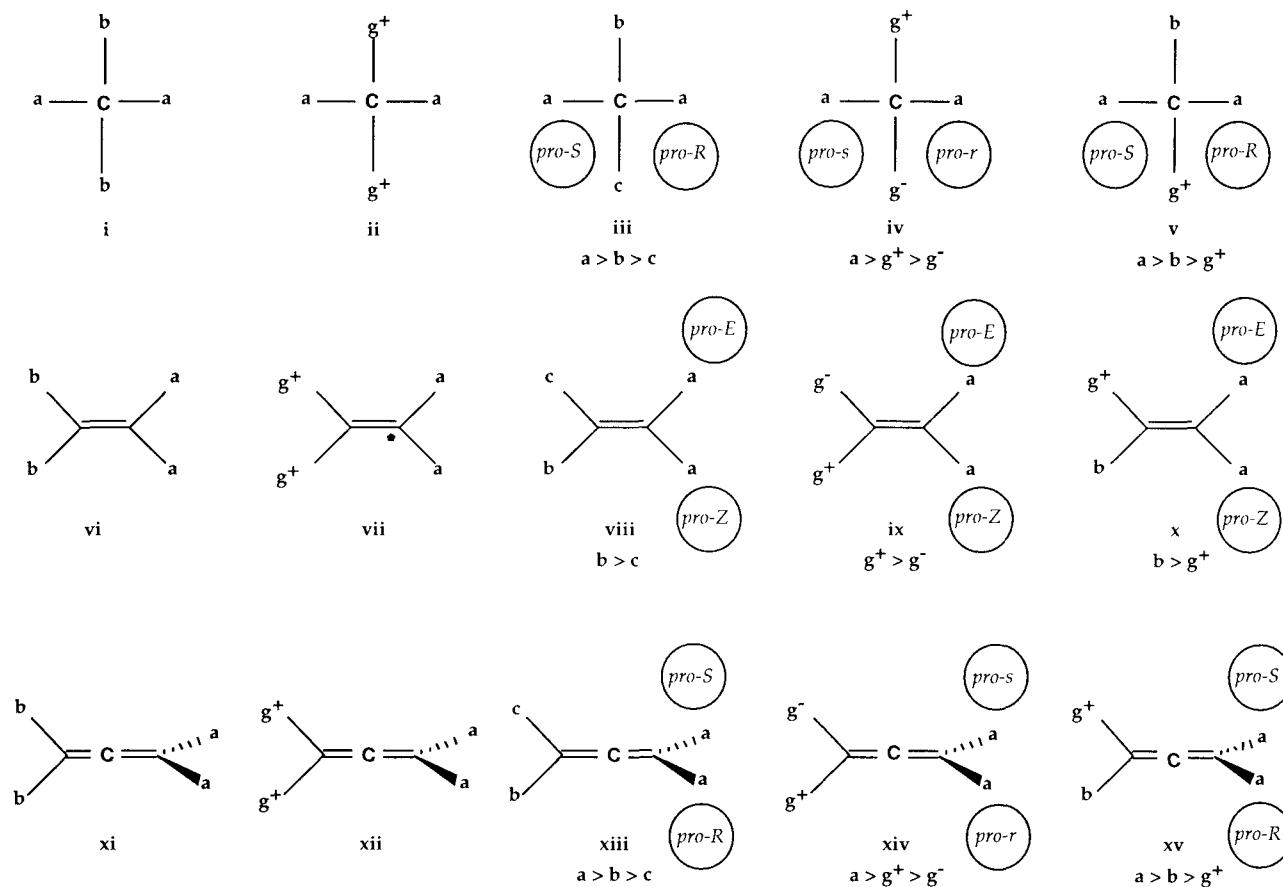
Paired geminal isomorphic ligands are necessarily stereotopic. Stereotopic ligands are not necessarily paired; they may be linked to identical or distinct skeletal/nonskeletal atoms. Similarly, paired molecular faces are necessarily stereotopic. However, stereotopic faces are not necessarily paired; they may correspond to topologically distinct portions of a molecule. We denote homotopic *ligands* by the letter h, enantiotopic ligands, by e and  $\ominus$ , and diastereotopic ligands, by d and f. Further, we denote homotopic *faces* by the letter H, enantiotopic faces, by E and  $\Xi$ , and diastereotopic faces, by D and F. If the achiral/chiral nature of the molecular field is relevant in a given instance, the chirality of the said field may be incorporated in the specification of paired ligands/faces using asterisks (see Table C.1).

#### I. Known Descriptors of Paired Ligands

In each of molecules i and ii in Figure C.1, nuclei a are homotopic; in molecule iii, they are enantiotopic; and, in iv and v, they are diastereotopic. And yet, *enantiotopic* ligands a in iii, and *diastereotopic* ligands a in v, are currently designated by the *same pro-R/pro-S* prochirality descriptors. Furthermore, *different* notations are used for *diastereotopic* ligands of v (*pro-R/pro-S*), on the one hand, and *diastereotopic* ligands of iv (*pro-r/pro-s*), on the other. In all the above cases, the existing notations are based on prochirality descriptors.

Further, in the case of molecules vi and vii, nuclei a are homotopic; in viii, they are enantiotopic; and in ix and x, they are diastereotopic. And yet, the *same pro-E/pro-Z* notation is used to designate *enantiotopic* ligands a in viii, and *diastereotopic* ligands a in ix and x. Here, the designations utilize prostereotopicity descriptors. Finally, there is no descriptor for homotopic ligands in vi and vii.

Last but not least, in each of molecules xi-xii, nuclei a are homotopic; in xiii, they are enantiotopic; in xiv and xv, they are diastereotopic. And yet, the *same pro-R/pro-S* notation is used to designate *enantiotopic* ligands a in xiii, and *diastereotopic* ligands a in xv. Furthermore, *different* notations are used for *diastereotopic* ligands of xiv (*pro-r/pro-s*), and *diastereotopic* ligands of xv (*pro-R/pro-S*). Here too, prochirality descriptors are used.



*a, b* = achiral ligands  
*g<sup>+</sup>, g<sup>-</sup>* = chiral ligands

**Figure C.1.** Known Descriptors of Paired Prochiral and Prostereogenic Ligands

Clearly, these prochiral and prostereotopic descriptors for paired ligands in molecules i-xv constitute a duplex system and, in any case, do not indicate the stereotopic relationships of the ligands in question. We propose an alternate, unified notation that specifies the concise stereotopicity of paired ligands on the one hand, and paired faces, on the other. The notation is further extended to accommodate the chirality of the molecular field (chirotropicity).

## II. Proposed Descriptors of Paired Ligands

There are five major classes of stereotopic ligands - achirohomotopic, chirohomotopic enantiotopic, achirodiastereotopic and chirodiastereotopic. Achirohomotopic (h/h), enantiotopic (e\*,\* $\ominus$ ) and achirodiastereotopic (d/f) ligands are found in achiral molecules; chirohomotopic (h\*,h\*) and chirodiastereotopic (d\*,f\*) ligands are found only in chiral molecules. The asterisks in the h\*,h\* and d\*,f\* designations indicate that the paired chirohomotopic and chirodiastereotopic ligands are chirotopic. Unasterisked descriptors h,h and d,f indicate that the homotopic and diastereotopic ligands are achirotopic. In contradistinction, enantiotopic ligands e\*,\* $\ominus$  are situated in achiral molecules; nevertheless, they are always chirotopic; their descriptors are asterisked. The proposed descriptors are shown in Figure C.2.

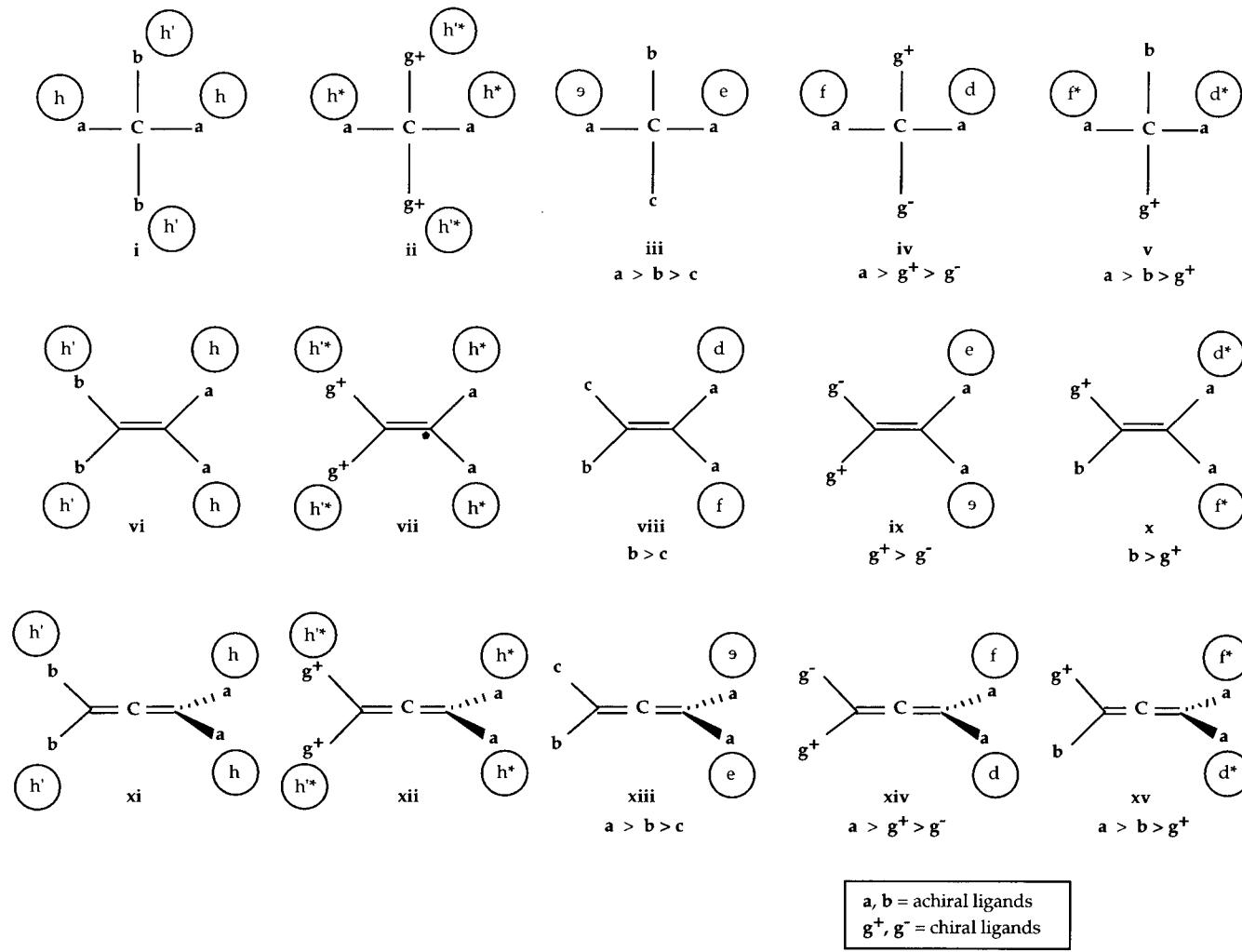
Table C.1 summarizes the known and proposed descriptors and shows the correspondence between the stereotopicity of ligands (at  $sp^3$  and  $sp^2$  centers) and prochirotopicity/prostereogenicity of these ligands:

Molecule	Stereotopicity of Ligands a (i-xv)	Current Descriptor	Proposed Descriptor	Chirality of Molecule
i	homotopic	-	h,h	achiral
ii	homotopic	-	h*,h*	chiral
iii	enantiotopic	pro-R, pro-S	e*,* $\ominus$ <sup>157</sup>	achiral
iv	diastereotopic	pro-r, pro-s	d,f	achiral
v	diastereotopic	pro-R, pro-S	d*,f*	chiral
vi	homotopic	-	h,h	achiral
vii	homotopic	-	h*,h*	chiral
viii	enantiotopic	pro-E, pro-Z	e*,* $\ominus$ <sup>158</sup>	achiral
ix	diastereotopic	pro-E, pro-Z	d,f	achiral
x	diastereotopic	pro-E, pro-Z	d*,f*	chiral
xi	homotopic	-	h,h	achiral
xii	homotopic	-	h*,h*	chiral
xiii	enantiotopic	pro-R, pro-S	e*,* $\ominus$	achiral
xiv	diastereotopic	pro-r, pro-s	d,f	achiral
xv	diastereotopic	pro-R, pro-S	d*,f*	chiral

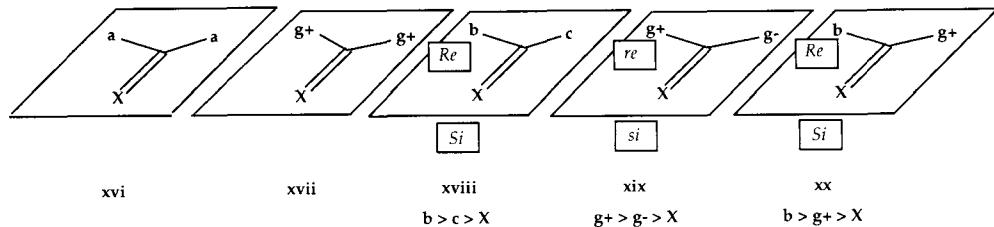
**Table C.1.** Comparison of Current and Proposed Descriptors of Paired Stereotopic Ligands

## III. Known Descriptors of Paired Molecular Faces

In Figure C.3, each of molecules xvi and xvii has homotopic faces; those in xviii are enantiotopic, whereas faces in xix and xx are diastereotopic. The same *Re/Si* descriptor is applied to *enantiotopic* faces of xviii, and *diastereotopic* faces of xx. Furthermore, *different* descriptors are used for *diastereotopic* faces of xix (*re/si*), and *diastereotopic* faces of xx (*Re/Si*).

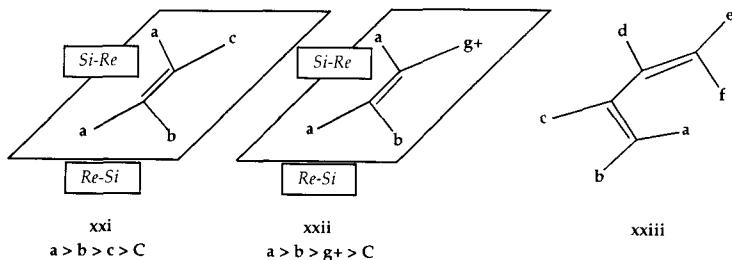


**Figure C.2.** Proposed Descriptors of Paired Prochiral and Prostereogenic Ligands



**Figure C.3.** Known Descriptors of Monocentric Paired (Stereotopic) Faces

In the case of bicentric<sup>159</sup> systems xxi and xxii, descriptors such as *Re-Re*, *Si-Re* or *Si-Si* do not reveal the stereotopicity of a molecular face, nor do they reveal stereochemical relationships between (paired) stereotopic molecular faces. A given *Si-Re* face may be enantiotopic (xxi) or diastereotopic (xxii) with respect to the paired *Re-Si* face. For polycentric cases, such as diene xxiii (tetracentric case), the extension of the *Re/Si* notation becomes undesirably cumbersome and confusing. In effect, there is no alternative system for naming planar molecular faces. Currently, in Diels-Alder reactions and sigmatropic rearrangements, one atom in one of the reactants is picked at random to designate the desired face; such a designation can be misleading. The novel descriptors given below overcome these difficulties, and provide an exact, simple and universal description of any set of paired molecular faces. The basis of this classification is stereotopicity, exactly as in the case of ligands.

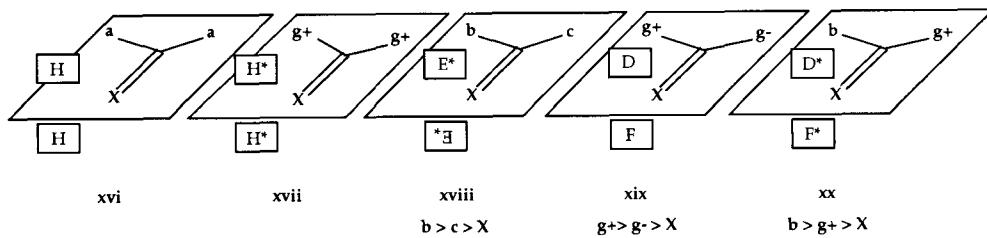


**Figure C.4.** Known Descriptors of Polycentric Paired (Stereotopic) Faces

#### IV. Proposed Descriptors of Paired Molecular Faces

A detailed analysis of stereotopic faces in organic molecules was given in Chapter 12. The eleven subclasses of stereotopic faces, in effect, belong to five categories - achirohomotopic, chirohomotopic enantiotopic, achirodiastereotopic and chirodiastereotopic. Achirohomotopic (H/H), enantiotopic (E\*,\*E) and achirodiastereotopic (D/F) faces are located in achiral molecules; chirohomotopic (H\*,H\*), and chirodiastereotopic (D\*,F\*) faces are found only in chiral molecules. The asterisks in the H\*,H\* and D\*,F\* descriptors indicate that the paired

chirohomotopic and chirodiastereotopic faces are chirotopic. Unasterisked descriptors H,H and D,F indicate that the homotopic and diastereotopic faces are achirotopic. In contradistinction, enantiotopic faces E\*,E\* are situated in achiral molecules; nevertheless, they are always chirotopic; their descriptors are asterisked. The proposed descriptors are illustrated in Figure C.5 and given in Table C.2 below.



**Figure C.5.** Proposed Descriptors of Paired Stereotopic Faces

As in the case of ligands, there is a correspondence between stereotopicity and chirotopicity of stereotopic faces. Table C.2 indicates the relationship between the stereotopicity of molecular faces and the in-plane, 2D-clocksense (chirotopicity) of these faces. The latter clocksense is defined with respect to an off-plane observer, on *either* side of the molecular face.

Molecule	Stereotopicity of Faces (xvi-xx)	Current Descriptor	Suggested Descriptor	Chirality of Molecule
xvi	homotopic	-	H,H	achiral
xvii	homotopic	-	H*,H*	chiral
xviii	enantiotopic	Re, Si	E*,E <sup>160</sup>	achiral
xix	diastereotopic	re, si	D,F	achiral
xx	diastereotopic	Re, Si	D*,F*	chiral

**Table C.2.** Comparison of Current and Proposed Descriptors for Paired Stereotopic Faces

The specification of faces of alkenes, dienes and other systems by the proposed system requires criteria for determining the 2D-clocksense in these systems. This is done in Addendum D for a wide range of acyclic and cyclic systems.

The proposed descriptors of homotopic/diastereotopic faces/ligands establish a common basis for the discussion of their reactivities and selectivities (*vide infra*). These descriptors are not intended to replace either the *pro-R*, *pro-S*, *pro-r*, *pro-s* descriptors for ligands, or the *Re/Si/re/si* descriptors for faces. The proposed specifications are short, concise, and universal; they emphasize the similarities in reactivity for ligands *and* faces; further, they reveal the stereotopic nature of the ligands (homotopic vs. enantiotopic vs. diastereotopic), as well as the chirotopicity vs. achirotopicity of the molecular environment.

## Addendum D

### Specification of Stereotopic Molecular Faces

The stereochemical designation of stereotopic/paired polycentric planar molecular faces (half-spaces) has remained unsolved. To date, there is no generalized system for assigning specific stereodescriptors to such faces. Designations of molecular faces as *Si/Re*, *si/re* are for monocentric planar moieties, while  $\alpha/\beta$ ,<sup>161</sup> *B/N*, *b/n*,<sup>162</sup> *pro-B/pro-N*, *pro-b/pro-n*, *ci/tr*,<sup>163</sup> *exo/endo*, *syn/anti*, concave/convex, have their usefulness for finite sets of molecules, in disparate families of organic compounds. In this Addendum we advance a novel, simple, and universal system (HED system) for specifying any molecular face of acyclic and cyclic planar systems. The HED system (i) identifies the relative stereotopicity of the paired faces (ii) differentiates between the stereotopic faces, and (iii) reveals chirotopicity of the molecule. The system incorporates the existing CIP rules for determining *R/S*,<sup>164</sup> as well as the Blackwood *E/Z* configurations.<sup>165</sup>

The planar molecular entities we will treat include acyclic systems **A1-A12** and monocyclic systems **C1-C4** (Figure D.1). Defining a common, finite and simple set of rules for these widely diverse molecular systems presents a challenge. Attention to special structural features in each family of compounds, however, does simplify the task at hand (*vide infra*).

The rules we will present help one assign a simple and unambiguous stereotopicity descriptor - *H*, *H\**, *E\**, *\*E*, *D*, *D\**, or *F\** - to each molecular face of an acyclic or monocyclic planar moiety. Paired homotopic (equivalent) faces are designated by the same descriptor *H/H* or *H\*/H\**. For enantiotopic faces, the rules will help determine which face is *E\** and which one is *\*E*; for diastereotopic faces they will help tell which face is *D*, which one is *F*, which one is *D\** and which one is *F\**. The rules for each molecular system will be detailed below.

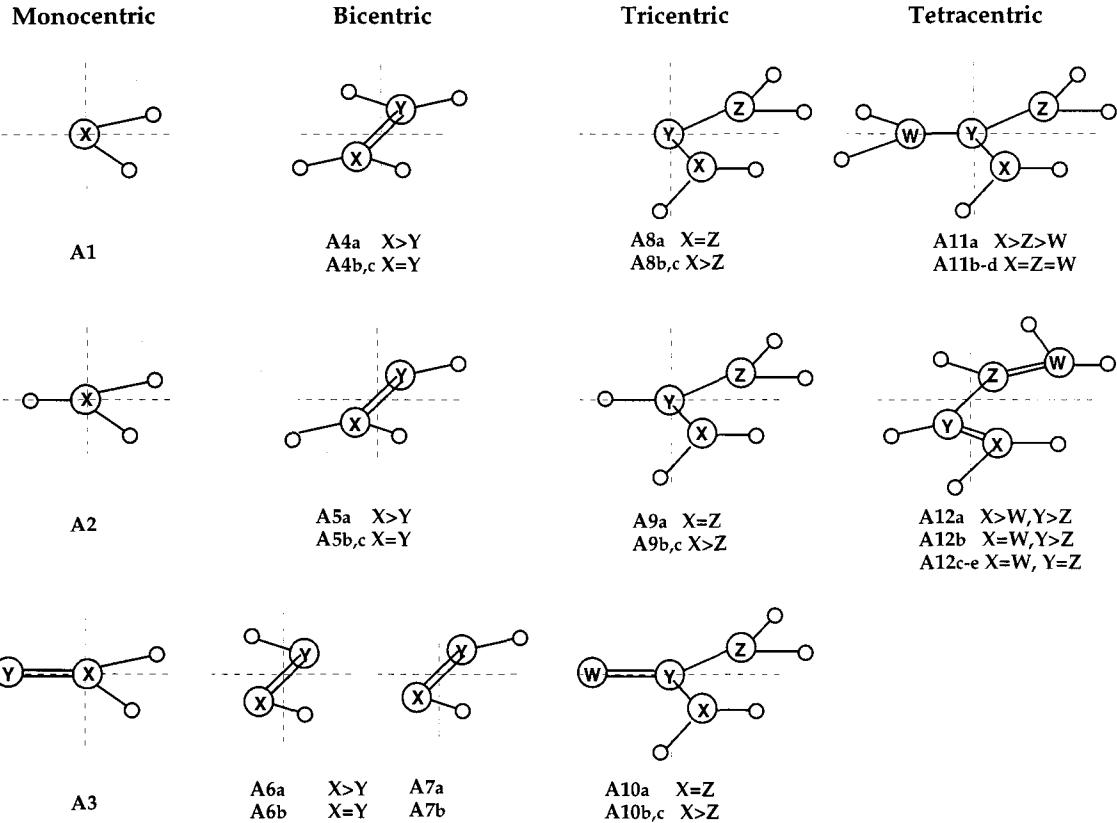
For space limitations, we limit the discussion to 3-6 membered monocyclic rings; the method is extendable to larger rings, and to alternant/non-alternant conjugated bicyclic and oligocyclic systems. In a molecule with two or more detached, isolated, or independent moieties - each with two stereotopic half-spaces, each moiety is considered independently.

#### I. Generalized Approach for Acyclic and Cyclic Systems

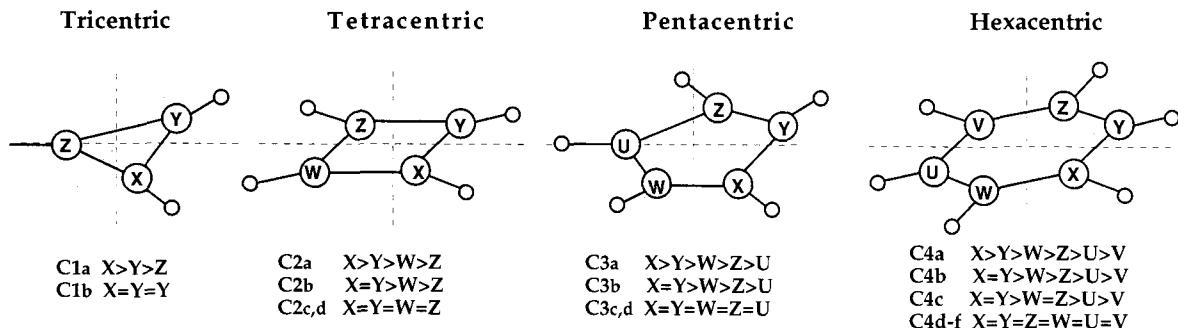
The assignment of stereodescriptors to molecular faces consists of the following steps:

- (a) Establish the stereotopic relationship between the paired faces - homotopic, enantiotopic, or diastereotopic.

## ACYCLIC CASES



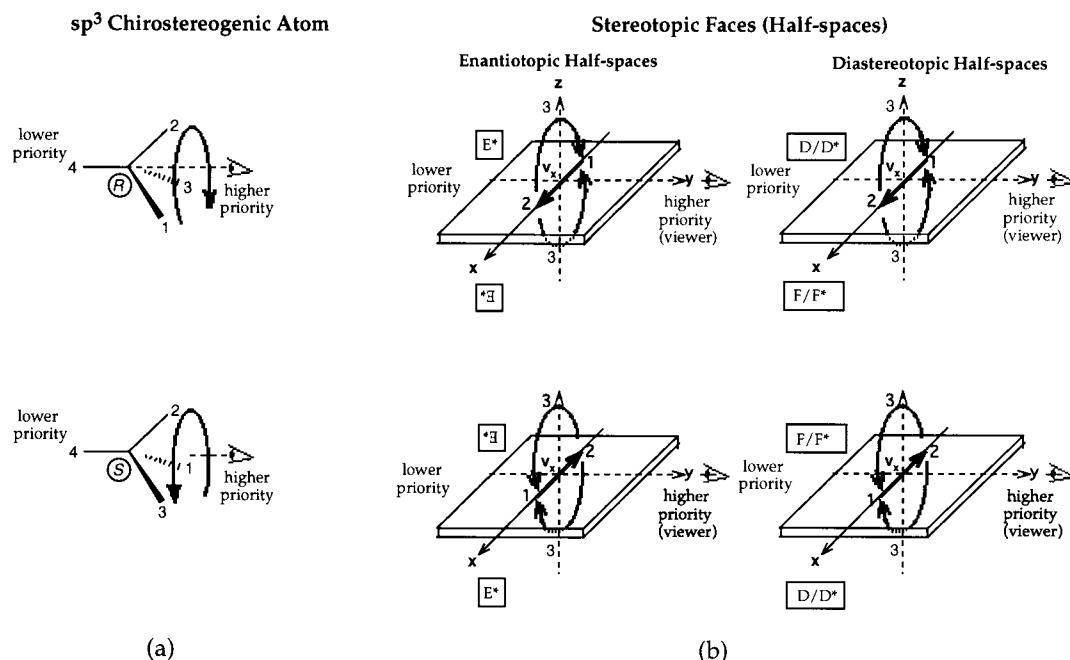
## CYCLIC CASES



**Figure D.1.** Monocentric, Bicentric, Tricentric Acyclic Prototypes A1-A12 and Cyclic Prototypes C1-C4

- (b) Orient properly the planar moiety of the molecule relative to the viewer, (or, equivalently, properly position the viewer relative to the planar moiety of the molecule).
- (c) Determine a specific clocksense (i.e. clockwise or anticlockwise) of a  $1 \rightarrow 2 \rightarrow 3$  priority sequence (*vide infra*). Clocksense is needed only for enantiotopic and diastereotopic cases.
- (d) Assign  $E^*$ , D, or  $D^*$  to the face relating to the clockwise sequence; assign  $*E$ , F or  $F^*$  to the paired face corresponding to a counterclockwise sequence.

To clarify rule (b) above, we show, in Figure D.2, the similarity between viewing of stereotopic half-spaces of acyclic/cyclic systems (to determine specific stereodescriptors), and that of an  $sp^3$  stereogenic atom (to determine R/S configurations). In both cases, the viewer looks at the molecular entity from a *preferred* side. In the case of the stereogenic atom  $C_{abcd}$ , the preferred side for the viewer is *opposite* to the ligand of lowest priority, or the side of higher priority (Figure D.2a). Analogously, one views the planar moiety in the XY-plane from the side *opposite* to skeletal atom(s) or ligands of lowest priority, or, on the side of skeletal atom(s) or ligands of higher priority (Figure D.2b) (*vide infra*).



**Figure D.2.** Viewing the  $sp^3$ -Chirostereogenic Atom (Sequence Rule) and Stereotopic Faces

With respect to rule (c) above, for the stereogenic atom, the viewer determines a  $1 \rightarrow 2 \rightarrow 3$  clocksense in a plane *perpendicular* to the axis of viewing (Figure D.2a).<sup>166</sup> For the planar moiety, the viewer similarly defines a  $1 \rightarrow 2 \rightarrow 3$  clocksense in a plane (parallel to or coincident with the XZ plane) *perpendicular* to the axis of viewing (Y-axis) (Figure D.2b). The alternative in-plane three-point priority sequence (as in the simplest case of *Si/Re* of monocentric systems) is much more cumbersome for bicentric and more complex systems, and is to be avoided.

For the chirostereogenic atom, the  $1 \rightarrow 2 \rightarrow 3$  clocksense is based on the Sequence Rule (CIP Rules),<sup>164</sup> (the clockwise sequence of ligands defines an *R* (*rectus*) configuration; the counterclockwise sequence defines an *S* (*sinister*) configuration; Figure D.2a). In contradistinction, for the planar moiety, the  $1 \rightarrow 2 \rightarrow 3$  clocksense is based on a vector  $v_x$  and a phantom point; the vector  $v_x$ <sup>167</sup> (in the XY-plane) defines the  $1 \rightarrow 2$  (higher to lower priority) portion of the  $1 \rightarrow 2 \rightarrow 3$  sequence, and the phantom point - either above or below the XY-plane - is always terminus 3 in the  $1 \rightarrow 2 \rightarrow 3$  sequence (Figure D.2b). The exact location of the point is unimportant. It is either in the upper half-space, or, in the lower one. In any case it is *off-the-plane*.

If the latter phantom point is above the plane, a clockwise  $1 \rightarrow 2 \rightarrow 3$  sequence leads to the "top" (or "bottom" face); if the phantom point is below the plane, an anticlockwise  $1 \rightarrow 2 \rightarrow 3'$  sequence points to the "bottom" face (or "top" face). If the faces are enantiotopic, a clockwise  $1 \rightarrow 2 \rightarrow 3$  sequence leads to top face E\*, whereas an anticlockwise sequence, to bottom face \*E (Figure D.2b). On the other hand, if the faces of an achiral molecule are diastereotopic, a clockwise  $1 \rightarrow 2 \rightarrow 3$  sequence leads to top face D, anticlockwise sequence, to bottom face F (Figure D.2b). For a chiral molecule with diastereotopic faces, clockwise  $1 \rightarrow 2 \rightarrow 3$  sequence leads to top face D\*, anticlockwise sequence, to bottom face F\* (Figure D.2b). As pointed out above, only achiral molecules possess E\*/\*E enantiotopic and D/F diastereotopic faces; and only chiral ones have D\*/F\* diastereotopic faces. (Clearly, no  $1 \rightarrow 2 \rightarrow 3$  sequence exists for homotopic faces, in either achiral or chiral molecules.) One is left with the issue of selecting the proper vector  $v_x$  for each of cases A1-A12 and C1-C4. In the determination of  $v_x$ , one considers skeletal atoms first, followed by the ligands. In sum, the order of priorities is as follows:

A1-A3	m>n>p
A4 -A7	X>Y >> m>n>p>q
A8-A10	X>Z >> m>n>p>q
A11	X>Z>W >> m>n>p>q>t>u
A12	X>W>Y>Z >> m>n>p>q>t>u, and
C1	X>Y>Z >> m>n>p
C2	X>Y>W>Z >> m>n>p>q
C3	X>Y>W>Z>U >> m>n>p>q>r
C4	X>Y>W>Z>U>V >> m>n>p>q>t>u

These are detailed below for each of the generalized systems, and exemplified for specific molecular entities in Figures D.3 (A1-A3, p. 194), D.5 (A4-A7, p. 197), D.7 (A8-A10, p. 200), D.8 (A11, p. 201), D.9 (A12, p. 203), and D.11-D.14 (A1-A3, pp. 206-209).

## II. Acyclic Systems

### A. Monocentric Cases A1-A3

In these three monocentric cases, the center X is assumed to be  $sp^2$ -hybridized - (it could also be  $sp^3$ -hybridized for A1); m,n are ligands that do not lend themselves to effective p-p overlap ( $\pi$ -type) with X.

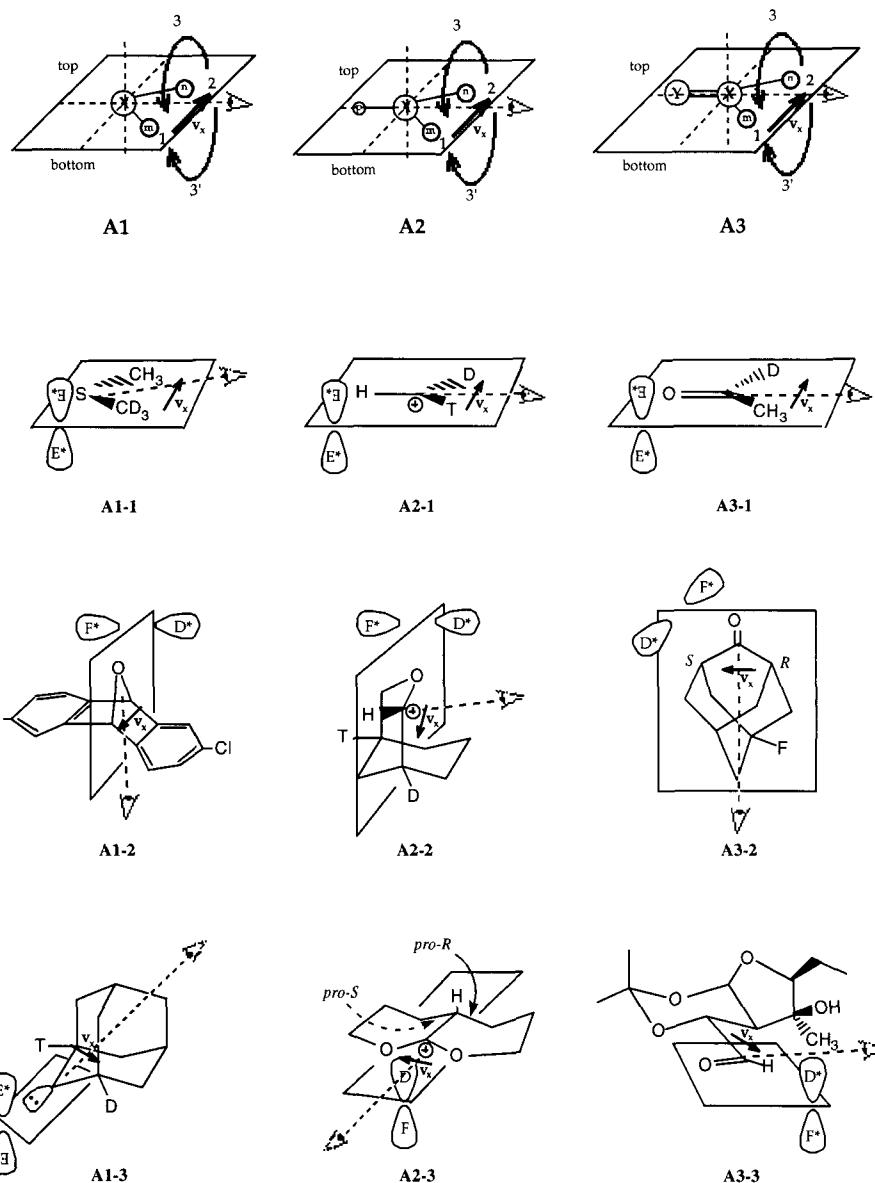
For A1,  $v_x$  is determined by the ligand sequence m->n (m>n by CIP rules). Where constitutional degeneracies occur in ligands m/n, the priority sequence is R>S, E>Z, pro-R>pro-S. Examples of A1 are given in Figure D.3 below; for added clarity we indicate, in each case, vector  $v_x$ , and the

position of the viewer. For achiral **A1-1**, the faces are enantiotopic i.e. E<sup>\*</sup>/<sup>\*</sup>E. Since CD<sub>3</sub>>CH<sub>3</sub>, v<sub>x</sub> is as shown, and the counterclockwise 1→2→3 sequence leads to top face <sup>\*</sup>E, while the clockwise 1→2→3 sequence points to bottom face is E. For chiral tetracyclic ether **A1-2**, the faces are diastereotopic i.e. D<sup>\*</sup>/F<sup>\*</sup>. Since, the rear C(-O) (closer to Br) > front C(-O) (closer to Cl), the orientation of vector v<sub>x</sub> of **A1-2** is as shown; it follows that the clockwise 1→2→3 sequence leads to the "right" face D<sup>\*</sup>, whereas the counterclockwise 1→2→3 sequence terminates at the "left" face F<sup>\*</sup>. In the case of achiral carbene **A1-3**, the faces are enantiotopic i.e. E<sup>\*</sup>/<sup>\*</sup>E. We have yet another position of the viewer, but the *relative* positioning of the viewer and the molecule follows **A1**. Here, C(-T)>C-(D), and thus the top face is E<sup>\*</sup>, and the bottom face is <sup>\*</sup>E.

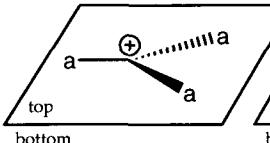
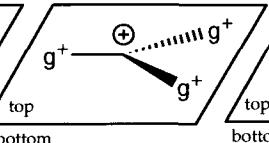
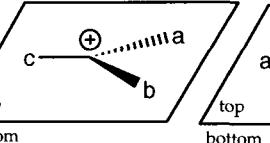
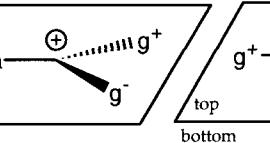
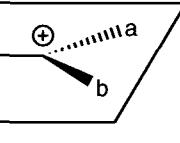
In the case of **A2**, there are three ligand permutations - a<sub>3</sub>, a<sub>2</sub>b, abc. If mnp = a<sub>3</sub>, a<sub>2</sub>b, the paired faces are achirohomotopic - H/H, and if m<sub>3</sub>= g<sub>3</sub><sup>+</sup>, m<sub>2</sub>n = a<sub>2</sub>g<sup>+</sup>, ag<sub>2</sub><sup>+</sup>, g<sub>2</sub><sup>+</sup>g<sup>-</sup>, g<sub>2</sub><sup>+</sup>h<sup>+</sup>, the faces are chirohomotopic - H<sup>\*</sup>/H<sup>\*</sup>. For mnp=abc, the faces are enantiotopic - E<sup>\*</sup>/<sup>\*</sup>E; for mnp=ag+g-, the faces are diastereotopic - D/F, and in the case of mnp=abg<sup>+</sup>, ag<sup>+</sup>h<sup>+</sup>, g<sup>+</sup>h<sup>+</sup>i<sup>+</sup>, the faces are diastereotopic - D<sup>\*</sup>/F<sup>\*</sup>. One orients the molecule (by rotation along the perpendicular pseudo-C3 axis, or by turning the molecule upside down to match that in **A2**, i.e. with the viewer on the side opposite to lowest-priority ligand p (m>n>p; Sequence Rule). Vector v<sub>x</sub> (m>n) and phantom point 3 above the plane define a 1→2→3 *counterclockwise* sequence, and the top faces are <sup>\*</sup>E (for mnp=abc), F (for mnp=ag<sup>+</sup>g<sup>-</sup>), and F<sup>\*</sup> (for mnp=abg<sup>+</sup>, ag<sup>+</sup>h<sup>+</sup>, g<sup>+</sup>h<sup>+</sup>i<sup>+</sup>). The corresponding 1→2→3 *clockwise* sequences lead to bottom faces E<sup>\*</sup>, D and D<sup>\*</sup>, respectively. Thus, in achiral carbocation **A2-1**, the top face is <sup>\*</sup>E, the bottom face is E<sup>\*</sup>; in the case of chiral oxocarbocation **A2-2**, the "right" face of the carbocation is D<sup>\*</sup>, and the "left" face is F<sup>\*</sup>; and in the case of achiral dioxacarbocation **A2-3**, the top face is D, and the bottom face is F. Interestingly, in the case of **A2**, the E, F<sup>\*</sup>, and F faces all correspond to Si, whereas the E, D<sup>\*</sup> and D faces correspond to Re. The perpendicular-to-plane 1→2→3 sequence we have defined for half-spaces of **A2** (but not **A3**) coincides (with a 90° rotation) with the in-plane clocksense defined for the specification of Re and Si.

We now turn to **A3**. To simplify the assignment of faces of **A3**, we place the viewer *arbitrarily* on the side *opposite* to the heteroatom group Y (Y=O,S,Se,Te) (*ignoring* the relative priority of Y in relation to ligands m and n which are linked through s, sp or sp<sup>3</sup>-hybridized, but not sp<sup>2</sup>-hybridized atoms).<sup>168</sup> This simplification allows an easier bipartite distinction between ligands m and n, instead of a tripartite comparison of Y, m and n. Here too, resonance structures are treated through their conventional canonical representations. For mn= a<sub>2</sub>, the faces are H/H; for mn= g<sub>2</sub><sup>+</sup> the faces are H<sup>\*</sup>/H<sup>\*</sup>. But, in acetaldehyde-*d* (**A3-1**), the "top" face is <sup>\*</sup>E (CH<sub>3</sub>>D by CIP), and the "bottom" face is E<sup>\*</sup>. In achiral (*meso*) **A3-2**, the "front" face is D since the vector v<sub>x</sub> points from right (R) to left (S); the "back" face is F. Finally in chiral aldehyde **A3-3**, the "top" face is D<sup>\*</sup> (v<sub>x</sub> points from C to H), and the bottom face is F<sup>\*</sup>. Note that "top" and "bottom" designations are relevant with reference to a clear structural drawing such as **A3-3**. Furthermore, for different conformations about the C<sub>α</sub>-to-C=O bond, "top" and "bottom" designations lose their meaning. In the proposed HED system, the stereochemical descriptor for a face makes no reference to a specific drawing, and remains unaltered for all conformations about the C<sub>α</sub>-to-C=O bond. This is analogous to specifying R and S absolute configurations of a chirostereogenic sp<sup>3</sup> atom with *no* direct need for a specific drawing. In examples **A3-1** - **A3-3**, the <sup>\*</sup>E, F and F<sup>\*</sup> faces (accidentally) correspond to Si, while the E<sup>\*</sup>, D and D<sup>\*</sup> correspond to Re faces. Note that here the smallest of the Y groups, *viz.* O, is of higher priority than C and H.

At this stage, a comparison of different nomenclatures here of monocentric cases is in order. To date, no stereodescriptors have been assigned to homotopic faces, obviously because of their equivalence. However, the assignment of H or H<sup>\*</sup> to homotopic faces allows one to (a) ascertain the homotopic/chirohomotopic nature of the half-spaces, (b) compare homotopic faces of different moieties in a molecule - H<sub>1</sub> vs. H<sub>2</sub>, (c) differentiate between homotopic H faces and chirohomotopic H<sup>\*</sup> faces of different molecules, and (d) contrast homotopic H or H<sup>\*</sup> faces to E<sup>\*</sup>,<sup>\*</sup>E,



**Figure D.3.** Designating Stereotopic Faces of Monocentric Cases A1-A3

						
<i>Re/Si</i> or <i>re/si</i>	top bottom	- -	- -	<i>Re</i> <i>Si</i>	<i>re</i> <i>si</i>	<i>Re</i> <i>Si</i>
<i>B/N</i> or <i>b/n</i>	top bottom	- -	- -	<i>B</i> <i>N</i>	<i>b</i> <i>n</i>	<i>B</i> <i>N</i>
HED	top bottom	H H	H* H*	E* *E	D F	D* F*

**Figure D.4.** Comparison of Facial Stereodescriptors for Monocentric Cases A1-A3

D, D\*, F, F\* faces – as in discussions of intermolecular selectivity (Figure D.4).<sup>169</sup> The literature  $\alpha/\beta$  system is inapplicable to these acyclic systems. Furthermore, the literature *Re/Si* (*re/si*), *B/N* (*b/n*) systems do not differentiate between enantiotopic faces, on the one hand, and diastereotopic faces, on the other. Thus, whether it is the enantiotopic faces of **iii**, or the diastereotopic faces of **iv** and **v**, the faces are described by the same *Re/Si* and *B/N* descriptors. In contrast, in the novel HED system, **iii** has enantiotopic faces E\*/\* $\exists$ , **iv** possesses diastereotopic faces D/F, and **v** incorporates chirodiastereotopic faces D\*/F\*. Thus, the HED system (a) identifies the relative stereopriority of the paired faces, including homotopic ones, (b) differentiates between enantiotopic and diastereotopic faces, and (c) reveals the chirality of the molecular field - e.g. homotopic vs. chirohomotopic (**i** vs. **ii**), and, diastereotopic vs. chirodiastereotopic (**iv** vs. **v**).

### B. Bicentric Cases A4a-c, A5a-c, A6a,b, A7a,b

We now turn to bicentric cases, where X and Y are skeletal  $sp^2$ -hybridized atoms, and m,n,p,q are ligands that are devoid of p orbitals that can overlap appreciably with the X=Y  $\pi$ -system. For each of cases **A4a**, **A5**, **A6a** and **A7a**, the molecule is oriented so that the best match is obtained with prototypes **A4**, **A5**, **A6**, and **A7**, with the priority sequences being X>Y followed by m>n>p>q. Where ligands are missing, as in **A5** and **A6**, one considers the electron pair in the  $sp^2$  orbital and assigns the lowest priority to it. The positioning of the viewer here depends on ligands m,n,p,q; the "preferred side" is on the side of m,n (Figure D.5). From here, the viewer must pick vector  $v_x$  based on skeletal atoms X and Y ( $X \neq Y$ ). The 1→2→3 sequence is placed in plane K (coincident with the XZ plane). If X = Y, vector  $v_x$  must be based on ligands m,n in plane L<sub>1</sub> (closest to the viewer); if m and n are isomorphic (identical in connectivity and configuration), the viewer must turn to ligands p,q (in plane L<sub>2</sub>).

In Figure D.5, we apply the HED rules to planar acyclic molecules of the type **A4-A7**. The viewer is positioned on the side of m,n (m,n>p,q). This is true for all the examples shown. In case there is a C<sub>2</sub> axis perpendicular to the planar moiety, the two viewer positions are equivalent. Hence, it makes no difference which side is picked, and the assignment of facial stereodescriptors remains unaffected. In defining vector  $v_x$ , the order of priority is skeletal atom X > skeletal atom Y >> ligand m > ligand n >> ligand p > ligand q. Thus, in **A4a-1**, **A4a-2**, **A5a-1**, **A5a-2**, **A6a-1** and **A7a-1**, one needs skeletal atom X and atom Y. In cases **A4b-1**, **A4b-2**, **A5b-1**, **A5b-2**, **A6b1**, and **A7b-1** (atom X = atom Y = C),  $v_x$  is based on ligands m and n. In the case of **A4c-1**, **A4c-2**, **A5c-1** (X=Y=C, and m=n),  $v_x$  is based on ligands p/q.

A comparison of different facial stereodescriptors for bicentric cases is in order (Figure D.6). The *Si/Re* (or *Re/Si*) descriptor may indiscriminately refer to homotopic (vii), or diastereotopic (xiii) faces. Similarly, *Re-Re* (or *Si-Si*) applies equally well to homotopic (ix), enantiotopic (x, xi), and diastereotopic (xiv) faces. Furthermore, the *Re/Si* nomenclature falls short for xii with diastereotopic faces, and is inapplicable to homotopic faces (vi,vii,viii). In contrast, as seen in the examples of Figure D.6, in the novel HED system presented here, every face gets a descriptor. In this manner, one is able to (a) specify the stereopriority of the faces, (b) differentiate between paired enantiotopic faces vs. paired diastereotopic faces, (c) and indicate the chirotopicity within facial half-spaces.

### C. Tricentric Cases A8-A10

The three centers X, Y and Z of tricentric cases are  $sp^2$ -hybridized skeletal atoms; m,n,p,q,t are ligands that are devoid of p orbitals that can overlap effectively with the XYZ  $\pi$ -system.

The molecules are oriented as shown in **A8**, **A9** and **A10** so that viewer is on the side opposite ligand t and is looking at the *concave* side of the sickle-shaped molecule, with X>Z and

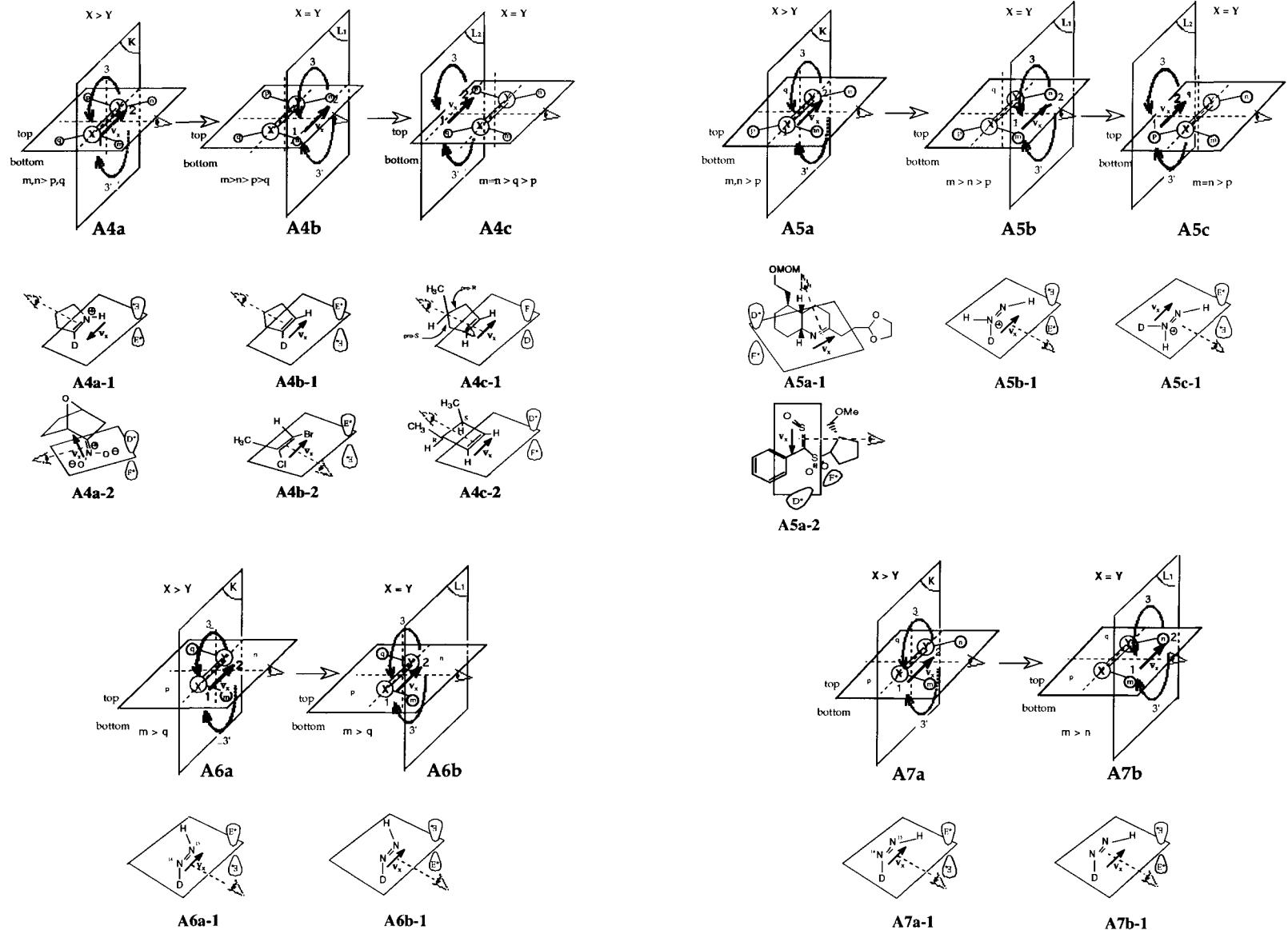


Figure D.5. Examples of Stereotopic Faces of Bicentric Cases A4a-c, A5a-c, A6a/b and A7a/b

	h2	h3	h5 <sup>*</sup>	h6 <sup>*</sup>	e	e	d2	d3	d4 <sup>*</sup>	
Re/Si or si/re	top	-	<i>Si-Re</i>	-	<i>Re-Re</i>	<i>Re-Re</i>	<i>Si-Si</i>	<i>Si-?</i>	<i>Re-Si</i>	<i>Si-Si</i>
	bottom	-	<i>Re-Si</i>	-	<i>Si-Si</i>	<i>Si-Si</i>	<i>Re-Re</i>	<i>Re-?</i>	<i>Si-Re</i>	<i>Re-Re</i>
HED	top	H	H	H*	H*	*E	*E	F	F	F*
	bottom	H	H	H*	H*	E*	E*	D	D	D*

Figure D.6. Comparison of Facial Stereodescriptors for Bicentric Cases

$m>n>p>q$ . This particular positioning of the viewer on the concave side (also for tetracentric case below) enables a simple determination of  $v_x$  based on atoms X and Z ( $X\neq Z$ ) in plane K. Should  $X=Z$ , one turns to ligands m/n (plane L1), and, if necessary, to ligands p/q (plane L2).

Figure D.7 illustrates the application of the rules to delocalized systems **A8a-1**, **A8b-1**, **A8c-1**, **A9a-1**, **A9b-1**, and **A9c-1**. In particular, 1,3-dipoles are prominent members of the tricentric cases. Azomethine ylids, azomethine imines, nitrones, carbonyl ylids (e.g. **A8c**), carbonyl imines, carbonyl oxides fit prototype **A8**; bent nitrile ylids, may also be treated as **A8**. The linear 1,3-dipoles are treated as a triply-bonded systems with two mutually orthogonal sets of paired faces.

Bent allenoid 1,3-dipoles from the diazoalkane families are also accommodatable in **A8**. The linear ones are treated like alenes with two pairs of faces. Each pair is treated separately, as in an isolated alkene.

In the six examples of **A10**, the assumed planarity presumes implicit overlap of the p orbitals of X, Z and Y. The application of the rules to systems **A10a-c** is also illustrated in Figure D.7. As in the related case of **A3**, the viewer is stationed on the side opposite W, *regardless* of the priorities of X, Z and W. One then proceeds in the order X/Z (plane K) > ligands m/n (plane L<sub>1</sub>) > ligands p/q (plane L<sub>2</sub>). Examples **A10a-1**, **A10a-2**, **A10b-1**, **A10b-2**, **A10c-1**, **A10c-2** have the facial stereodescriptors shown in Figure D.7.

Bent 1,3-dipolar systems such as ozone, nitrile imines, nitrile oxides, nitrous oxide, and bent allenoid azides are devoid of stereochemical handles at the termini; nevertheless they have well-defined molecular faces, and if needed, the HED system can be applied to them as well.

#### D. Tetracentric Cases **A11** and **A12**

In these tetracentric cases, the four centers X,Y,Z,W are skeletal  $sp^2$ -hybridized atoms; ligands m,n,p,q,t,u are devoid of p orbitals that can overlap with the XYZW  $\pi$ -system.

The molecules in **A11** are oriented on the basis of skeletal atoms X>Z>W, followed by ligands m>n>p>q>t>u. The order of priorities, in determining  $v_x$ , is as follows: X>W (plane K<sub>1</sub>) >> Y>Z (plane K<sub>2</sub>) >> m>n (plane L<sub>1</sub>) >> p>q (plane L<sub>2</sub>) >> t>u (plane L<sub>3</sub>). When these priorities are followed, the viewer ends up on the side opposite the lowest-priority skeletal atom W (closest to higher-priority skeletal atoms X,Z) or closest to highest-priority ligands m,n, (farthest from lowest-priority ligands t,u). The assignment of facial descriptors by the HED system to **A11a-1**, **A11a-2**, **A11b-1**, **A11b-2**, **A11c-1**, **A11c-2**, **A11d-1**, **A11d-2** is illustrated in Figure D.8 below.

Along with **A3** and **A4**, tetracentric case **A12** (assumed to be *cisoid* here) is of special interest to the synthetic organic chemist. The application of the terminology to the *transoid* system, if needed, is straightforward and is not presented here.

As in the case of system **A8-A9**, for simplicity, the viewer of **A12** should face the concave side of the *cisoid* molecule, while the molecule is oriented with X>W >> Y>Z >> m>n>p>q>t>u.

From the vantage point of the viewer, the order of priorities would be X/W (plane K<sub>1</sub>) > Y/Z (plane K<sub>2</sub>) >> m/n (plane L<sub>1</sub>) > p/q (plane L<sub>2</sub>) > t/u (plane L<sub>3</sub>).

Figure D.9 portrays the 4-electron delocalized systems **A12a-1**, **A12a-2**, **A12b-1**, **A12c-1**, **A12c-2**, **A12d-1**, **A12d-2**, **A12e-1**, and **A12e-2**.

In Diels-Alder reactions, descriptors *Si* or *Re* at either reactive terminus of the four-atom dienic

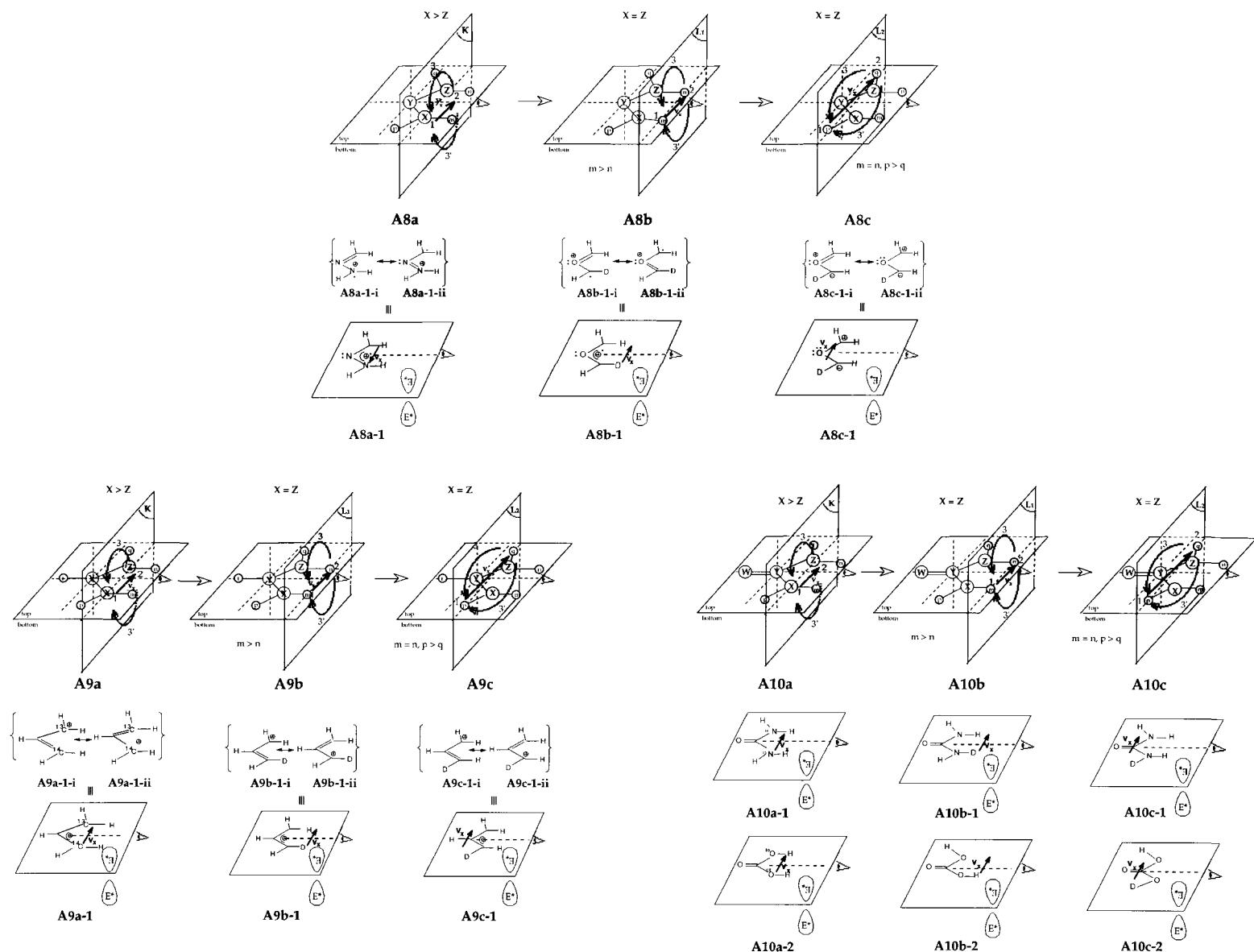
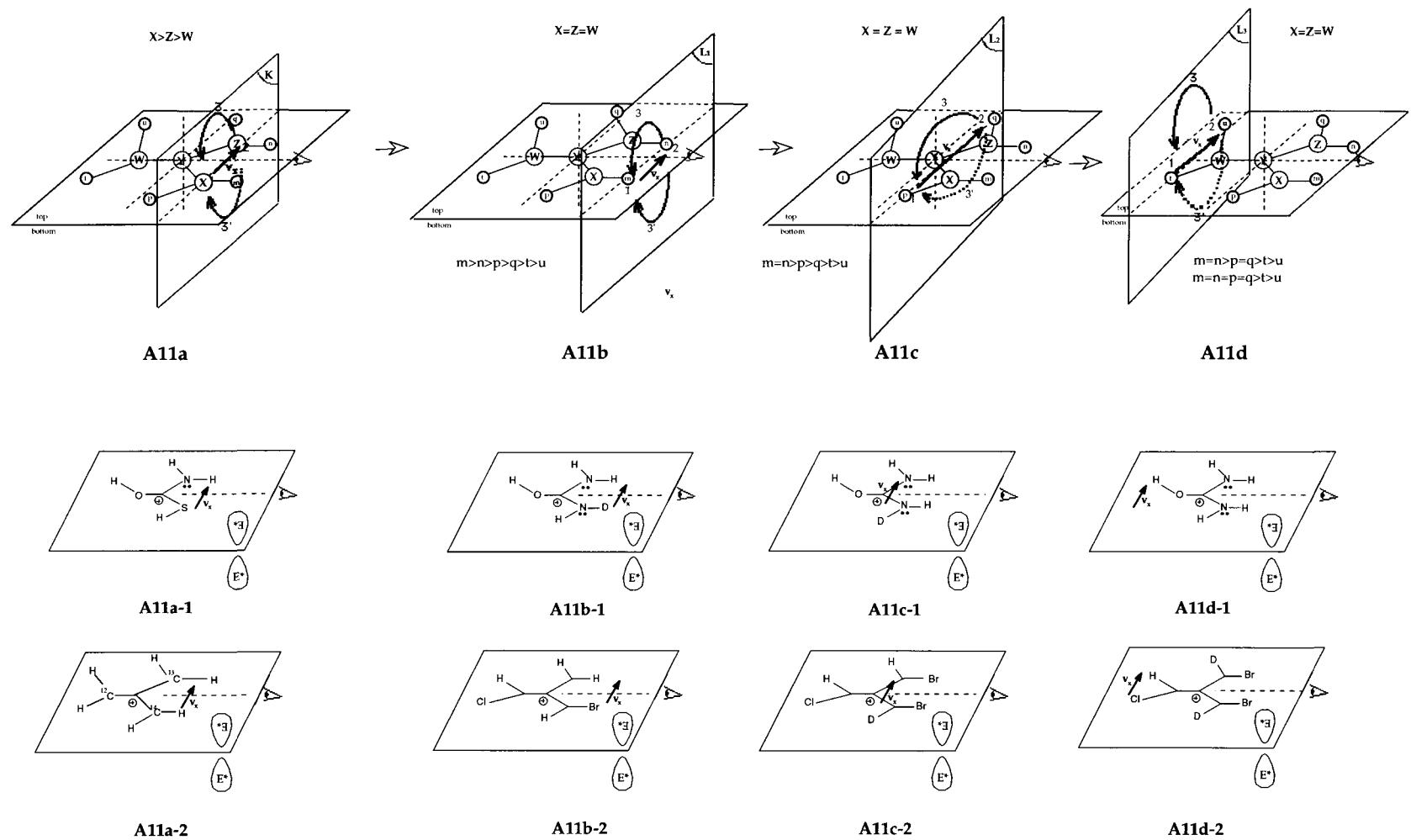


Figure D.7. Specifying Facial Stereodescriptors of Tricentric Cases A8-A10



**Figure D.8.** Specifying Facial Stereodescriptors for Tetracentric Cases A11

$\pi$ -system are commonly used.<sup>103</sup> The complete *Re/Si* designation of a linear tetracentric face, however, would be cumbersome, albeit melodious e.g. *Re-Re-Re-Si*, *Si-Si-Re-Re*. In contrast, the HED system assigns a single-letter stereodescriptor to any dienic face. Consequently, electrocyclic reactions - including Diels-Alder reactions, and 1,3-dipolar cycloadditions - can be described with the help of the HED stereodescriptors, without recourse to specific drawings. Representative examples from the literature are given in Figure D.10 below. The first three reactions are [ene + 1,3-dipole] cycloadditions,<sup>101,102,94</sup> and the depicted transition states [3], [7], and [10] involve [ $E^*+*E$ ], [ $E^*+F$ ], and [ $F^*+D^*$ ] faces, respectively. For [ene+1,3-dipole] cycloadditions, the stereodescriptor for the alkene precedes that of the dipole. For [ene + diene] electrocyclic reactions, the stereodescriptor for the alkene precedes that of the diene. In cases where two alkenes are involved, the smaller molecular mass is specified first; with isomeric alkenes,  $Z > E$ .

The remaining five reactions in Figure D.10 are [ene + diene] Diels-Alder reactions,<sup>103,104,95-97</sup> and the depicted transition states [14], [18], [21], [24], and [27] involve interactions of [ $*E+F^*$ ], [ $D^*+*E$ ], [ $F^*+F^*$ ], [ $D^*+F^*$ ], and [ $D^*+D^*$ ] faces, respectively. Along with these facial descriptors, one may also specify vectoselectivity (regioselectivity) (see Chapter 13). Thus, the above reactions proceeding through [3], [7], and [10] (Figure D.10) may be described as *par-[E<sup>\*</sup>+\*E]*, *aper-[E<sup>\*</sup>+F]*, and *aper-[F<sup>\*</sup>+D<sup>\*</sup>]*, respectively. The remaining five – those proceeding through [14], [18], [21], [24], and [27] – would be described as *par-[\*E+F<sup>\*</sup>]*, *aper-[D<sup>\*</sup>+\*E]*, *aper-[F<sup>\*</sup>+F<sup>\*</sup>]*, *aper-[D<sup>\*</sup>+F<sup>\*</sup>]*, and *aper-[D<sup>\*</sup>+D<sup>\*</sup>]*, respectively.

### III. Cyclic Systems C1-C4

The four cyclic cases are viewed using the preferred relative orientations depicted in Figures D.11-D.14. In every case, one must orient the molecule, relative to the viewer, so that  $X>Y>W>Z>U>V \gg m>n>p>q>t>u$ . The particular orientations of the cyclic systems are chosen in order to maximize the choices between pairs of skeletal atoms and/or pairs of ligands in defining  $v_x$ .<sup>170</sup> In determining  $v_x$ , the order of priorities is:

C1	$X>Y>Z \gg m>n>p$
C2	$X>Y>W>Z \gg m>n>p>q$
C3	$X>Y>W>Z>U \gg m>n>p>q>r$
C4	$X>Y>W>Z>U>V \gg m>n>p>q>t>u$

#### A. Tricentric Case C1

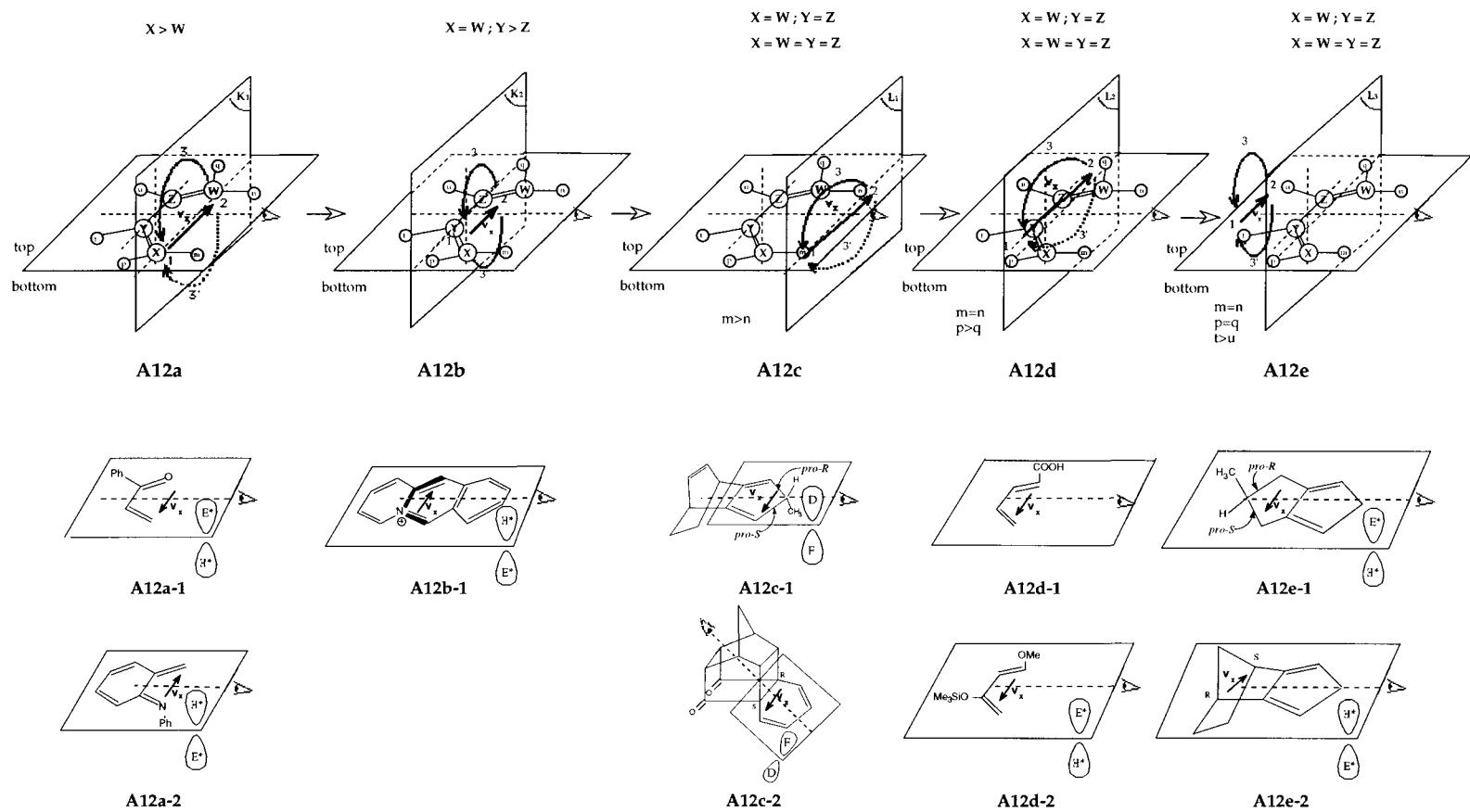
For tricentric cases, the molecule is oriented such that the viewer is opposite lowest-priority  $Z$ , or lowest priority ligand  $p$ , keeping the order  $X>Y>Z \gg m>n>p$ . For the determination of  $v_x$ , the first comparison is made, in plane K, of skeletal atoms X/Y as in **C1a-1** ( $^{15}\text{N} > ^{14}\text{N}$ ) and **C1a-2** (N>C). When  $X=Y (\geq Z)$  as in **C1b-1**, one compares ligands m/n in plane L1; here F>D. The resultant top faces, as drawn, are  $*E$ , and the bottom faces are  $E^*$ .

#### B. Tetracentric Case C2

In tetracentric cases, the viewer faces the X-Y edge, with  $X>Y>W>Z \gg m>n>p>q$ . In the determination of  $v_x$ , the first comparison is in plane K<sub>1</sub>, for skeletal atoms X/Y as in **C2a-1**, **C2a-2**, and **C2a-3**. In case of degeneracy, one looks at skeletal atoms W/Z in plane K<sub>2</sub>, as in **C2b-1**. If degeneracies persist up to this point, one turns to ligands m/n (plane L<sub>1</sub>) as in **C2c-1**, and then ligands p/q in plane L<sub>2</sub>, as in **C2d-1** and **C2d-2**.

#### C. Pentacentric Case C3

For pentacentric planar systems represented by **C3**, the viewer is facing edge of X-Y, so that  $X>Y>W>Z>U \gg m>n>p>q>r$ . Vector  $v_x$  is based on X/Y(plane K<sub>1</sub>), as in **C3a-1** - **C3a-3**.



**Figure D.9.** Specifying Facial Stereodescriptors for Tetracentric Cases A12

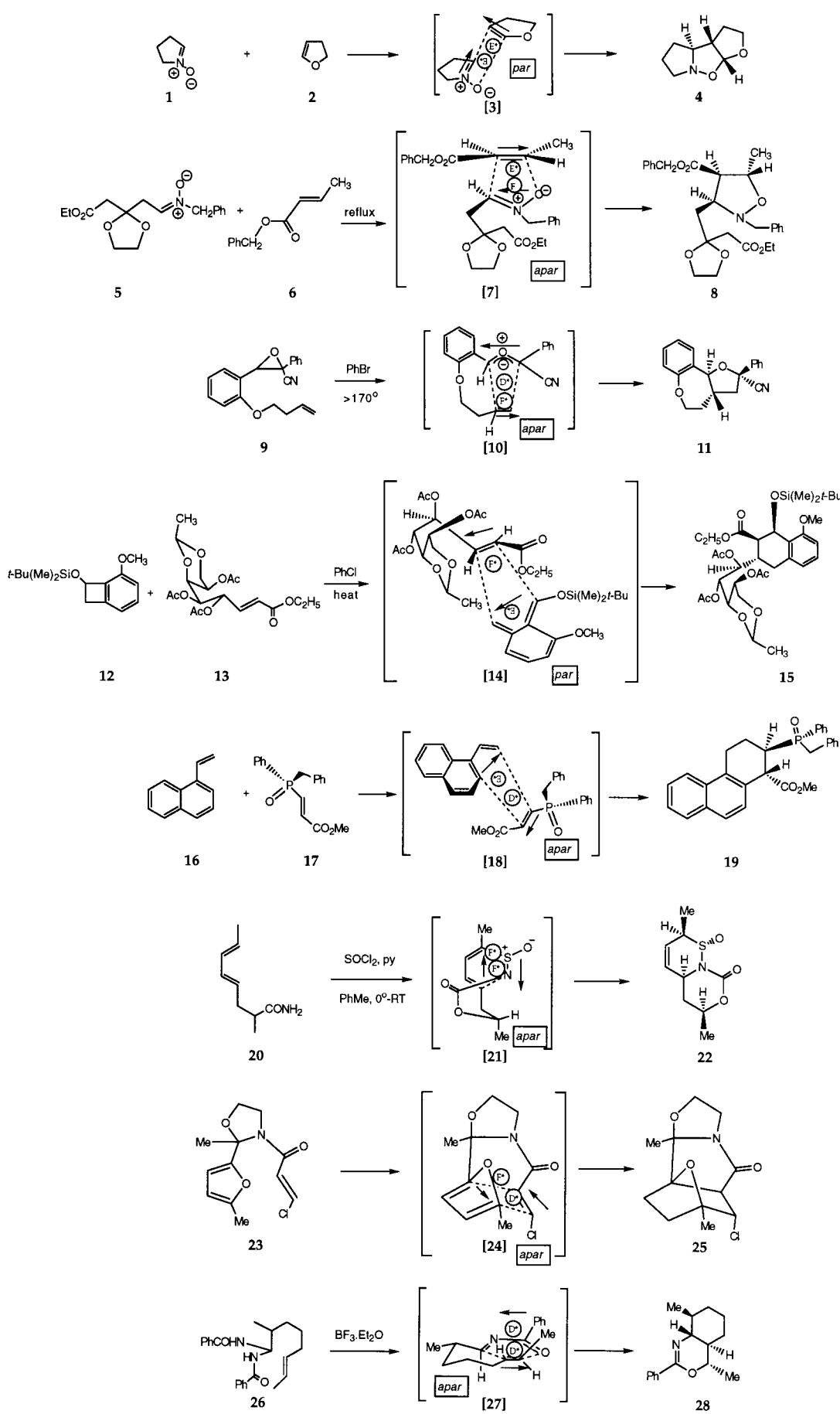
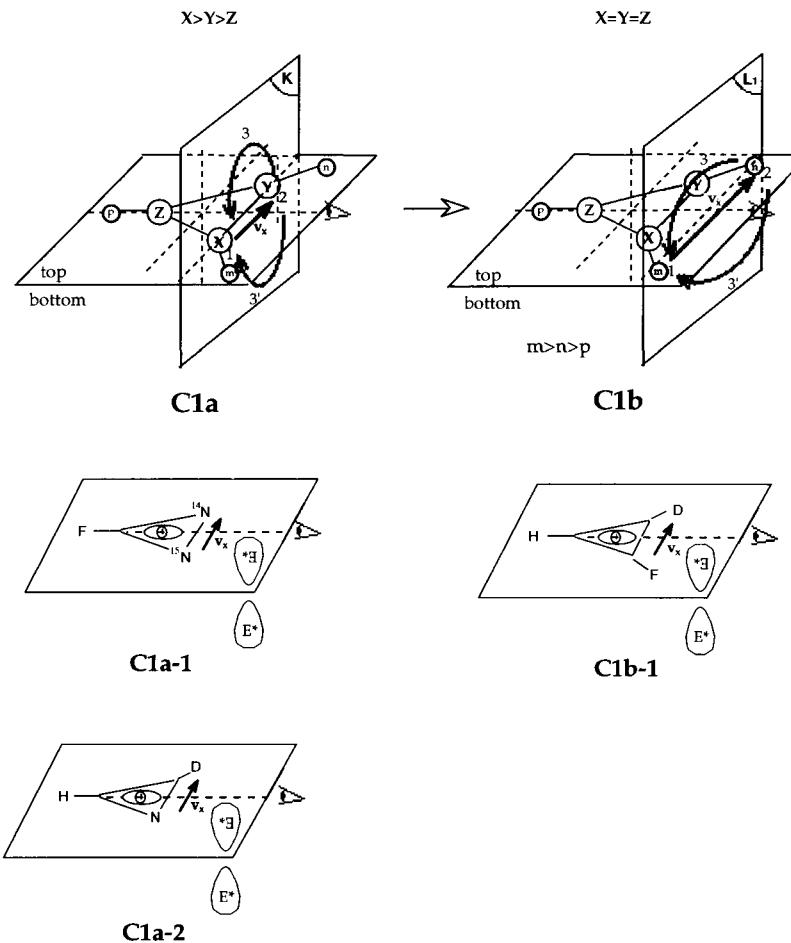


Figure D.10. Examples of Selective Face/Face Associations

When X=Y, one looks at skeletal atoms W/Z in plane K<sub>2</sub>, as in **C3b-1**. In case of a degeneracy of skeletal atoms, one examines ligands m/n in plane L<sub>1</sub> as in **C3c-1**; finally, as a last resort, one looks at ligands p/q in plane L<sub>2</sub>, as in **C3d-1** and **C3d-2**.

#### D. Hexacentric Case C4

Finally, for hexacentric cases represented by **C4**, the viewer faces edge X-Y keeping the order of priorities of skeletal atoms and ligands in the order X>Y>W>Z>U>V >> m>n>p>q>t>u. To determine vector v<sub>x</sub>, the sequential comparisons are made until the degeneracy is removed; the order of comparisons is X/Y (plane K<sub>1</sub>) as in **C4a-1** and **C4a-2**, followed by W/Z (plane K<sub>2</sub>) as in **C4b-1** and **C4b-2**, and then skeletal atoms U/V (plane K<sub>3</sub>) as in **C4c-1** and **C4c-2**. When the skeletal atoms have been exhausted, and the degeneracy has not been removed, one turns to ligands m/n (plane L<sub>1</sub>) as in **C4d-1**, **C4d-2**, followed by ligands p/q (plane L<sub>2</sub>) and, finally, ligands t/u (plane L<sub>3</sub>).



**Figure D.11.** Specifying Facial Stereodescriptors for Tricentric Cases A13

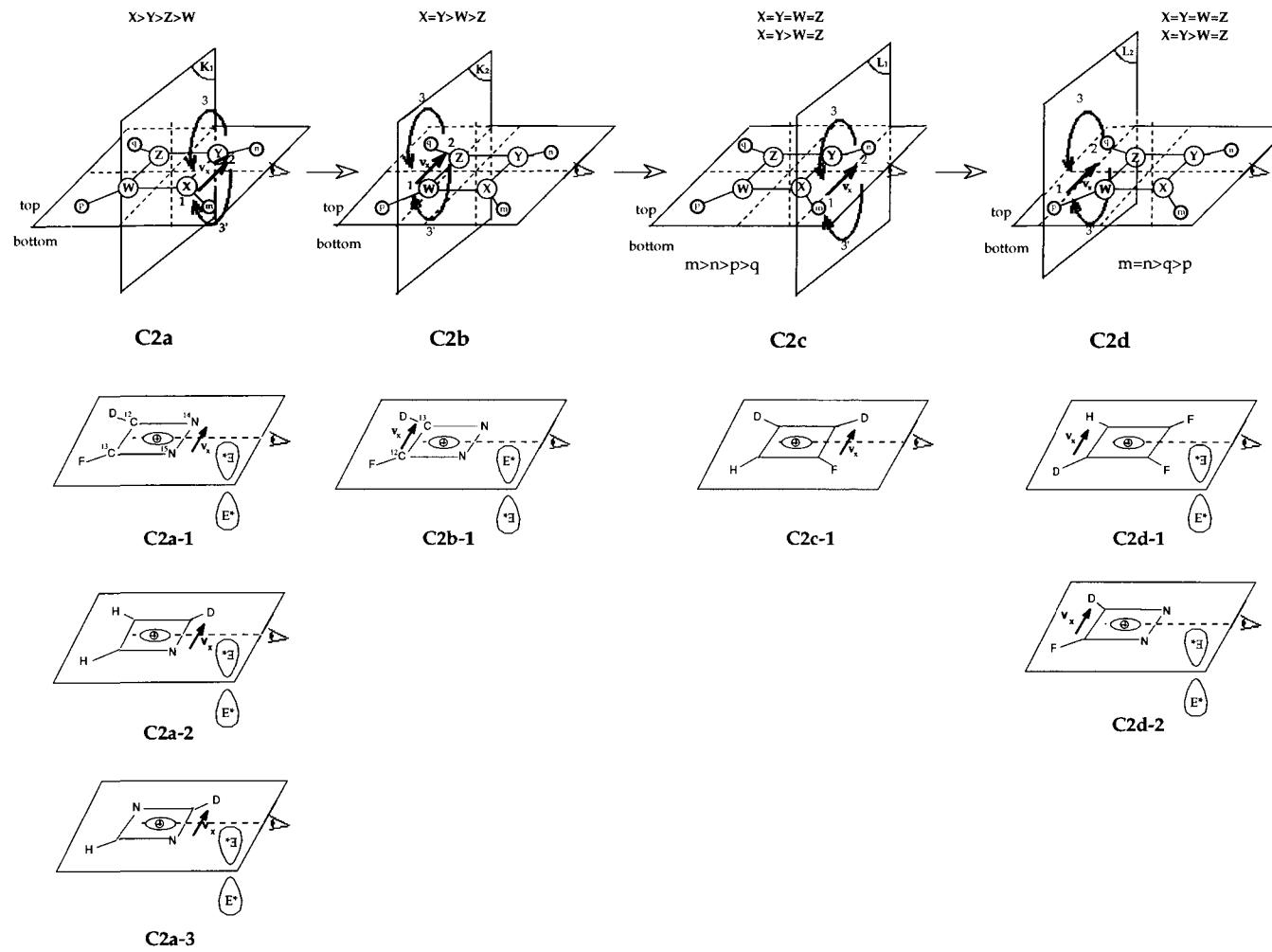
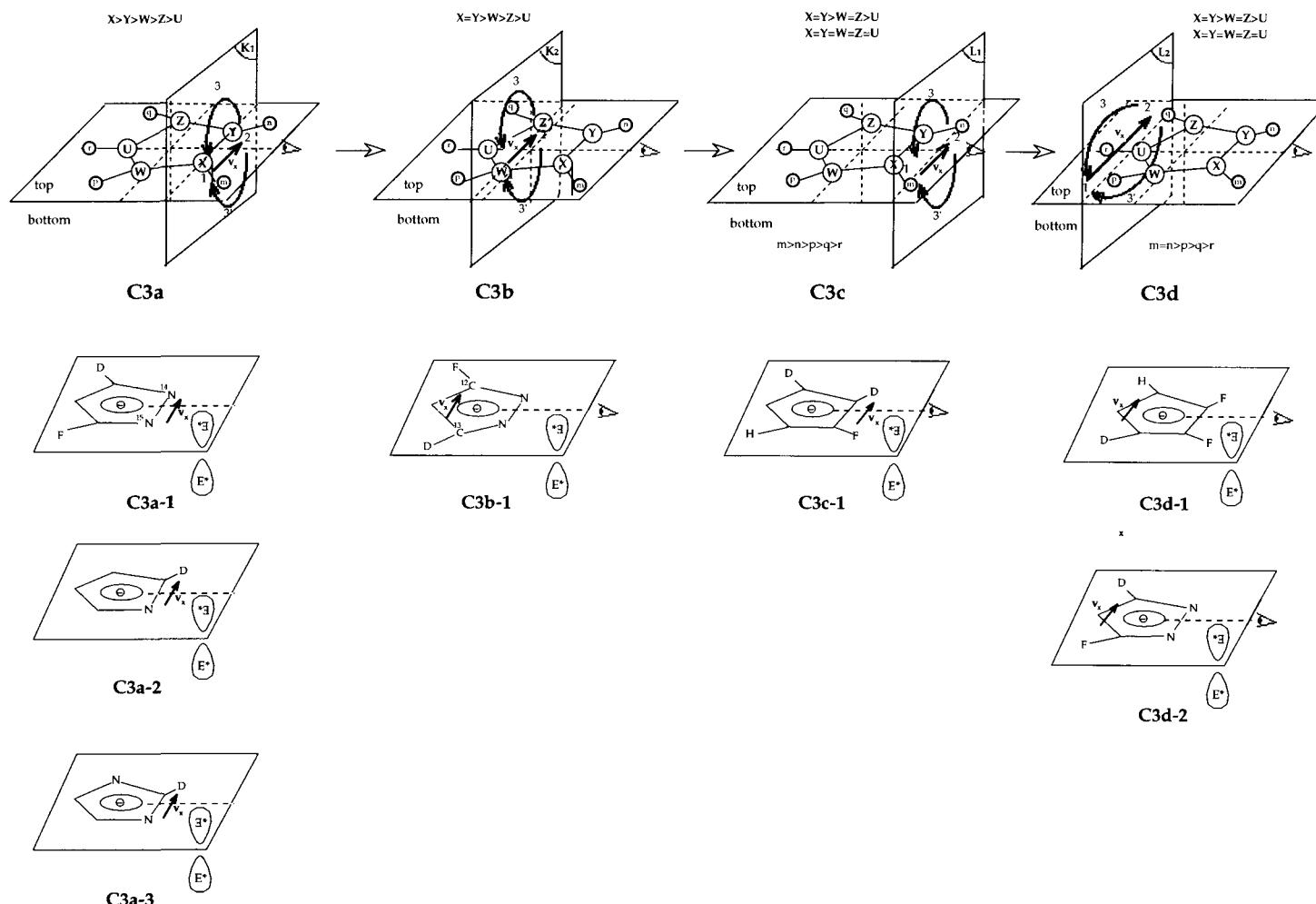
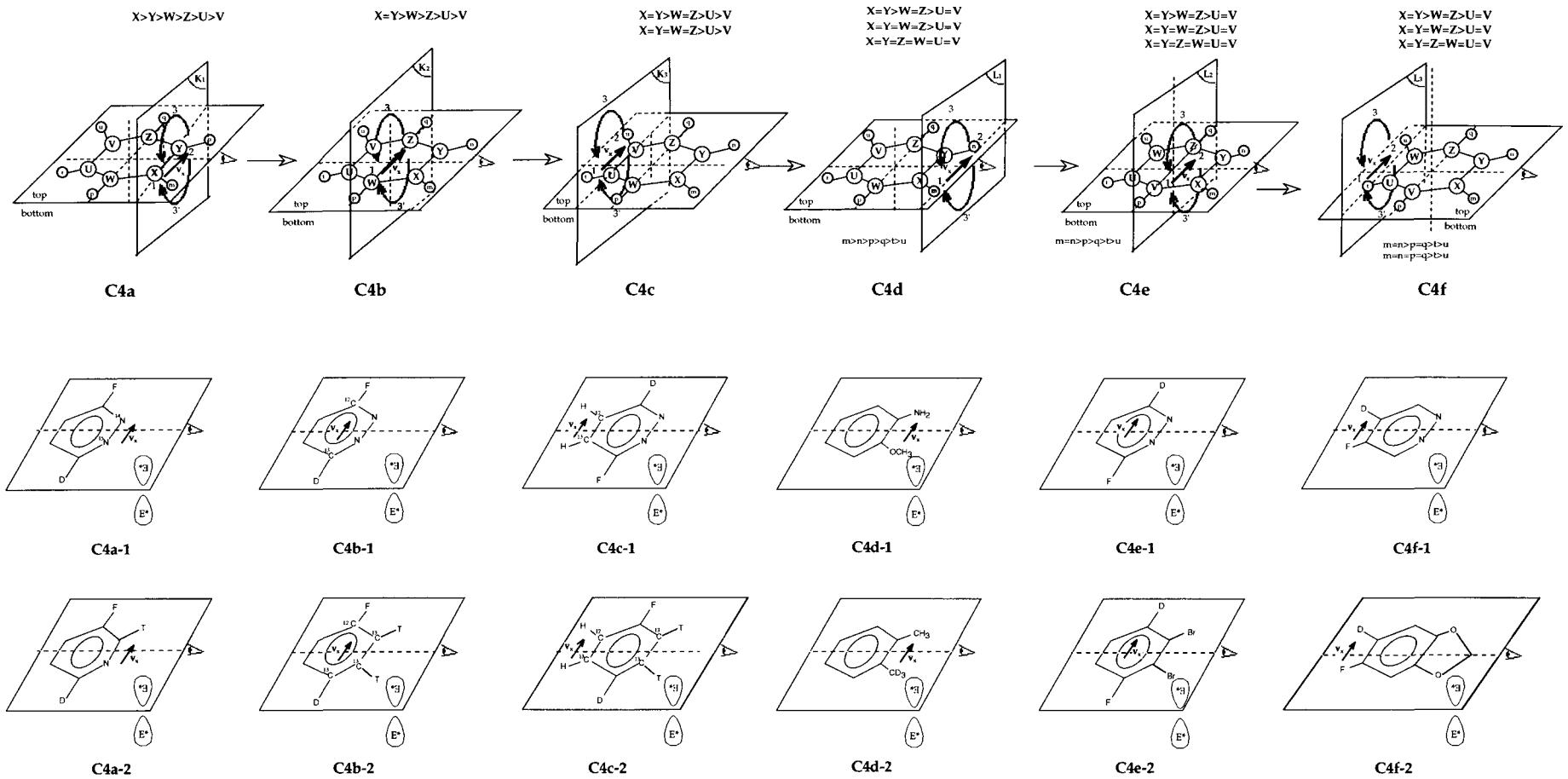


Figure D.12. Specifying Facial Stereodescriptors for Tetracentric Cases C2



**Figure D.13.** Specifying Facial Stereodescriptors for Pentacentric Cases C3



**Figure D.14.** Specifying Facial Stereodescriptors for Hexacentric Cases C4

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## References & Notes

- <sup>1</sup> Prof. B. M. Trost has proposed the term *conjunctive reagent* to represent a reagent with a simple building block that is incorporated, in whole or in part, into a more complex system (e.g. methyl vinyl ketone); in contradistinction, the term *simple reagent* is one that operates on, but is not incorporated into, a reactant (chromic acid). (cf. Trost, B. M., *Acc. Chem. Res.*, **1978**, *11*, 453; footnote 42).
- <sup>2</sup> An *associative* process refers to the coming together of molecular entities, whereas a *junctive* process refers to the bonding aspect accompanying the association; for examples see Cotton, F. A.; Wilkinson, G., *Advanced Inorganic Chemistry*, 5<sup>th</sup> ed.; Wiley: New York, 1988; p. 37.
- <sup>3</sup> A directed bond includes partial  $\sigma$ -bonding,  $\pi$ -bonding, and directed ionic bonding (as in  $R^-Li^+$ , or  $Li^+Br^-$ ); non-bonded interactions (van der Waals interactions, steric interactions, hydrophobic interactions) and mechanical forces (as in trapping of He in fullerene, or the fit of rotaxane rods) are non-directional and are ignored in this treatment.
- <sup>4</sup> An atom with empty, partially filled or completely filled atomic orbitals.
- <sup>5</sup> In effect, a bond is equivalent to two atomic sites that are  $\sigma$ -linked. A molecular  $\pi$ -system generally consists of two or more atomic sites, but these are linked through a  $\pi$ -system superimposed on a  $\sigma$ -network.
- <sup>6</sup> A *conjunctive state* is an associated form of the reactive simplexes through directed bonding - partial or complete (ligojunctive or ligogenic); this state can be a transition state, intermediate state or final state (product).
- <sup>7</sup> In these designations, we note that (a) binary precedes ternary, (b) within binary sets, the numerically smaller set is specified first, (c) for numerically identical sets, junctive precedes disjunctive. In designations of the corresponding reverse processes, the subscripts <sub>j</sub> (for junctive) or <sub>d</sub> (for disjunctive) are interchanged. For example, the reverse of  $(1,1)_j(1,1)_d$ ,  $(1,2)_d(2,2)_j(1,1,2)_j$  and  $(1,1)_j(1,1)_d(1,2)_j$  processes are  $(1,1)_j(1,1)_d$ ,  $(1,2)_j(2,2)_d(1,1,2)_d$  and  $(1,1)_j(1,1)_d(1,2)_d$ , respectively.
- <sup>8</sup> Liu, K.; Loeser, J. G.; Elrod, M. J.; Host, B. C.; Rzepiela, J. A.; Pugliano, N.; Saykally, R. J., *J. Am. Chem. Soc.*, **1994**, *116*, 3507.
- <sup>9</sup> Higher-order combinations and composite combinations are possible; see Figures 8.9 (p. 11) and 8.11 (p. 13).
- <sup>10</sup> Haque, T. S.; Little, J. C.; Gellman, S. H., *J. Am. Chem. Soc.*, **1996**, *118*, 6975.
- <sup>11</sup> Colominas, C.; Luque, F. J.; Orozco, M., *J. Am. Chem. Soc.*, **1996**, *118*, 6811.
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(b) Nowick, J. S.; Feng, Q.; Tjivikua, T.; Ballester, P.; Rebek, J., Jr., *J. Am. Chem. Soc.*, **1991**, *113*, 8831.
- <sup>14</sup> Heaney, H., *Aldrichim. Acta*, **1993**, *26*, 35.
- <sup>15</sup> Wang, Y.; Patel, D. J., *Structure*, **1993**, *1*, 263.

<sup>16</sup> Betzel, C; Saenger, W.; Hingerty, B. E.; Brown, G. M., *J. Am. Chem. Soc.*, **1984**, 106, 7545.

<sup>17</sup> In  $[m,n,p]$ ,  $[m,n]$  and  $[m]$ , m is the number of junctive atoms in molecule 1, n is the number of junctive atoms in molecule 2, and p is the number of junctive atoms in molecule 3; the total number of numerals between the square brackets reflects the number of molecules/molecular entities taking part in the junctive process. Thus,  $[m,n,p]$  involves three molecules,  $[m,n]$  involves two, and  $[m]$  involves only one. The numerical value of each numeral indicates the number of junctive atoms in a molecule taking part in the junctive process. For example, in junctive process  $[3]_j$  the reactant molecule has 3 reactive atomic sites whereas in  $[1,2]_j$ , one molecule has 1 atomic site, the second molecule has 2.

<sup>18</sup> Richman, J. E.; Kubale, J. J., *J. Am. Chem. Soc.*, **1983**, 105, 749.

<sup>19</sup> In molecular cases,  $j_{d}$  means both junctive and disjunctive components are found.

<sup>20</sup> Wheland, G. W., *Advanced Organic Chemistry*, 3<sup>rd</sup> ed.; Wiley: New York, 1960, p. 41.

<sup>21</sup> Atom junctivity ( $j_j$ ) is not to be confused with (junctive) atomicity ( $a_s$ ). (Junctive) atomicity, ( $a_s$ ), identifies the number of bonding atoms in a simplex - fundamental or topological; it determines the notation for the junctive process (1,1) vs. (1,2). Atom junctivity, ( $j_j$ ), on the other hand, denotes the number of directed bonds being formed at a given junctive atom.

<sup>22</sup> Fundamental simplex junctivity,  $j_s$ , is the sum of atom junctivities ( $j_{a'_i}$ ) of all reacting atomic sites in a fundamental simplex  $s$ , and is given by Equation 8.2:

$$j_s = \sum_p j_{a'_i} \quad (8.2)$$

where  $j_{a'_i}$  is the atomic junctivity of the  $i^{\text{th}}$  atom in the simplex, and  $p$  is the number of reacting atomic sites in the simplex ( $p = 1, 2, 3, \dots, p$ ). In effect,  $j_s$  is equal to the net number of incipient directed bonds formed by all reacting atoms of simplex  $s$ , during a given transformation. Simplex  $s$  is monojunctive, bijunctive, trijunctive, ...,  $p$ -junctive a simplex, if  $j_s = 1, 2, 3, \dots, p$ , respectively. The  $j_s$  value of a simplex  $s$  depends on the process it undergoes. For example, the  $j_s$  value of the *atomic simplex H* in 92a is 1, while that of the *C-H bond simplex* in 92b is  $1+1 = 2$ .

Topological simplex junctivity,  $j_{s_t}$ , is the sum of atom junctivities ( $j_{a'_i}$ ) of all reacting atomic sites in a topological simplex  $s_t$ , and is given by Equation 8.3:

$$j_{s_t} = \sum_{p_t} j_{a'_i} \quad (8.3)$$

where  $j_{a'_i}$  is the atomic junctivity of the  $i^{\text{th}}$  atom in the topological simplex, and  $p_t$  is the number of reacting atomic sites in the topological simplex ( $p_t = 1, 2, 3, \dots, p_t$ ). In effect,  $j_{s_t}$  is equal to the net number of incipient directed bonds formed by all reacting atoms of simplex  $s_t$ , during a given transformation. Topological simplex  $s_t$  may be monojunctive, bijunctive, trijunctive, ...,  $p$ -junctive a simplex, with  $j_{s_t} = 1, 2, 3, \dots, p_t$ , respectively.

- <sup>23</sup> Molecular junctivity,  $j_m$ , is the sum of atom junctivities ( $j_{a_i}$ ) of all  $p_t$  reacting atomic sites in a molecular system M, and is given by Equation 8.4:

$$j_m = \sum_{p_t} j_{a_i} \quad (8.4)$$

where  $j_{a_i}$  is the atomic junctivity of the  $i^{\text{th}}$  atom, and  $p_t$  is the number of reacting atomic sites in the molecule ( $p_t = 1, 2, 3, \dots, p_m$ ). In effect,  $j_m$  is equal to the net number of incipient directed bonds formed by all reacting atoms of molecule M, during a given transformation. Molecule M may be monojunctional, bijunctional, trijunctional, ...,  $p$ -junctional a *simplex*, with  $j_m = 1, 2, 3, \dots, p$ , respectively.

- <sup>24</sup> A bijunctional molecule may have two monojunctional atomic sites; a tetrajunctional molecule may have two bijunctional simplexes. The  $j_m$  value of M depends on the process it undergoes. For that molecule, *in the specified transformation*,  $j_m$  is the sum of the  $j_{s/s_t}$  values of all of its *reacting* junctive simplexes - fundamental and/or topological - taking part in the transformation (Equation 8.5):

$$j_m = \sum_q j_{s/s_t} = \sum_q \sum_{p/p_t} j_{a_i} \quad (8.5)$$

where q is the number of independent fundamental and topological simplexes in the molecule.

- <sup>25</sup> For a process involving r simplexes,  $J_{\text{for}}$  is given in terms of the contributing junctivity of the contributing simplexes by Equation 8.7:

$$J_{\text{for}} = 1/2 \sum_r j_m = 1/2 \sum_r \sum_q j_{s/s_t} = 1/2 \sum_r \sum_q \sum_{p/p_t} j_{a_i} \quad (8.7)$$

where  $j_{s/s_t}$  is the junctivity of the  $j^{\text{th}}$  simplex (fundamental or topological), and r is the number of simplexes involved in the forward process ( $q=1, 2, 3, \dots, q$ ).

- <sup>26</sup> Reich, H. J.; Borst, J. P.; Dykstra, R. R., *Organometallics*, **1994**, 13, 1.

- <sup>27</sup> Cotton, F. A.; Wilkinson, G., *Advanced Inorganic Chemistry*, 5<sup>th</sup> ed., Wiley-Interscience: New York, 1988, p. 38.

- <sup>28</sup> In a  $\sigma/\pi$  bond, the  $\sigma$  and the  $\pi$  components are conuclear or superimposed, i.e. both types of bonds are formed between the same set of atoms that are being joined. The formation of only  $\pi$  bonds (without the formation of a superimposed  $\sigma$  bond), or the transposition of existing  $\pi$  bonds is, therefore, not considered to be junctive.

- <sup>29</sup> In transformations in which superimposed  $\sigma/\pi$  bonds are broken, the process is termed disjunctive, and the reverse of the said transformation would be a junctive process.

- <sup>30</sup> The formation of a given  $\sigma$  bond in a junctive process may be *homogenic (homogenesis)* if each partner donates one electron (as in the combination of radicals), or, *heterogenic (heterogenesis)* if one of the partners contributes both electrons (as in ion-ion or Lewis acid-Lewis base combinations). The cleavage of a given  $\sigma$  bond in a disjunctive process may be *homolytic (homolysis)* if each partner receives one electron (as in the dissociation into radicals), or, *heterolytic (heterolysis)* if one of the partners receives both electrons (as in dissociations of ion-ions or of Lewis acid-Lewis base complexes).

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<sup>31</sup> Ligogenicity manifests in the formation of additional  $\sigma$  bonds in excited states (high-energy molecular species), intermediates (unstable ground-state molecular species) or products (stable ground-state molecular species).

<sup>32</sup> Simplex ligogenicity,  $l_s$ , is the sum of atom ligogenicities ( $l_{a_i}$ ) of all reacting atomic sites in a fundamental simplex  $s$ , and is given by Equation 9.2:

$$l_s = \sum_p l_{a_i} \quad (9.2)$$

where  $l_{a_i}$  is the atomic ligogenicity of the  $i^{\text{th}}$  atom in the simplex, and  $p$  is the number of reacting atomic sites in the simplex ( $p=1,2,3,\dots,p_i$ ). In effect,  $l_s$  is equal to the net number of  $\sigma/\pi$  bonds formed at all reacting atoms of simplex  $s$  during a given transformation. Simplex  $s$  can be monoligogenic, biligogenic, triligogenic,...,  $p$ -ligogenic a *simplex*, with  $l_s=1,2,3,\dots,p$ , respectively. The  $l_s$  value of the simplex  $s$  depends on the process it undergoes.

Topological ligogenicity,  $l_{s_t}$ , is the sum of atom ligogenicities ( $l_{a_i}$ ) of all reacting atomic sites in a skeletal simplex  $s_t$ , and is given by Equation 9.3:

$$l_{s_t} = \sum_{p_t} l_{a_i} \quad (9.3)$$

where  $l_{a_i}$  is the atomic ligogenicity of the  $i^{\text{th}}$  atom in the topological simplex, and  $p_t$  is the number of reacting atomic sites in the topological simplex ( $r=1,2,3,\dots,p$ ). In effect,  $l_t$  is equal to the net number of  $\sigma/\pi$  bonds formed by all reacting atoms of simplex  $s_t$  during a given transformation. Topological simplex  $s_t$  can be monoligogenic, biligogenic, triligogenic, ...,  $p$ -ligogenic a *simplex*, with  $j_{s_t}=1,2,3,\dots,p_t$ , respectively.

<sup>33</sup>  $M$  is monoligogenic, biligogenic, triligogenic,...,  $n$ -ligogenic a *molecule*, with  $j_m = 1,2,3,\dots,n$ , respectively. A biligogenic molecule may have two monoligogenic atomic sites; a tetraligogenic molecule may have two biligogenic simplexes. The  $l_m$  value of  $M$  depends on the process it undergoes. For that molecule, *in the specified transformation*,  $l_m$  is the sum of the  $l_s$  values of all of its *reacting* ligogenic simplexes - fundamental and/or topological - taking part in the transformation (Equation 9.4):

$$l_m = \sum_q \sum_{s_t} l_{s,s_t} = \sum_q \sum_{p/p_t} l_{a_i} \quad (9.4)$$

where  $q$  is the number of independent simplexes - fundamental and topological - in the molecule. Examples are given below.

<sup>34</sup> This equation may be expanded into the following form:

$$L_{\text{for}} = 1/2 \sum_r \sum_q l_{s,s_t} = 1/2 \sum_r \sum_q \sum_{p/p_t} l_{a_i} \quad (9.6)$$

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- <sup>42</sup> Longuet-Higgins, H. C. in *Theoretical Organic Chemistry. The Kekule Symposium*, Butterworths: London, 1959; p. 17.
- <sup>43</sup> MacAlpine, G. A.; Warkentin, J., *Can. J. Chem.*, **1978**, *56*, 308.
- <sup>44</sup> Doddi, G.; Illuminati, G.; Insam, N.; Stegel, F., *J. Org. Chem.*, **1982**, *47*, 960.
- <sup>45</sup> The related term *substrate specificity* (cf. Crans, D. C.; Whitesides, G. M., *J. Am. Chem. Soc.*, **1985**, *107*, 7008; Zaks, A.; Klibanov, A. M., *J. Am. Chem. Soc.*, **1986**, *108*, 2767) refers to the productive interaction of a specific substrate with an enzyme, e.g. glycerol kinase, chymotrypsin, subtilisin. While each substrate is examined *individually* and the kinetics of each is established separately, it is conceivable that a *mixture* of two or more substrates, when treated with the same enzyme in a given reaction mixture, would exhibit morpholytic selectivity - the generalized concept discussed in this chapter.
- <sup>46</sup> Attiná, M. ; Cacace, F., *J. Am. Chem. Soc.*, **1986**, *108*, 318.
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<sup>52</sup> The *consumption* of a reactant/substrate (starting material) can occur by either a change of the chemical structure of reactant, or complexation/binding of the substrate. In the former instance, the structural change occurs by breaking /making of s and/or  $\pi$  bonds; that is, the primary connectivity (constitutional graph) is altered. Competing pathways for this type of process of type are characterized by *morpholytic selectivity*. In contrast, in a complexation/binding/molecular recognition process, no principal  $\sigma$  and/or  $\pi$  bonds are broken/formed, but the reactant molecule (cf. Kato, Y.; Conn, M. M.; Rebek, J., Jr. *J. Am. Chem. Soc.*, **1994**, 116, 3279) undergoes changes in van der Waals, hydrogen bonding, or dipolar interactions; strictly, only secondary associations (edge-weighted graph) are affected. Selective complexation of one substrate vs. another substrate in an intermolecular competition in the same reaction medium is revealed in *morphojunctive selectivity*. In effect, morpholytoselectivity and morphojunctoselectivity have the same conceptual basis; the distinction between the two, if desired, stems from the differing types of bonding changes accompanying the chemical transformations.

<sup>53</sup> In this connection, see Ault, A., *J. Chem. Ed.*, **1977**, 54, 614; this author prefers to reserve the term *selectivity* for morphogenic processes, and to retain *specificity* for morpholytic processes.

<sup>54</sup> Jones, J. B., *Aldrichim. Acta*, **1993**, 26, 105-112, and references cited therein.

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<sup>61</sup> The preferential complexation of only  $\text{Li}^+$  (in the presence of  $\text{Na}^+$ ,  $\text{Rb}^+$ ,  $\text{Cs}^+$ ) with bis(diaryl)ether **36** (cf. Kaneda, T.; Umeda, S.; Tanigawa, H.; Misumi, S.; Kai, Y.; Morii, H.; Miki, K.; Kasai, N., *J. Am. Chem. Soc.*, **1985**, 107, 4802) is a special instance of nonequimorphojunctive selectivity.

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- <sup>74</sup> Isoenergetic states (ground state, transition state, or excited state) are either homomorphic (in the presence or absence of chiral influence), or enantiomeric (in the absence of chiral influence). Non-isoenergetic states are enantiomorphic (in the presence of chiral influence), or, diastereomeric, astereomeric or nonequimorphic (in the presence or absence of chiral influence).
- <sup>75</sup> We prefer the term *siteselectivity* over *toposelectivity* because the former is unambiguously associated with the word "site," and the association with the accepted term "topology" is avoided. We use the adjective *topic*, to describe the spatial relationship between a given pair of sites. The term *siteselectivity* refers to selective reactivity at a molecular site (*situs*) *irrespective* of the topic relationship of that site to another site or other sites. Thus, selectivity between enantiotopic sites is *enantiositeselectivity*. Since a site is a "region" in the molecule, the temptation in the chemical literature has been to substitute the term "siteselectivity" for "regioselectivity" to designate, erroneously, selectivity in a given region of the reactant molecule.
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<sup>86</sup> To ensure uniformity of designations, we consider the two *half-spaces*, defined by a planar functional group at a given site in the molecule, as *sub-sites*. In turn, these sub-sites also bear a (stereo)topic relationship with respect to each other.

<sup>87</sup> In a single molecule, subsites  $t_1$  and  $t_2$  may be exemplified by the two molecular faces of an alkene or a carbonyl moiety (Figure 11.1, case (a)). Alternatively, in a *single* molecule,  $t_1$  and  $t_2$  may represent two distinct alkene sites (case (b)). On the other hand,  $t_1$  and  $t_2$  may represent two alkene sites in two *distinct* molecules - one in each (case (c)).

<sup>88</sup> Bisituselectivity is operative in double differentiation, double stereodifferentiation, and double asymmetric induction, and, has led to the terms *matched/mismatched pairs*.

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$$\%S_1 = \frac{(C_{S_1}^{T_0} - C_{S_1}^T)}{(C_{S_1}^{T_0} - C_{S_1}^T) + (C_{S_2}^{T_0} - C_{S_2}^T)} \quad \%S_2 = \frac{(C_{S_2}^{T_0} - C_{S_2}^T)}{(C_{S_1}^{T_0} - C_{S_1}^T) + (C_{S_2}^{T_0} - C_{S_2}^T)} \quad (11.6a, 11.6b)$$

$$\%P_1 = \frac{(C_{P_1}^{T_0} - C_{P_1}^T)}{(C_{P_1}^{T_0} - C_{P_1}^T) + (C_{P_2}^{T_0} - C_{P_2}^T)} \quad \%P_2 = \frac{(C_{P_2}^{T_0} - C_{P_2}^T)}{(C_{P_1}^{T_0} - C_{P_1}^T) + (C_{P_2}^{T_0} - C_{P_2}^T)} \quad (11.7a, 11.7b)$$

where the C terms are the concentrations of reactants S<sub>1</sub> and S<sub>2</sub> in the same reaction mixture that have reacted for the same period of time - from the beginning (t=to) to the end (t=t) of the competitive processes.; the C terms are the concentrations of reactants P<sub>1</sub> and P<sub>2</sub> in the same reaction mixture that have reacted for the same period of time - from the beginning (T=T<sub>0</sub>) to the end (T=T) of the competitive processes.

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<sup>130</sup> The term *half-space* concisely represents the region in space, either above or below a flat molecular moiety. Stereotopic or paired half-spaces are separated by a surface that may or may not be planar. The alternative term *molecular face* is more descriptive of a given molecular structure. Two stereotopic molecular faces are separated by a surface that is assumed to coincide with the plane of a finite, flat molecular framework. We use *molecular face*, in preference to *half-space*, as it is intimately linked to the term *facioselectivity*. Ring systems in carbohydrates, heterocyclic bases, steroids, porphyrins (see refs. 129(a), 129(b) above) are also said to have molecular faces, albeit in a generalized sense.

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<sup>132</sup> We replace the F,F,F" designations of homotopic faces, F,I designations of enantiotopic faces and F,G,H designations for diastereotopic faces - all given in ref. 131 above - by H or H\* for homotopic, by E\*,\*E, for enantiotopic, and D,F for diastereotopic faces. The letters H for homotopic, E for enantiotopic and D for diastereotopic are easy to remember because they correspond to the corresponding first letters. We consider the priority sequences: clockwise > counterclockwise, E\*>\*E, D>F, and D\*>F\*.

<sup>133</sup> The sign // means parallel to the major axis of the planar moiety e.g. double bond or backbone of a diene; ⊥ means perpendicular to the molecular faces.

<sup>134</sup> Among enantiotopic faces (E\*,\*E) which face is E\*, and which one is \*E? Similarly, among diastereotopic faces which is D (D\*) and which is F (F\*)? The answers to these questions require rules for the specification of each individual face. These are given in Addendum D, pp. 189-209.

<sup>135</sup> Facioselectivity may be operative during the formation of incipient transition states, and, may or may not be evident in the products. However, in principle, it can manifest itself in unequal amounts of enantiomeric products.

<sup>136</sup> We prefer this term over *nonfacioselective* to indicate that facioselectivity is inherently not possible. In contradistinction, *faciononselective* would mean that facioselectivity is possible, in principle, but not observed.

<sup>137</sup> There is no need here to consider cases of astereofacioselectivity and nonequifacioselectivity, since paired faces are always stereotopic. This is not so for cases of vectoselectivity (Chapter 13).

<sup>138</sup> This definition of stereofacioselectivity as the *difference* of two numbers is analogous to those for "ee" - enantiomer excess - and "de" - diastereomer excess (cf. ref. 126 above).

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Alternatively, stereofacieselectivity may be defined as a *ratio* of two numbers:

$$\text{stereofacieselectivity} = |(m_1 + m_1')/(m_2 + m_2')|$$

in a manner analogous to that of diastereoselectivity (*cf.* ref. 127 above).

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<sup>157</sup> The corresponding for ligands in i-v and xi-xvi are as follows:

e*	pro-R
* <sub>9</sub>	pro-S
d	pro-r
f	pro-s
d*	pro-R
f*	pro-S

<sup>158</sup> In compounds vi-x, the correspondence between the two designations is as follows:

e*	pro-E
* <sub>9</sub>	pro-Z
d,f	pro-E
d*,f*	pro-Z

<sup>159</sup> Centricity is defined as the number of atoms with participating atomic orbitals.

<sup>160</sup> For compounds xvi-xx, the correspondence between the two terminologies is as shows:

R <sub>e</sub>	E*
S <sub>i</sub>	* <sub>3</sub>
r <sub>e</sub>	D
s <sub>i</sub>	F
R <sub>e</sub>	D*
S <sub>i</sub>	F*

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<sup>166</sup> This orientation simplifies the process of placing the viewer in relation to the molecule. As this is mastered, one can see that a molecule can be looked in any orientation, if it is viewed from the correct vantage point. In the CIP rules the determination of R/S configurations is carried out by (a) orienting the molecule in the framework of the XYZ coordinates and specifying the position of the viewer, or, (b) keeping the molecule stationary (as drawn) and moving the viewer to the proper, relative observation point. The two approaches are equivalent. The same is true for naming molecular faces. We have deliberately adopted the orientation of A1-2 to show that the viewer's position is adjusted, as the molecule is held stationary.

---

<sup>167</sup> The vector  $v_x$  is parallel to the X-axis. Its choice is arbitrary and is meant to simplify the description of the model. The vector is based on ligands or skeletal (backbone) atoms and is always from higher to lower priority. Vector  $v_x$  in facioselectivity, and  $v_v$  for vectoselectivity (Chapter 13) are defined differently. Generally, these vectors are not expected to coincide; in some instances, they do so, albeit accidentally.

<sup>168</sup> Despite the fact that when Y is a heteroatom heavier than C, and that one is viewing from the side opposite to it (contrary to the usual CIP Rules), the correspondence in the *Re/Si* and EDG Rules for the designations of enantiotopic and diastereotopic faces i.e. E\*, D, D\* vs. *Re*, and \*E, F, F\* vs. *Si*, as seen in case 1, is retained. It is clear that the in-plane CCW 1(atomY)-to-2-to-3 sequence viewed from the top (*Re*) is equivalent to 1-to-2(=vector  $v_x$ )-to-3 (phangom point above plane).

<sup>169</sup> Indeed, intramolecular and intermolecular comparison of molecular faces can be made, in principle, with astereotopic and nonstereotopic faces. However, since each molecular half-space is associated with its own other half-space, and therefore has an H,E or D/F assigned to it, it would be confusing to introduce new stereodescriptors to denote the intramolecular and intermolecular relationship of *unpaired* (not stereotopic = astereotopic or nonstereotopic) half-spaces.

<sup>170</sup> The arbitrary orientations are not unlike ones used in molecular orbital theory (*cf.* Salem, L., *The Molecular Orbital Theory of Conjugated Systems*, W. A. Benjamin: New York, 1966; pp. 116-123.

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# Concepts and Terminology in Organic Stereochemistry 3

The Stereochemical Classification of Organic Reactions

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# Concepts and Terminology in Organic Stereochemistry 3

The Stereochemical Classification of Organic Reactions

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To Semiramis,  
for her love and devotion

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## Preface

The history of organic chemistry goes back to the days of Friedrich Wöhler, two centuries ago. The stereochemical underpinnings of organic chemistry were set by Louis Pasteur, and the concept of chirality was advanced by Lord Kelvin, nearly a century later. The first stereochemical notation - that of the asymmetric carbon atom - had to await the Cahn-Ingold-Prelog (CIP) R/S rules - a half century later; it took yet another quarter century for the E/Z configurational notation for double bonds to be formulated. Indeed, the development of organic stereochemical language has lagged, and continues to lag experimental organic chemistry. In the last quarter century or so, there have been only two seminal contributions - both by Kurt Mislow and his coworkers - ones that have clarified the basic concepts of stereotopicity and chirotopicity. Notwithstanding a few other sporadic contributions by others, to date there have been no systematic attempts to unify and develop the conceptual framework and terminology of organic stereochemistry. Existing terms are frequently misused or abused, needed terms - redundant, confusing or controversial - are invented randomly, and yet other needed terms have not seen the light of day. This three-part work is an attempt to present the elements of a simple, uniform and comprehensive language of organic stereochemistry.

In Volume 1, we analyze the geometric basis of metric and topic relationships (Chapters 1 and 3), and derive a novel, simple, and universal framework - the HEDAN (*homometric/homotopic, enantiometric/enantiotopic, diastereometric/diastereotopic, astereometric/astereotopic and nonequitopic/nonequitopic*) scheme - for classifying (a) relationships between molecules (morphic relationships) (Chapter 2), (b) relationships between parts of molecules (topic relationships) (Chapter 4), (c) interconversions between molecules (morphization processes) (Chapter 2), and (d) interchanges between parts of molecules (topizations) (Chapter 4). We then establish heretofore-unknown stereochemical correlations between overall molecular structure (morphicity) and molecular sites (topicity), on the one hand, and between molecular transformations (morphizations) and molecular site interchanges (topizations), on the other (Chapter 5).

The geometric *segmentation* of a molecular state (ground state, excited state, transition state) into geometric simplexes (*geplexes*) (Chapter 6) enables us (a) to identify the *stereogeoplex* (or *stereoplex*) as the smallest geometric element of stereogenicity (segmental stereogenicity), (b) to provide the geometric basis for defining molecular *astereogens* and *stereogens*, and (c) to prove that the concept of stereogenicity inherently encompasses the concept of chirality (enantiogenicity). The method of segmentation provides a rationale of stereoisomerism different from that based on elements of stereoisomerism (Hirschmann and Hanson) and/or elements of chirality (Prelog).

Finally, we examine the geometric segmentation of carbogenic molecules with angular (non-perpendicular and/or noncoplanar) joins (Chapter 7), and discover that the *angular join* is a fundamental geometric

element of stereogenicity (angular stereogenicity) - complementary to the *stereoplex* (shown earlier to be the fundamental unit of *segmental* stereogenicity). The method of geometric segmentation provides the common geometric basis for both configurational and conformational stereogenicity.

At the end of Volume 1, we present a very useful and also heretofore-unavailable method of describing the compositions of two-, three- and four-component mixtures (Addendum A), and define a novel logarithmic scale for denoting their compositions (Addendum B).

In Volume 2, we identify the basic reactant molecular fragments - *fundamental junctive simplexes* - and utilize them in a novel notational description of fundamental junctive/disjunctive processes (Chapter 8). We also define *topological junctive simplexes* for a parallel notation of topological junctive/disjunctive processes. The two notations are jointly used in describing composite junctive/disjunctive processes. The concepts of *site junctivity* (for an atomic site), *fundamental simplex junctivity*, *topological simplex junctivity*, *molecular junctivity*, and *process junctivity* are also defined. The terminology advanced here (a) provides a simple, generalized and useful way of describing the progressive bonding in elementary mechanistic steps, (b) specifies incipient connectivity in transition states, (c) denotes connectivity in ground-state aggregated/associated supramolecular entities, and (d) presents the framework for specifying the regioselectivity, vectoselectivity, and facioselectivity in junctive/disjunctive processes. The concept of junctivity/disjunctivity is subsequently extended to ligogenic/ligolytic processes, thereby enabling a simple and universal notation for denoting such processes, and for providing the framework for specifying the regioselectivity, vectoselectivity, and facioselectivity in each process (Chapter 9).

Having set the framework for molecular connectivity, we proceed to discuss the concept of selectivity in all its facets. We start with *morphoselectivity* (Chapter 10), and draw a clear distinction between morpholytic selectivity (selective consumption of substrate S<sub>1</sub> over substrate S<sub>2</sub>) and morphogenic selectivity (selective formation of product P<sub>1</sub> over product P<sub>2</sub>). Each of these two types of morphoselectivity is classified further on the basis of the morphic relationship between reacting substances S<sub>1</sub> and S<sub>2</sub>, and of products P<sub>1</sub> and P<sub>2</sub>.

We then broach *situselectivity* (selective reaction at molecular site t<sub>1</sub> over molecular site t<sub>2</sub>) and classify it on the basis of the topic relationships of reacting sites (Chapter 11). Where the focus of attention is on *site* selectivity, we emphasize that the correct term should be *situselectivity* and *not* oft-misused and -abused term *regioselectivity*. We also discuss *bisituselectivity* for transformations involving two reactant molecules/moieties each with its own preferred site of attack.

To clarify selectivity at faces of planar molecular fragments, or *facioselectivity*, we present a complete classification of all eleven types of stereotopic molecular faces (Chapter 12). We define the different modes of facioselectivity *viz.* facioaselectivity, faciononselectivity and stereofacioselectivity at each type of molecular face. We also discuss *difacioselectivity* for conjunctive processes involving the interactions of two molecular faces.

We then proceed to define *vectoplexes* and *avectoplexes* (vectogenic and avectogenic junctive simplexes, respectively), in order to introduce the novel concept of *vectoselectivity* *viz.* junctive selectivity resulting from orientational preferences of reactants (Chapter 13). We examine the interactions of two and three junctive vectoplexes/avectoplexes and derive therefrom the five modes of vectoselectivity - vectoaselectivity, vectononselectivity, stereovectoselectivity, astereovectoselectivity and nonequivvectoselectivity. We demonstrate that Hassner's original definition of regioselectivity, and the subsequent IUPAC endorsement of that term, encompass two conceptually distinct ideas. Where the focus of attention is on site selectivity, *regioselectivity* is inapplicable and should be abandoned; the correct term should be *situselectivity*/toposelectivity. The term *regioselectivity* denotes selectivity due to parallel/antiparallel "Markovnikov-sense" alignment/bonding/association of "unsymmetrical" reactants with "unsymmetrical" reagents. Further, we demonstrate that the broader concept of *vectoselectivity* (a) encompasses Hassner-regioselectivity for two reactants, (b) applies to junctive processes involving three or more reactants, and (c) covers a wider range of orientational possibilities of all reactants/reagents. We examine conjunctive states in vectoselective processes, and determine vectoselectivity at all eleven types of stereotopic molecular faces. In transformations involving

additions to planar molecular moieties, we consider facioselectivity and vectoselectivity jointly, and uncover twelve subclasses of facioselectivity-vectoselectivity, each with unique characteristics. Finally, the joint consideration of difaciocoselectivity-vectoselectivity in various processes leads to eighteen subclasses of difaciocoselectivity-vectoselectivity, each also with characteristic attributes.

In the last chapter of Volume 2, we introduce and discuss the novel concept of *anguloselectivity* (Chapter 14). In a ligogenic process, each sigma bond is formed by the approach of the reacting moieties along specific trajectories and through vectospecific or nonvectospecific alignments. For a given vectospecific or nonvectospecific alignment, the exact alignment of the two moieties with respect to each other, at a given point in time, represents an angulospecific alignment. Anguloselectivity refers to the preference for one angulospecific alignment over another (or others). We demonstrate that anguloselectivity complements elegantly the concept of vectoselectivity.

At the end of Volume 2, we append a generalized system for assigning specific stereodescriptors to stereotopic/paired polycentric planar molecular faces (half-spaces) (Addendum C), and a designation of paired stereotopic molecular faces and stereotopic ligands (at tetrahedral and trigonal carbon atoms) (Addendum D).

Volume 3 starts with the definition of the prostereogenicity and prochirotopicity of atoms (Chapter 15). Since stereotopicity and chirotopicity are *independent* attributes of ligand atoms, we derive *four* composite designations of an atom - achiroastereogenic (achirotopic/astereogenic, type o), chiroastereogenic (chirotopic/astereogenic, type o\*), achirostereogenic (achirotopic/stereogenic, type s), and chirostereogenic (chirotopic/stereogenic, type s\*) – and provide a subclassification of achirostereogenic (type o) and chirostereogenic (type o\*) atoms. We then proceed to define and illustrate stereogenization/destereogenization (generation/loss of a stereogenic atom), chirogenization/dechirogenization (generation/loss of a chirotopic atom), and chirostereogenization/dechirostereogenization (generation/loss of a chirostereogenic atom) in organic reactions (Chapter 16).

In Chapter 17, we develop a universal, systematic stereochemical classification of chemical transformations based on the overall changes in stereogenicity of the atoms involved during a given transformation. Three types of stereotopoprocesses are discerned – *viz.* those that are accompanied by (a) overall loss, (b) no gain/loss, and (c) overall gain of *stereogenic* atoms; we label these transformations as stereopolysis, stereopomutation, and stereopogenesis, respectively. Further subclassification is effected using the joint criteria of rotativity (expected optical activity) and stereoselectivity (preferential formation of one stereoisomers over another). Lastly, we provide a novel definition of stereospecificity. The merits of the classification of stereotopoprocesses are examined in relation to asymmetric synthesis, chiral synthesis, asymmetric induction, asymmetric destruction, kinetic resolution, and asymmetric desymmetrization.

Finally, in Chapter 18 we present an alternative, universal stereochemical classification of chemical transformations based on (a) overall loss, (b) no loss/gain, and (c) overall gain of *chirotopic* atoms; we label these chirotopoprocesses as chirotopolysis, chirotopomutation and chirotopogenesis, respectively. Further subclassification is carried out using the dual criteria of rotativity (expected optical activity) and stereoselectivity (preferential formation of one stereoisomer over another). We also introduce and define the novel concepts of chiroselectivity and chirospecificity. Finally, the merits of the classification of chirotopoprocesses are discussed, and the stereotopoprocesses and chirotopoprocesses are correlated in relation to the stereotopic molecular faces.

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December , 2001  
Tarrytown, New York

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"Everybody knows more than somebody,  
but nobody knows more than everybody."

E. Esar, 20,000 Quips & Quotes, p.456.

# 15

## On the Stereogenicity and Prostereogenicity of Bonded Atoms

### I. Stereogenicity and Chirotopicity of $sp^2$ and $sp^3$ Atoms

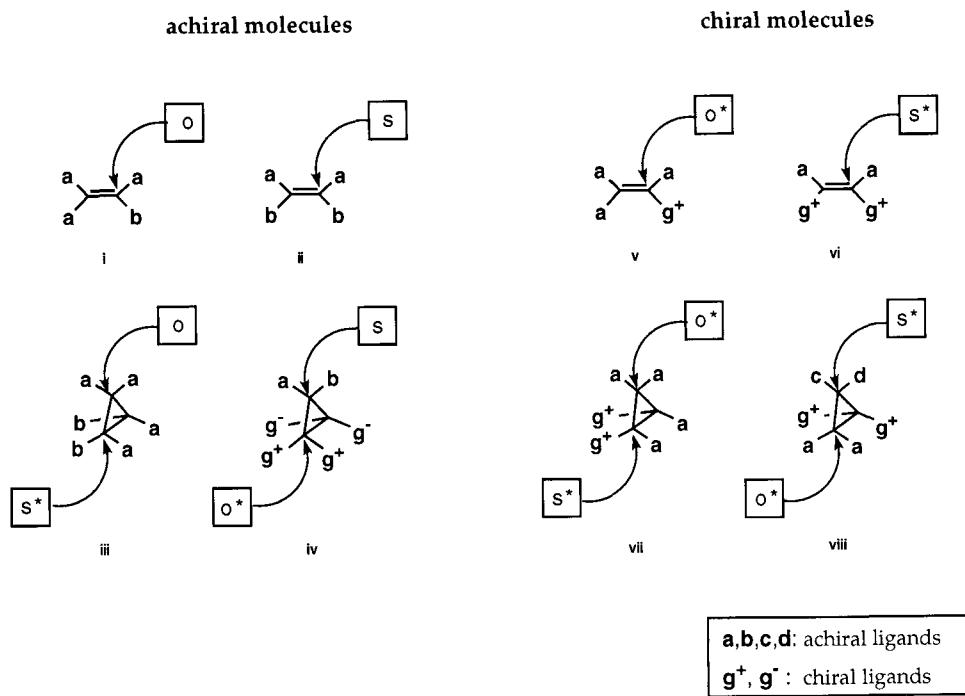
According to Mislow and Siegel, an atom in a given molecule possesses two independent but intimately intertwined stereochemical attributes - *stereogenicity* and *chirotopicity*.<sup>1</sup> The former attribute is defined by a specific relationship between two given sites, whereas the latter attribute describes the chirality/achirality of the molecular field. An n-coordinate ( $n \geq 3$ )  $sp^2$ - or  $sp^3$ -hybridized C atom in a molecule is said to be *stereogenic*, if interchange of any two of its ligands generates a different stereomorphic (enantiomeric or diastereomeric) form of the molecule, or, *astereogenic*, if interchange of said two ligands transforms the molecule to a homomer. An atom is *chirotopic*, if it resides in a chiral molecular field, or, *achirotopic*, if it is situated in an achiral field. One should recall that points/atoms situated in the two complementary enantiotopic hemispheres of an achiral molecule are necessarily chirotopic.

It follows that there are four composite designations of an atom - *achirotopic/astereogenic* (ac/as, type o), *achirotopic/stereogenic* (ac/s, type s), *chirotopic/astereogenic* (c/as, type o\*), and *chirotopic/stereogenic* (c/s, type s\*). The condensed, single-term descriptions of these atoms are *achiroastereogenic* (type o), *chiroastereogenic* (type o\*), *achirostereogenic* (type s), and *chirostereogenic* (type s\*), respectively (Table 15.1). For carbon, each of these atoms may be  $sp^2$ - or  $sp^3$ -hybridized; sp-hybridized atoms may be only type o or o\*.

Composite Description	Abbreviated Description	Atom Type	Single-term Description
achirotopic/astereogenic	ac/as	o	<i>achiroastereogenic</i>
chirotopic/astereogenic	c/as	o*	<i>chiroastereogenic</i>
achirotopic/stereogenic	ac/s	s	<i>achirostereogenic</i>
chirotopic/stereogenic	c/s	s*	<i>chirostereogenic</i> <sup>2</sup>

Table 15.1. Classification of Astereogenic/Stereogenic, Achirotopic/Chirotopic Atoms

The eight examples in Figure 15.1 illustrate the four types of astereogenic/stereogenic, achirotopic/chirotopic atoms - o, o\*, s, and s\*. It turns out that (a) all four types of atoms - o, o\*, s and s\* - are present in achiral molecules, and (b) only o\* and s\* are found in chiral molecules.



**Figure 15.1.** Achirostereogenic (o), Chiroastereogenic (o\*), Achirostereogenic (s) and Chirostereogenic (s\*) sp<sup>2</sup> and sp<sup>3</sup> Atoms in Achiral and Chiral Molecules

In Chapter 12, we introduced the fundamental eleven types of stereotopic molecular faces, and pointed out the distinctions between the different subclasses of molecular faces. With the help of the o/s/o\*/s\* designations given above, one can discern further distinctions among the eleven types of faces. In Figure 15.2, we provide examples of the four types of atoms in molecules incorporating the eleven molecular faces. In sum, one finds o atoms in molecules with h1, h2, h3, e, d2, d3 faces, s atoms in molecules possessing h3, e, d1, d2 faces, o\* atoms in those with h4, h5, h6, d3, d4 faces, and, s\* atoms in molecules incorporating h6, e, d3 and d4 faces. Figure 15.2 also shows the type of atoms found in each subclass in the bottom row of each frame. Thus, classes h1 and h2 have atoms type o; class h3 - types o and s; classes h4, h5 - type o\*; class h6 - o\* and s\*. Molecules with enantiotopic faces can have atom types o, s, and s\*. Among molecules with diastereotopic faces, d1 has atom type s; d2 - types o, and s; d3 - types o, o\* and s\*; d4 - types o\* and s\*. As shown in Chapters 16-18, changes in the specific types of all reactant atoms (o, o\*, s, s\*) serve as the basis for the stereochemical classification of organic transformations. This leads to discussions of stereotopoprocesses (stereotopogenesis, stereotopomutation, and stereotopolysis; Chapter 17), and, chirotopoprocesses (chirotopolysis, chirotopomutation, and chirotopogenesis; Chapter 18). The relationships of these new terms to stereoselectivity, asymmetric synthesis, and stereospecificity are also presented.

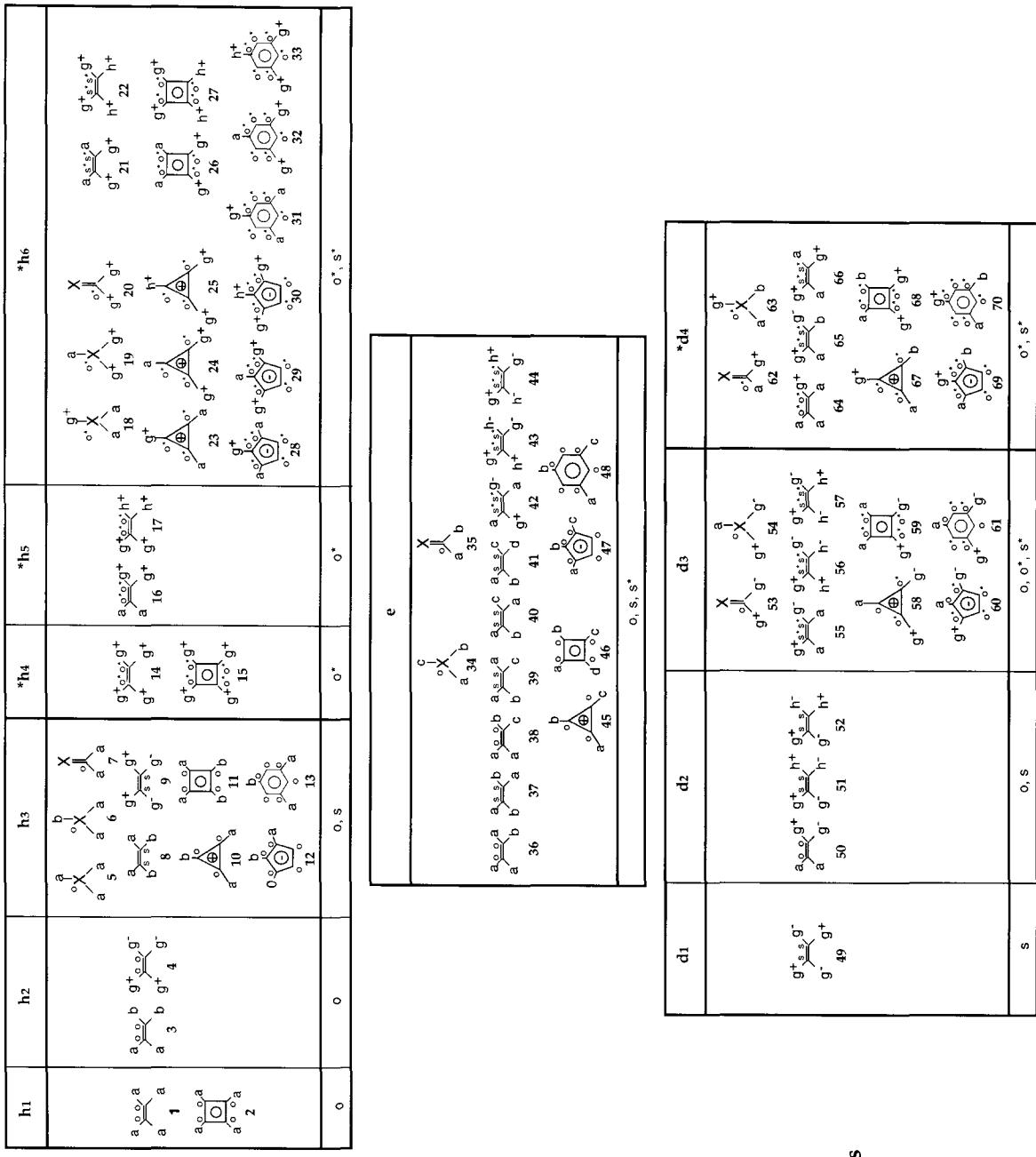


Figure 15.2. Achirostereogenic (o), Achirostereogenic (s), Chirostereogenic (o\*) and Chirostereogenic (s\*) Atoms in Stereotopic Molecular Faces

## II. Prostereogenicity and Chirotopicity of $sp^2$ and $sp^3$ Atoms

It turns out that astereogenic atoms (types o and o\*) can be subclassified into prostereogenic subclasses (*vide infra*) - either *proachirostereogenic* (precursor of s) or *prochirostereogenic* (precursor of s\*). This subclassification is based on the removal of the degeneracy of homomorphic ligands, by a stepwise substitution of the homomorphic ligands (e.g. achiral ligand a, or chiral ligand g+) on atoms o or o\*, by appropriate test ligands (e.g. achiral ligands b,c,d, or chiral ligands h+,i+,j+), until o (or o\*) is transformed into an atom of type s or s\*. The number of substitution steps (n) needed to go from atom o (or o\*) in the substrate to stereogenic system atom s (or s\*) atom in the substituted derivative, is termed the *degree of prostereogenicity* of atom o (or o\*), and is indicated as (pro)<sup>n</sup> in the designation of the original o (or o\*) atom. Figures 15.3 and 15.4 show how these ligand substitutions are effected in the case of divalent, trivalent and tetrahedral carbons, alkenes and allenes.

Figure 15.3 illustrates the process of determining the prostereogenicity of divalent  $sp^3$  and trivalent  $sp^3$  and  $sp^2$  atoms.

### A. Divalent $sp^3$ Atom

- (a) For divalent  $sp^3$  (or  $sp^2$ ) atom  $Ca_2$ : replace achiral ligand "a" by achiral ligand "b" (71→72).
- (b) For divalent  $sp^3$  (or  $sp^2$ ) atom  $Ca_b$ : add an achiral ligand "c" (72→73).
- (c) For divalent  $sp^3$  (or  $sp^2$ ) atom  $Cg_2^+$ : replace chiral ligand "g+" by chiral ligand "h+" (74→75).
- (d) For divalent  $sp^3$  (or  $sp^2$ ) atom  $Cg^+h^+$ , add achiral ligand "a" (75→76).

### B. Trivalent $sp^3$ Atom

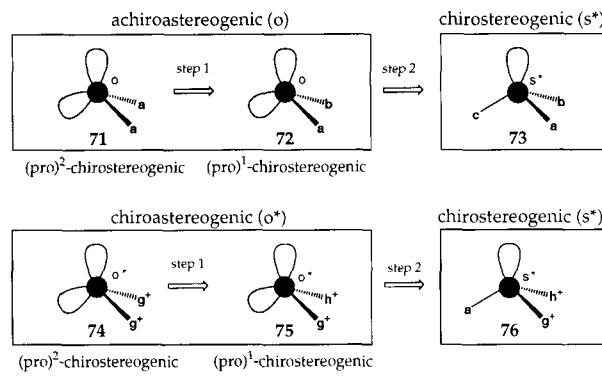
- (a) For trivalent  $sp^3$  atom  $Ca_3$ : replace achiral ligand "a" by achiral ligand "b" (77→78).
- (b) For trivalent  $sp^3$  atom  $Ca_2b$ : replace achiral ligand "a" by achiral ligand "c" (78→79).
- (c) For trivalent  $sp^3$  atom  $Cg_3^+$ : replace chiral ligand "g+" by chiral ligand "h+" (80→81).
- (d) For trivalent  $sp^3$  atom  $Cg_2^+h^+$ : replace chiral ligand "g+" by chiral ligand "i+" (81→82).

### C. Trivalent $sp^2$ Atom

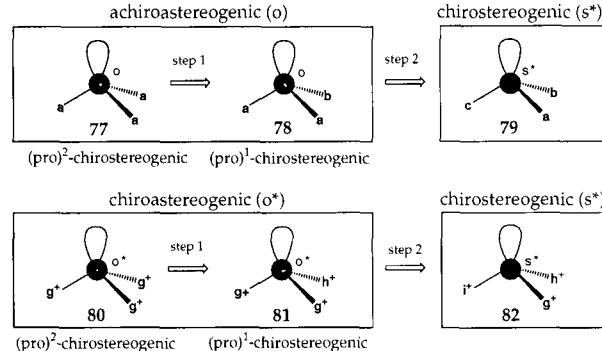
- (a) For trivalent  $sp^2$  atom  $Ca_2X$ : replace achiral ligand "a" by achiral ligand "b" (83→84).
- (b) For trivalent  $sp^2$  atom  $Ca_bX$ : add an achiral ligand "c" (84→85).
- (c) For trivalent  $sp^2$  atom  $Cg_2^+X$ : replace chiral ligand "g+" by chiral ligand "h+" (86→87).
- (d) For trivalent  $sp^2$  atom  $Cg^+h^+X$ , add achiral ligand "a" (87→88).
- (e) For trivalent  $sp^2$  atom  $Ca_2Xa$  (X=C,N,O<sup>+</sup>): replace achiral ligand "a" by achiral ligand "b" (89→90).
- (f) For trivalent  $sp^2$  atom  $Cg_2^+Xg^+$ : replace chiral ligand "g+" by chiral ligand "h+" (91→92).

Figure 15.4 illustrates the process of determining the prostereogenicity of tetraivalent  $sp^3$  and trivalent  $sp^2$  atoms. The rules for breaking the degeneracy of homomorphic ligands of tetraivalent  $sp^3$  and  $sp^2$  atoms are given below.

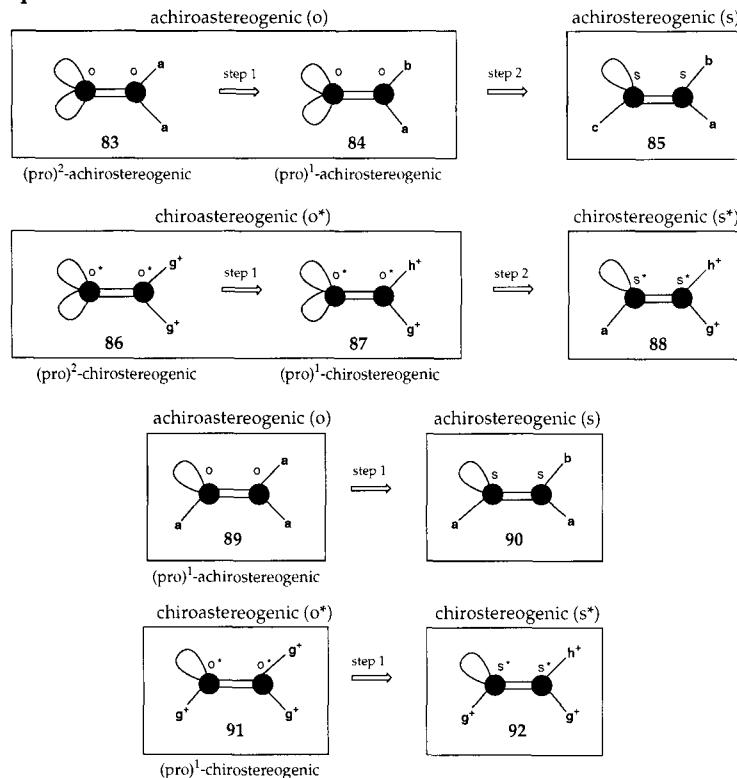
### Divalent $sp^3$ Atom



### Trivalent $sp^3$ Atom

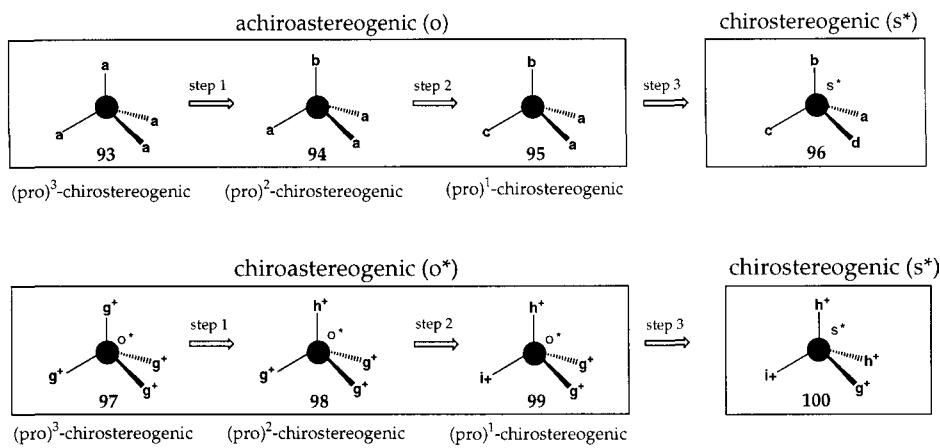


### Trivalent $sp^2$ Atom

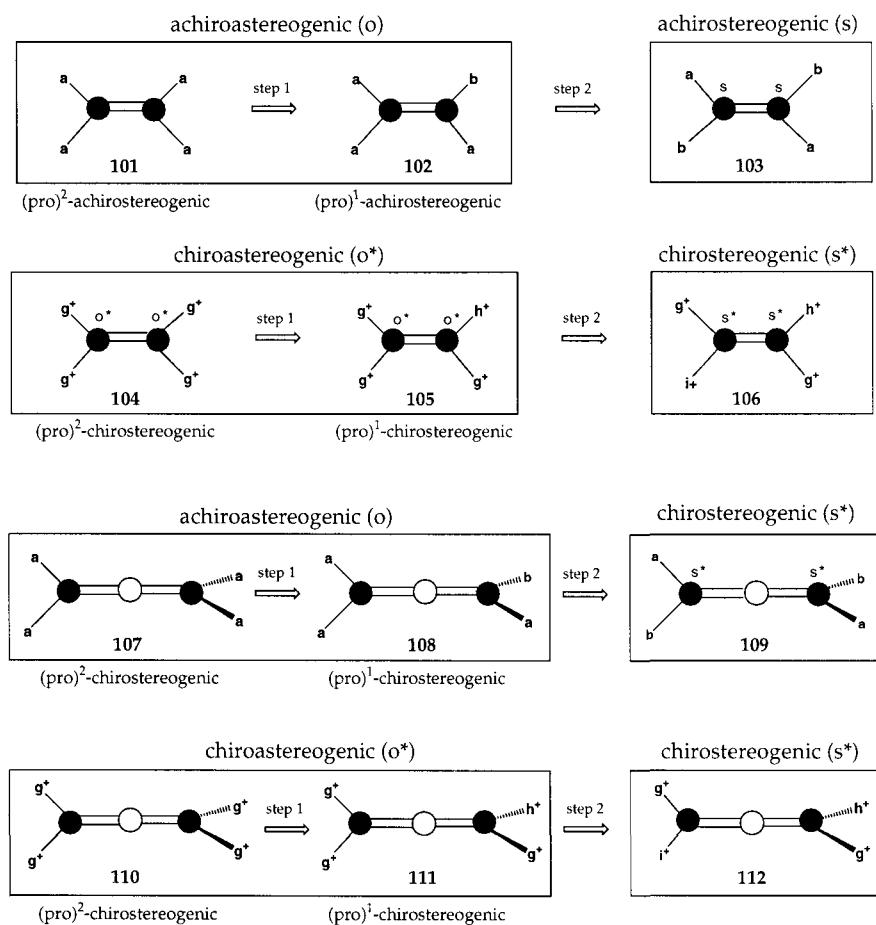


**Figure 15.3.** Stepwise Substitutions of Homomorphous Ligands to Determine Prochirostereogenicity and Proachirostereogenicity of  $sp^2$  and  $sp^3$  Carbons (atoms marked with black dots)

## Tetrahedral sp<sup>3</sup> Atom



## Trivalent sp<sup>2</sup> Atom



**Figure 15.4.** Stepwise Substitutions of Homomorphous Ligands to Determine Prochirostereogenicity and Proachirostereogenicity of Tetrahedral Carbon, Alkenes and Allenes (atoms marked with black dots)

#### D. Tetravalent $sp^3$ Atom

(a) For  $Ca_4$ , replace "a" with "b" (93→94), for  $Ca_3b$  replace "a" with "c" (94→95), and for  $Ca_2cb$ , replace "a" with "d" (95→96). For  $Ca_2b_2$ , replace "a" with "c", and subsequently, replace "b" with "d".

(b) For  $Cg_4^+$ , replace "g<sup>+</sup>" with "h<sup>+</sup>" (97→98), for  $Cg_3^+h^+$  replace "g<sup>+</sup>" with "i<sup>+</sup>" (98→99), and for  $Cg_2^+h^+i^+$  replace "g<sup>+</sup>" with "j<sup>+</sup>" (99→100). For  $Cg_2^+h_2^+$ , replace "g<sup>+</sup>" with "i<sup>+</sup>", and subsequently, replace "h<sup>+</sup>" with "j<sup>+</sup>".

(c) For  $Ca_2g^+g^-$  - break the degeneracy of a's first (replace "a" with "b") and, subsequently, replace "g<sup>+</sup>" with "h<sup>+</sup>".

#### E. Trivalent $sp^2$ Atom

For alkenes and allenes of type  $a_2C=Ca_2$  and  $a_2C=C=Ca_2$ , respectively, break the degeneracy  $a_2$  at one end, by substitution with achiral ligand "c" (101→102, 107→108), and subsequently, at the other end replace "b" with "d" (102→103 and 108→109). For  $g_2^+C=Cg_2^+$  and  $g_2^+C=C=Cg_2^+$ , break the degeneracy of g<sup>+</sup> by substitution of "g<sup>+</sup>" with "h<sup>+</sup>" (104→105 and 110→111), and subsequently, at the other end, replace "g<sup>+</sup>" with "i<sup>+</sup>" (105→106 and 111→112). The descriptions of the atom types are summarized in Table 15.2.

Description	Abbreviated Description	Atom Type	Single-term Description
achirostereogenic atom o (pro) <sup>3</sup> -chirostereogenic (pro) <sup>2</sup> -achirostereogenic (pro) <sup>2</sup> -chirostereogenic (pro) <sup>1</sup> -achirostereogenic (pro) <sup>1</sup> -chirostereogenic	(pro) <sup>3</sup> -cs (pro) <sup>2</sup> -as (pro) <sup>2</sup> -cs (pro) <sup>1</sup> -as (pro) <sup>1</sup> -cs	o o o o o	(pro) <sup>3</sup> -o (pro) <sup>2</sup> -o (pro) <sup>2</sup> -o (pro) <sup>1</sup> -o (pro) <sup>1</sup> -o
chirostereogenic atom o <sup>*</sup> (pro) <sup>3</sup> -chirostereogenic (pro) <sup>2</sup> -chirostereogenic (pro) <sup>1</sup> -chirostereogenic	(pro) <sup>3</sup> -cs <sup>*</sup> (pro) <sup>2</sup> -cs <sup>*</sup> (pro) <sup>1</sup> -cs <sup>*</sup>	o <sup>*</sup> o <sup>*</sup> o <sup>*</sup>	(pro) <sup>3</sup> -o <sup>*</sup> (pro) <sup>2</sup> -o <sup>*</sup> (pro) <sup>1</sup> -o <sup>*</sup>

**Table 15.2.** Classification of Prostereogenic Atoms o and o<sup>\*</sup>

Figure 15.5 (p. 8) presents the overall classification of stereogenic and prostereogenic atoms. The first criterion is that of stereogenicity. Stereogenicity is determined by interchanging paired ligands at a given skeletal atom and comparing the initial molecule (before interchange) and final molecule (after interchange). If the two states are stereomeric with respect to each other, then the atom bearing the two ligands in question is stereogenic. The second criterion is that of chirotopicity. A ligand is chirotopic, if it lies in a chiral molecular field; it is achirotopic, if it lies on a plane of symmetry or at a center of symmetry. Thus, astereogenic atoms are achirostereogenic (type o) or chirostereogenic (type o<sup>\*</sup>). In turn, stereogenic atoms are achirostereogenic (type s) or chirostereogenic (type s<sup>\*</sup>). Achirostereogenic atoms (type o) are subdivided into (pro)<sup>3</sup>- (e.g. 113), (pro)<sup>2</sup>- (e.g. 114-118), and (pro)<sup>1</sup>-prostereogenic atoms (e.g. 119-125). The (pro)<sup>2</sup>- atoms are either (pro)<sup>2</sup>-achirostereogenic (leading to s; e.g. 114,115) or (pro)<sup>2</sup>-chirostereogenic (leading to s<sup>\*</sup>; e.g. 116-118). The (pro)<sup>1</sup> atoms, in turn, are either (pro)<sup>1</sup>-achirostereogenic (leading to s; e.g. 119,120) or (pro)<sup>1</sup>-chirostereogenic (leading to s<sup>\*</sup>; e.g. 121-125). Chirostereogenic atoms (type o<sup>\*</sup>) are also (pro)<sup>3</sup>- (e.g. 126), (pro)<sup>2</sup>- (e.g. 127-135) and (pro)<sup>1</sup>- (e.g. 136-143).

Is skeletal atom stereogenic?

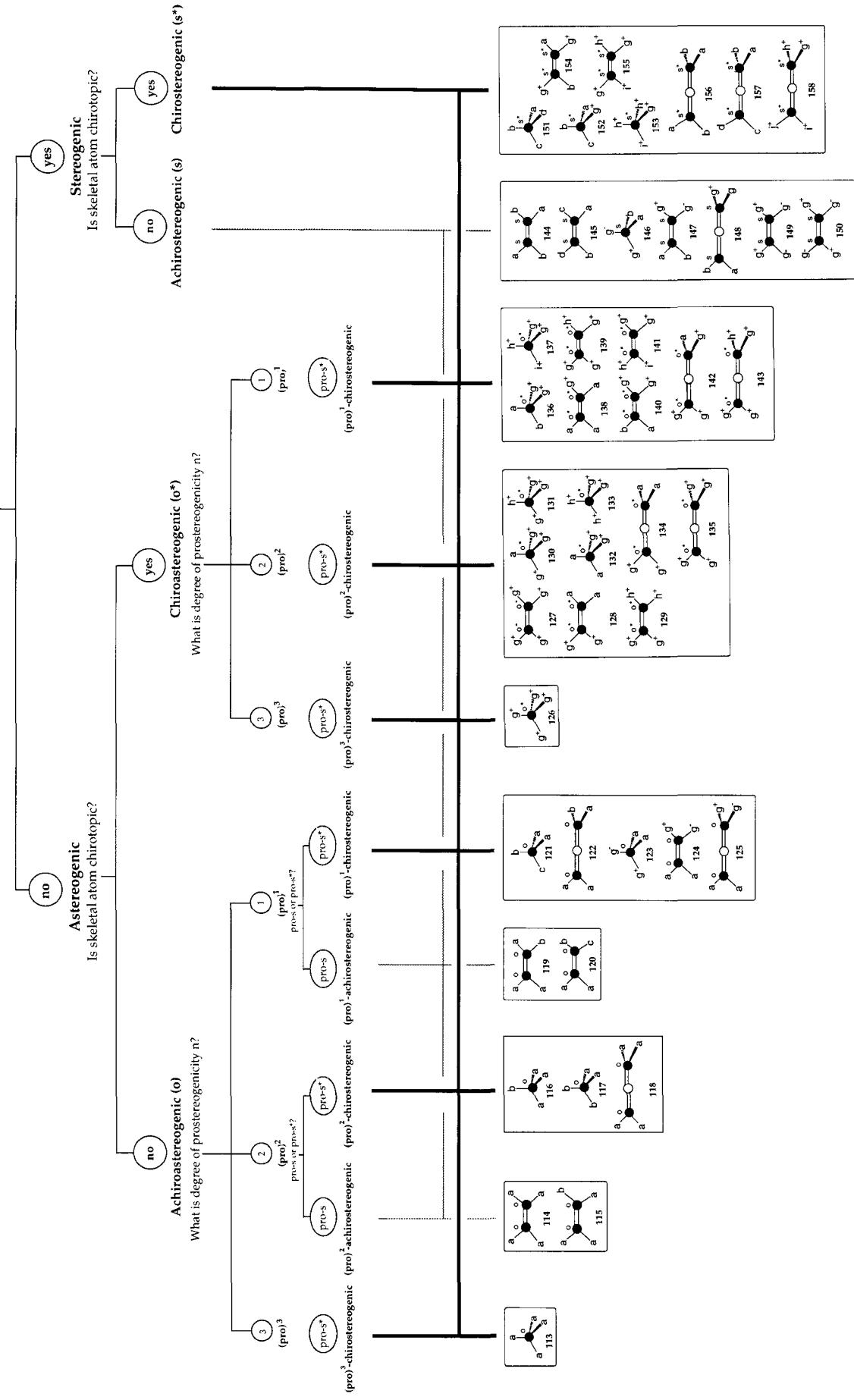


Figure 15.5. Classification of Astereogenic and Stereogenic Atoms

Stereogenic atoms are either achirostereogenic (e.g. 144-150) or chirostereogenic (e.g. 151-158).

The classifications given above will be used to define the stereochemical characteristics of chemical transformations (see Chapters 16-18).

### **Summary**

Since stereotopicity and chirotopicity are *independent* attributes of ligand atoms, we derived *four* composite designations of an atom - achiroastereogenic (achirotopic/astereogenic, type o), chiroastereogenic (chirotopic/astereogenic, type o\*), achirostereogenic (achirotopic/stereogenic, type s), and chirostereogenic (chirotopic/stereogenic, type s\*) – and also derived a subclassification of achiroastereogenic (type o) and chiroastereogenic (type o\*) atoms. Astereogenic atoms (types o and o\*) were subclassified into prostereogenic subclasses - either *proachirostereogenic* (precursor of s) or *prochirostereogenic* (precursor of s\*).

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"They always say time changes things, but you actually have to change them yourself."

**Andy Warhol**, *The Philosophy of Andy Warhol*.

# 16

## Defining Stereogenization/Destereogenization, Chirogenization/Dechirogenization, and Chirostereogenization/Dechirodestereogenization

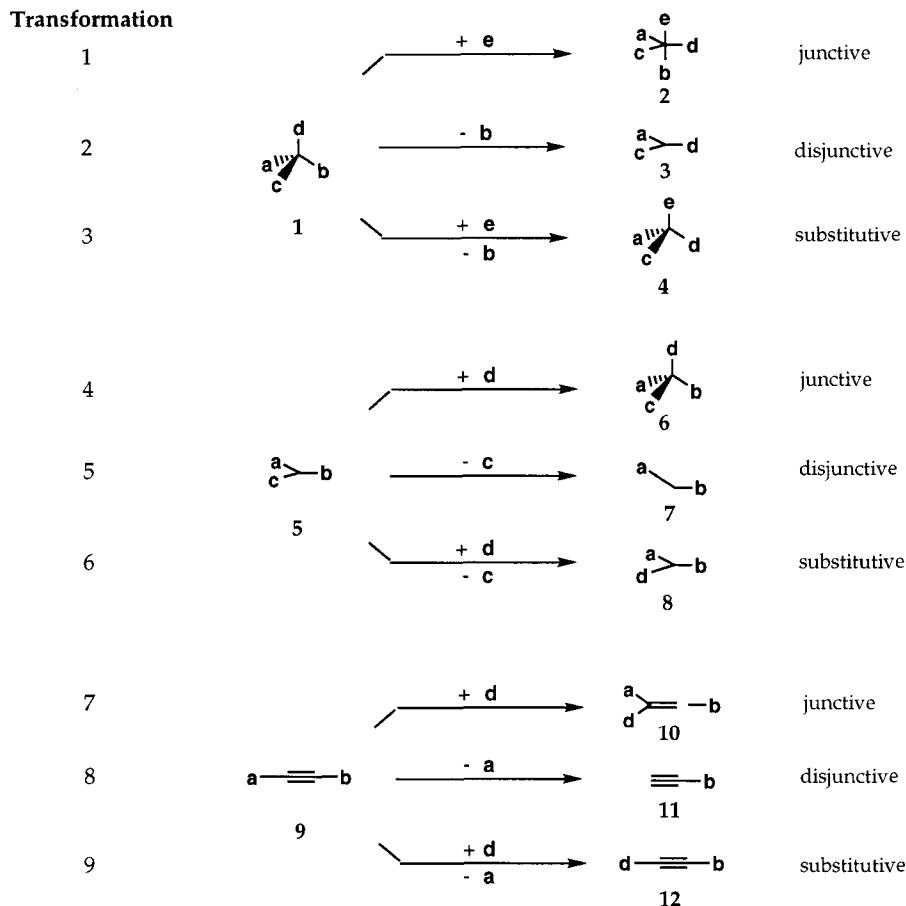
In the course of chemical reactions, every reactive atom of a reactant molecule transforming into that of a product may undergo changes in connectivity, hybridization and stereochemical attributes. The overall transformation embodies changes at all reacting atoms. We hereby zero-in on the changes in the stereochemical attributes of bonded atoms, and describe such changes concisely and unambiguously.

### I. Configurational Changes at $sp^3$ , $sp^2$ and $sp$ Carbon

The fundamental processes at atomic sites are *junctive* (associative, additive or complexative), *disjunctive* (dissociative, eliminative or decomplexative), or *synchronous* (substitutive, simultaneously junctive and disjunctive). The concept of junctivity/disjunctivity was discussed in Chapter 8.

In a given chemical transformation, reactive atoms may undergo changes in hybridization and valency. For example, a tetravalent  $sp^3$  atom in a reactant molecule may change to a (a)  $dsp^2$  pentavalent, (b)  $sp^2$  trivalent or (c) different  $sp^3$  tetravalent atom in the conjunctive state or product. The first of these is a junctive process (Figure 16.1, 1→2). The second one is a disjunctive process (1→3). In the third case, the process is substitutive (1→4, as in an  $S_N2$  transformation) - it is simultaneously "lytic" and "genic".

In the case of a trivalent  $sp^2$  atom, the changes are to a (a)  $sp^3$  tetravalent, (b)  $sp^2$  divalent, or (c) different  $sp^2$  trivalent atom, in the conjunctive state or product. The first of these is junctive ( $5 \rightarrow 6$ ); the second one is disjunctive ( $5 \rightarrow 7$ ); the last one is substitutive ( $5 \rightarrow 8$ ). Finally, in the case of an  $sp$  atom, the process transforms it to a (a) trivalent, (b) monovalent, or (c) a different divalent atom. The first one is junctive ( $9 \rightarrow 10$ ); the second one is disjunctive ( $9 \rightarrow 11$ ); and the last one is substitutive ( $9 \rightarrow 12$ ). Figure 16.1 portrays these idealized transformations.



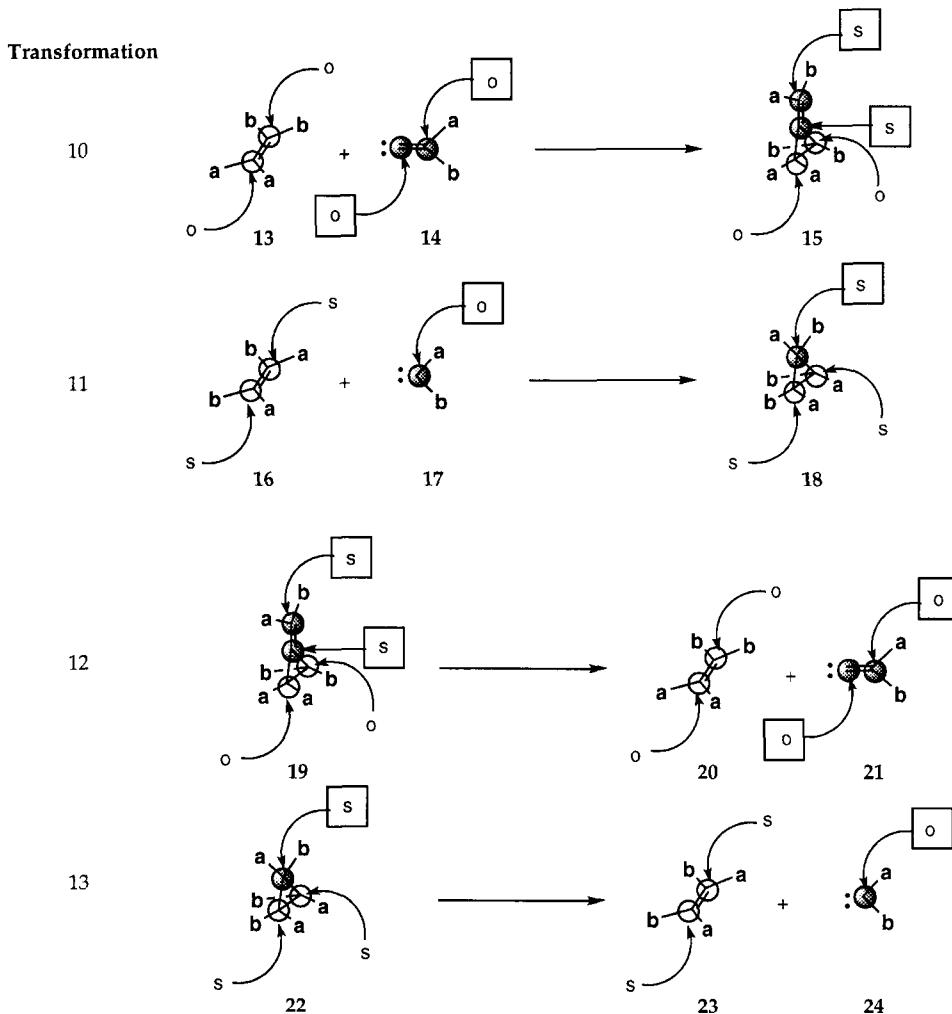
**Figure 16.1.** Junctive, Disjunctive and Substitutive Processes at  $sp^3$ ,  $sp^2$  and  $sp$  Carbons

## II. Stereogenization and Destereogenization of a Bonded Atom

We define *stereogenization* as the generation of a new stereogenic atom<sup>3</sup> (type s or  $s^*$ ) in the conjunctive state (transition state or product), from either an achiroastereogenic atom (type o), or a chiroastereogenic atom (type  $o^*$ ) in the reactant molecule.<sup>4</sup> Thus, stereogenizations involve changes of the type  $o^* \rightarrow s$ ,  $o \rightarrow s$ ,  $o^* \rightarrow s^*$ , and  $o \rightarrow s^*$ . Examples are given in Figure 16.2. The sum total of such changes, for all atoms in a reactant molecule undergoing a given transformation, constitutes the basis for stereotopoprocesses and chirotopoprocesses used in the universal stereochemical classification of chemical transformations (Chapters 17 and 18).

In transformation 10, the  $\text{sp}^2$  atoms of vinylcarbene **14** undergo junctive stereogenization, as they change from type o (in **14**) to type s (in **15**). The  $\text{sp}^2$  carbon atoms of **13** undergo no stereogenization (tantamount to a nonstereogenization), as they remain type o (in **13**), despite the fact that they undergo concomitant hybridizational changes. Similarly, in transformation 11, the central atom of **17** (type o) undergoes junctive stereogenization as it changes into type s (in **18**).

The transformation of a stereogenic atom (type s or  $s^*$ ) to an astereogenic atom (type o or  $o^*$ ) is termed *destereogenization*. We consider only disjunctive destereogenizations - ones that include such cases - transformations 12 and 13. In the former transformation, the alkenic  $\text{sp}^2$  carbons in **19** (type s) undergo destereogenization, as they change into type o in **21**; the two lower  $\text{sp}^3$  cyclopropyl carbons of **19** (type o) rehybridize into  $\text{sp}^2$ , but remain type o (nonstereogenization) in **20**. In transformation 13, the top  $\text{sp}^3$  carbon in **22** (type s) undergoes destereogenization as it is transformed into type o ( $\text{sp}^2$ ) in **24**; the two lower  $\text{sp}^2$  cyclopropyl carbons of **22** (type s) become  $\text{sp}^2$ -hybridized but remain type s (nonstereogenizations) in **23**.

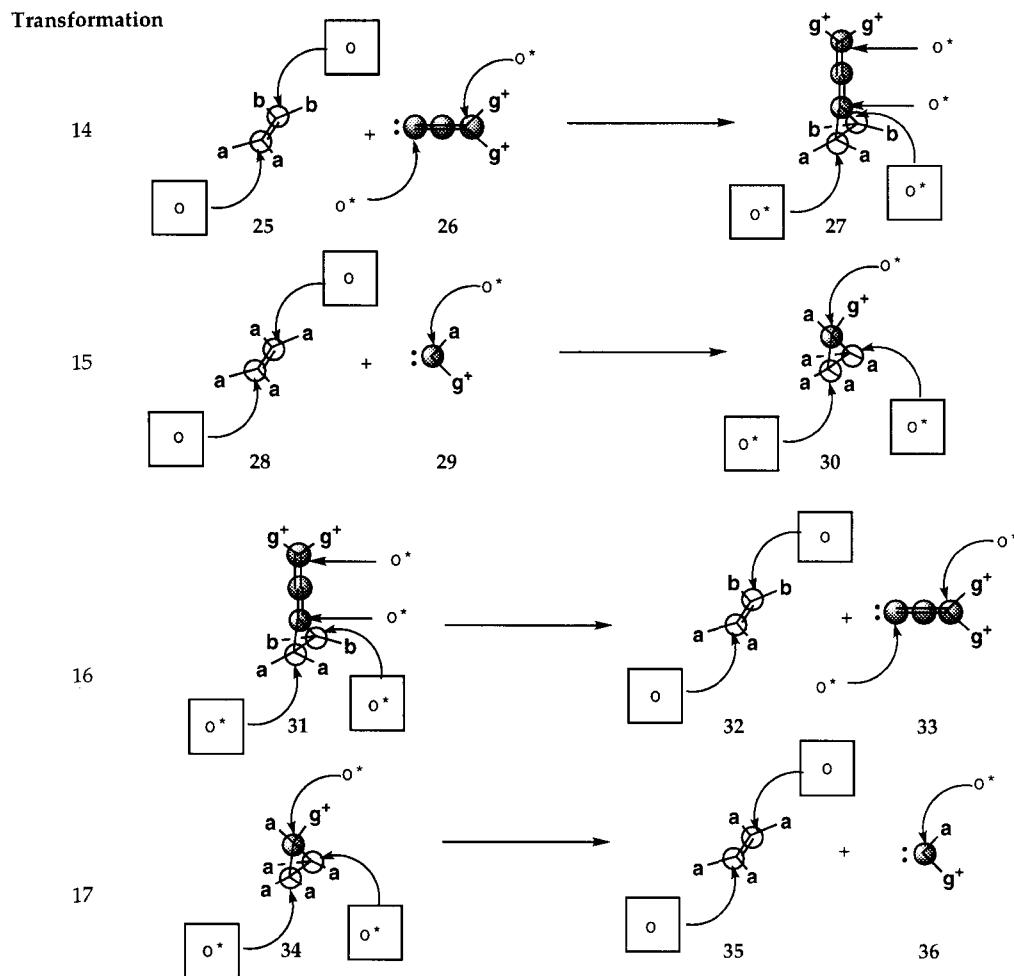


**Figure 16.2.** Stereogenization and Destereogenizations of Bonded Atoms

In nonstereogenizations, the changes involve  $s^*\rightarrow s$ ,  $o^*\rightarrow o$ ,  $o\rightarrow o$ ,  $o^*\rightarrow o^*$ ,  $s\rightarrow s$ ,  $s^*\rightarrow s^*$ ,  $s\rightarrow s^*$ , and  $o\rightarrow o^*$  conversions. In Figure 16.2, transformations 10 and 12 show  $o\rightarrow o$  nonstereogenizations, whereas transformations 11 and 13 involve  $s\rightarrow s$  nonstereogenizations.

### III. Chirogenization and Dechirogenization of a Bonded Atom

The generation of a chirotopic atom (type  $\text{o}^*$  or  $\text{s}^*$ ) from a precursor achirotopic atom (type  $\text{o}$  or  $\text{s}$ ) is termed *chirogenization*.<sup>5</sup> One sees such changes in atom→atom conversions of the following types:  $\text{o}\rightarrow\text{o}^*$ ,  $\text{s}\rightarrow\text{o}^*$ ,  $\text{o}\rightarrow\text{s}^*$ , and  $\text{s}\rightarrow\text{s}^*$ . In transformation 14 (Figure 16.3), the  $\text{sp}^2$  atoms of alkene 25 undergo junctive chirogenization as they are transformed from type  $\text{o}$  (in 25) to type  $\text{o}^*$  (in 27); the  $\text{sp}^2$  carbon atoms of 26 undergo no chirogenization (i.e. overall nonchirogenization), as they remain type  $\text{o}^*$  (in 27). Similarly, in transformation 15, the type  $\text{o}$  atoms of 28 become  $\text{o}^*$  in 30;  $\text{o}^*$  in 29 remains  $\text{o}^*$  (nonchirogenization), despite the change in hybridization from  $\text{sp}^2$  to  $\text{sp}^3$ .



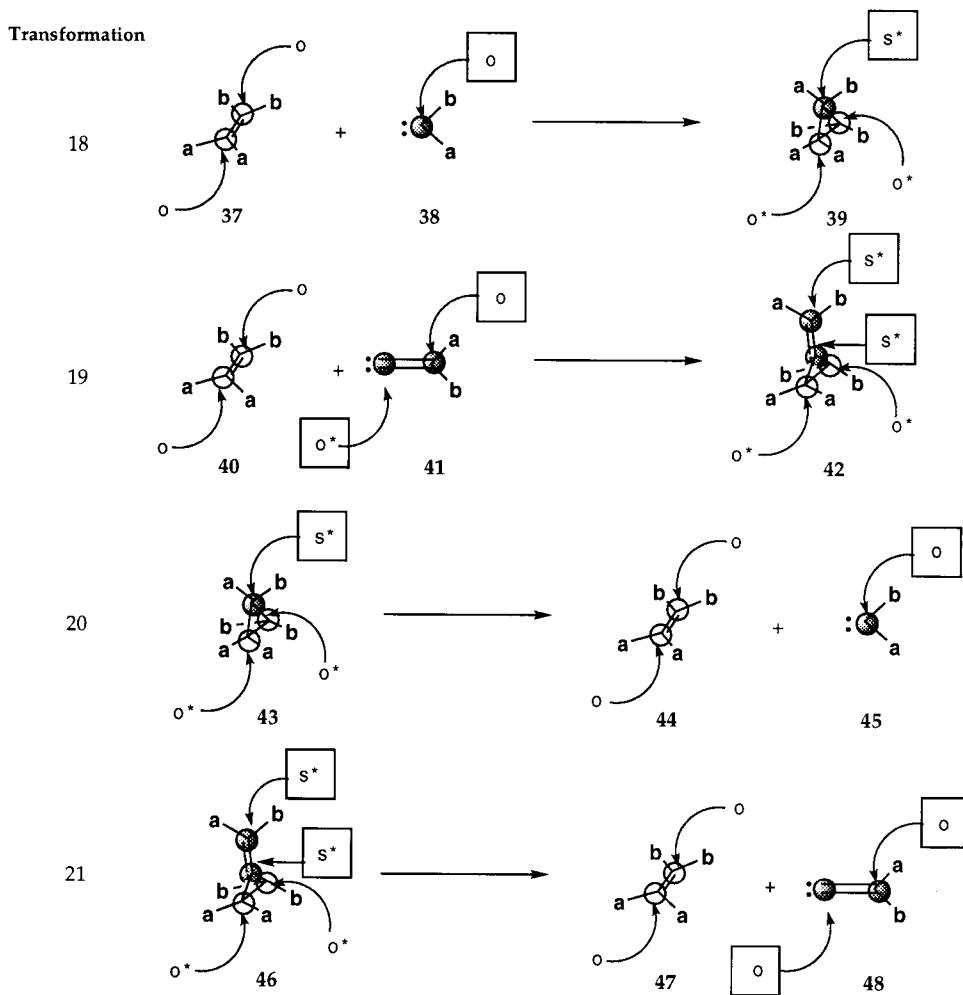
**Figure 16.3.** Chirogenizations and Dechirogenizations of Bonded Atoms

The conversion of a chirotopic atom (type  $\text{o}^*$  or  $\text{s}^*$ ) to an achirotopic atom (type  $\text{o}$  or  $\text{s}$ ) is known as *dechirogenization*. One observes such changes in  $\text{o}^*\rightarrow\text{o}$ ,  $\text{o}^*\rightarrow\text{s}$ ,  $\text{s}^*\rightarrow\text{o}$ , and  $\text{s}^*\rightarrow\text{s}$  conversions. Figure 16.3 also portrays two such cases – transformations 16 and 17. In transformation 16, the  $\text{sp}^3$  carbons of 31 (type  $\text{o}^*$ ) undergo dechirogenization as they are transformed into type  $\text{o}$  in 32; the two upper  $\text{sp}^2$  allenic carbons of 31 (type  $\text{o}^*$ ) remain type  $\text{o}^*$  in 33 (nonchirogenization). In

transformation 17, the lower  $sp^3$  carbons in 34 (type o\*) undergo dechirogenization, as they are transformed into type o ( $sp^2$ ) in 35; the upper  $sp^3$  carbon of 34 (type o\*) becomes  $sp^2$  but remains type o\* (nonchirogenization) in 36. Nonchirogenizations occur in  $o^*\rightarrow s^*$ ,  $o\rightarrow s$ ,  $s\rightarrow o$ ,  $s^*\rightarrow o^*$ ,  $o\rightarrow o$ ,  $o^*\rightarrow o^*$ ,  $s\rightarrow s$ , and  $s^*\rightarrow s^*$  interconversions. Each of transformation 14-17 involves  $o^*\rightarrow o^*$  nonchirogenizations.

#### IV. Chirostereogenization and Dechirodestereogenization of a Bonded Atom

The conversion of a chirostereogenic atom (type  $s^*$ ) from a precursor achiroastereogenic atom (type o) is a *chirostereogenization*. Figure 16.4 depicts two transformations involving chirostereogenization *viz.* transformations 18 and 19. In the former one, the  $sp^2$  atom of carbene 38 undergoes junctive chirostereogenization, as it is transformed from type o (in 38) to type  $s^*$  (in 39). The  $sp^2$  carbon atoms of 37 undergo chirogenization, as they become only type o\* (in 39). Similarly, type o atoms of 41 become type  $s^*$  in 42 (chirostereogenization), but atoms type o in 40 become type o\* (chirogenization), with concomitant change in hybridization from  $sp^2$  to  $sp^3$ .



**Figure 16.4.** Chirostereogenizations and Dechirodestereogenizations of Bonded Atoms

The transformation of a chirostereogenic atom (type  $s^*$ ) to an achiroastereogenic atom (type o) is known as a *dechirodestereogenization*. Figure 16.4 also portrays two such cases – transformations 20 and 21. In 20, the top  $sp^3$  carbon of 43 (type  $s^*$ ) undergoes

dechirodestereogenization as it is transformed into type o in **45**; the two lower sp<sup>3</sup> cyclopropyl carbons of **43** (type o\*) become type o in **44** (as a result of dechirogenization). In transformation 21, the allenyl sp<sup>2</sup> carbons in **46** (type s\*) undergo dechirodestereogenizations as they are transformed into type o in **48**; the two lower sp<sup>3</sup> carbons of **46** (type o\*) become type o in **47** (dechirogenization), with change of hybridization from sp<sup>3</sup> to sp<sup>2</sup>.

## V. Degree of Stereogenicity (s<sub>a</sub>) and Degree of Chirotopicity of an Atom (c<sub>a</sub>)

A given atom "a" is characterized by a degree of stereogenicity s<sub>a</sub>, and a degree of chirotopicity c<sub>a</sub>. For a stereogenic atom of type s and s\*, s<sub>a</sub>=+1; an astereogenic atom of type o and o\* is characterized by s<sub>a</sub>=0. For a chirotopic atom of type o\* and s\*, c<sub>a</sub>=+1; in the case of an achirotopic atom of type o or s, c<sub>a</sub>=0. Each atom "a" in a transformation is characterized by a change in the degree of stereogenicity Δs, where  $\Delta s = s_{a_2} - s_{a_1} = +1, 0 \text{ or } -1$ ; it is also characterized by a change in chirotopicity Δc, where  $\Delta c = c_{a_2} - c_{a_1} = +1, 0, \text{ or } -1$ . These changes are shown in Table 16.1 for destereogenizations, nonstereogenizations, stereogenizations, as well as dechirogenizations, nonchirogenizations, and chirogenizations:

	$\Delta s (s_{a_2} - s_{a_1})$	$\Delta c (c_{a_2} - c_{a_1})$
destereogenization		
s* → o	-1	-1
s → o	-1	0
s* → o*	-1	0
s → o*	-1	+1
nonstereogenization		
s* → s	0	-1
o* → o	0	-1
o → o	0	0
o* → o*	0	0
s → s	0	0
s* → s*	0	0
s → s*	0	+1
o → o*	0	+1
stereogenization		
o* → s	+1	-1
o → s	+1	0
o* → s*	+1	0
o → s*	+1	+1
dechirogenization		
o* → o	0	-1
o* → s	+1	-1
s* → o	-1	-1
s* → s	0	-1
nonchirogenization		
s* → o*	-1	0
s → o	-1	0
o → o	0	0
o* → o*	0	0
s → s	0	0
s* → s*	0	0
o* → s*	+1	0
o → s	+1	0
chirogenization		
o → o*	0	+1
s → o*	-1	+1
o → s*	+1	+1
s → s*	0	+1

**Table 16.1.** Δs and Δc in Stereogenizations and Chirogenizations

In Figure 16.5 we present further  $\Delta s$  and  $\Delta c$  values for junctive, disjunctive and substitutive changes of atoms.

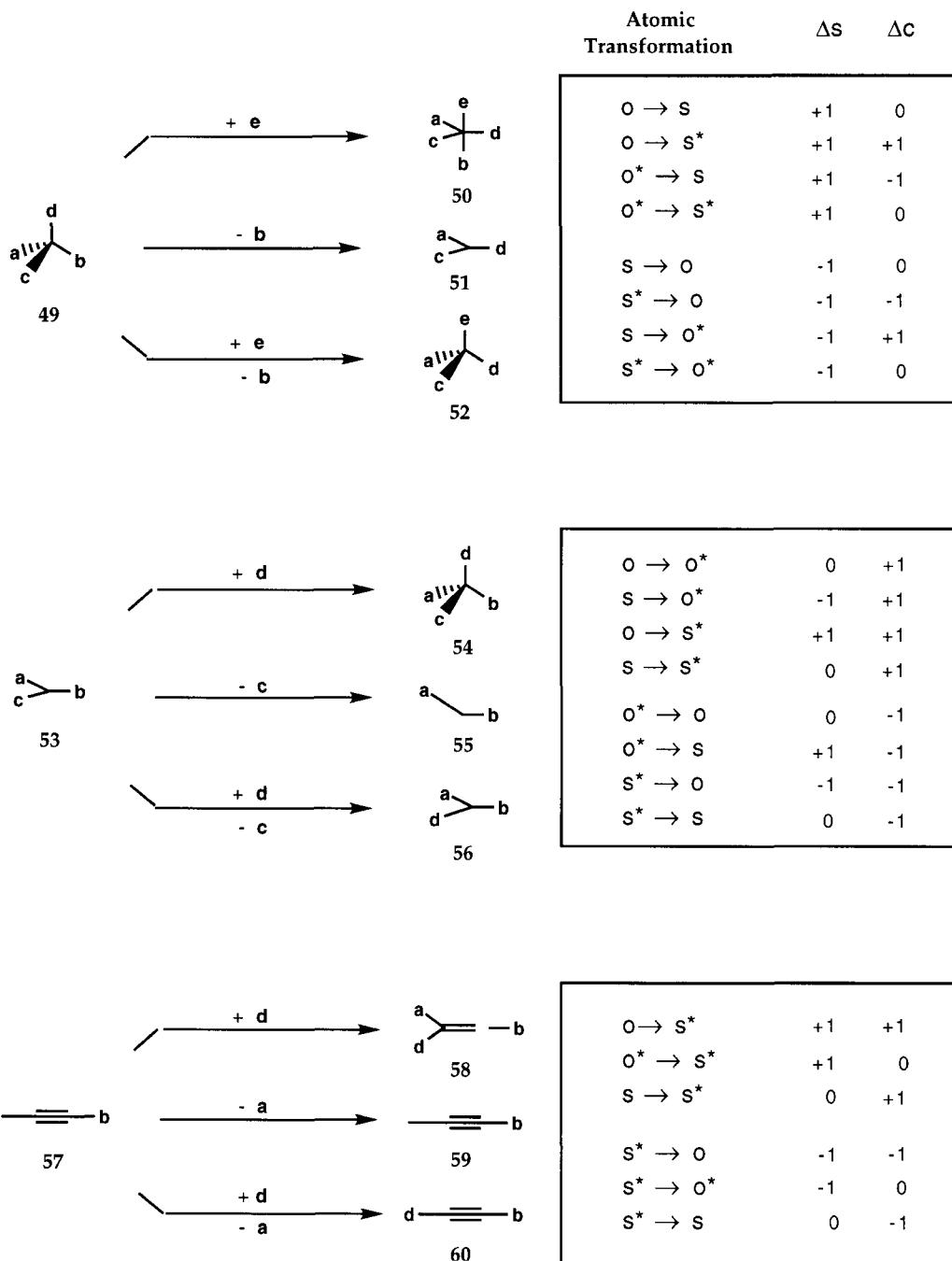


Figure 16.5.  $\Delta s$  and  $\Delta c$  in Junctive, Disjunctive and Substitutive Changes of Atoms

When changes in both attributes – stereogenicity and chirotopicity - are considered jointly, Table 16.1 is transformed into Table 16.2:

	$\Delta s (s_{a_2} - s_{a_1})$	$\Delta c (c_{a_2} - c_{a_1})$
<b>destereogenization</b>		
dechirodestereogenization $s^* \rightarrow o$	-1	-1
nonchirodestereogenization $s \rightarrow o$ $s^* \rightarrow o^*$	-1 -1	0 0
chirodestereogenization $s \rightarrow o^*$	-1	+1
<b>nonstereogenization</b>		
dechirononstereogenization $s^* \rightarrow s$ $o^* \rightarrow o$	0 0	-1 -1
nonchirononstereogenization $o \rightarrow o$ $o^* \rightarrow o^*$ $s \rightarrow s$ $s^* \rightarrow s^*$	0 0 0 0	0 0 0 0
chirononstereogenization $s \rightarrow s^*$ $o \rightarrow o^*$	0 0	+1 +1
<b>stereogenization</b>		
dechirostereogenization $o^* \rightarrow s$	+1	-1
nonchirostereogenization $o \rightarrow s$ $o^* \rightarrow s^*$	+1 +1	0 0
chirostereogenization $o \rightarrow s^*$	+1	+1

**Table 16.2.** Composite Classification of Destereogenizations, Nonstereogenizations and Stereogenizations

The processes in Table 16.2 may be classified alternatively by noting which ones engender (a) changes in both  $\Delta s$  and  $\Delta c$ , (b) changes only in  $\Delta s$  or  $\Delta c$ , or (c) no changes. The results are tabulated in Table 16.3 below:

Changes in both  $\Delta s$  and  $\Delta c$ :

	$\Delta s (s_{a_i} - s_{a_j})$	$\Delta c (c_{a_i} - c_{a_j})$
destereogenization		
dechirodestereogenization $s^* \rightarrow o$	-1	-1
chirodestereogenization $s \rightarrow o^*$	-1	+1
stereogenization		
dechirostereogenization $o^* \rightarrow s$	+1	-1
chirostereogenization $o \rightarrow s^*$	+1	+1

Changes only in  $\Delta s$ :

destereogenization			
nonchirodestereogenization $s \rightarrow o$	-1	0	
stereogenization			
nonchirostereogenization $o \rightarrow s$	+1	0	
$o^* \rightarrow s^*$	+1	0	

Changes only in  $\Delta c$ :

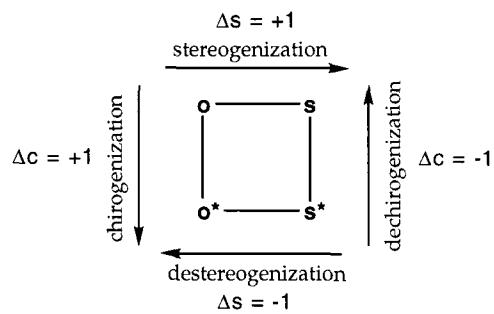
nonstereogenization			
dechirononstereogenization $s^* \rightarrow s$	0	-1	
$o^* \rightarrow o$	0	-1	
chirononstereogenization			
$s \rightarrow s^*$	0	+1	
$o \rightarrow o^*$	0	+1	

No changes in  $\Delta s$  and  $\Delta c$ :

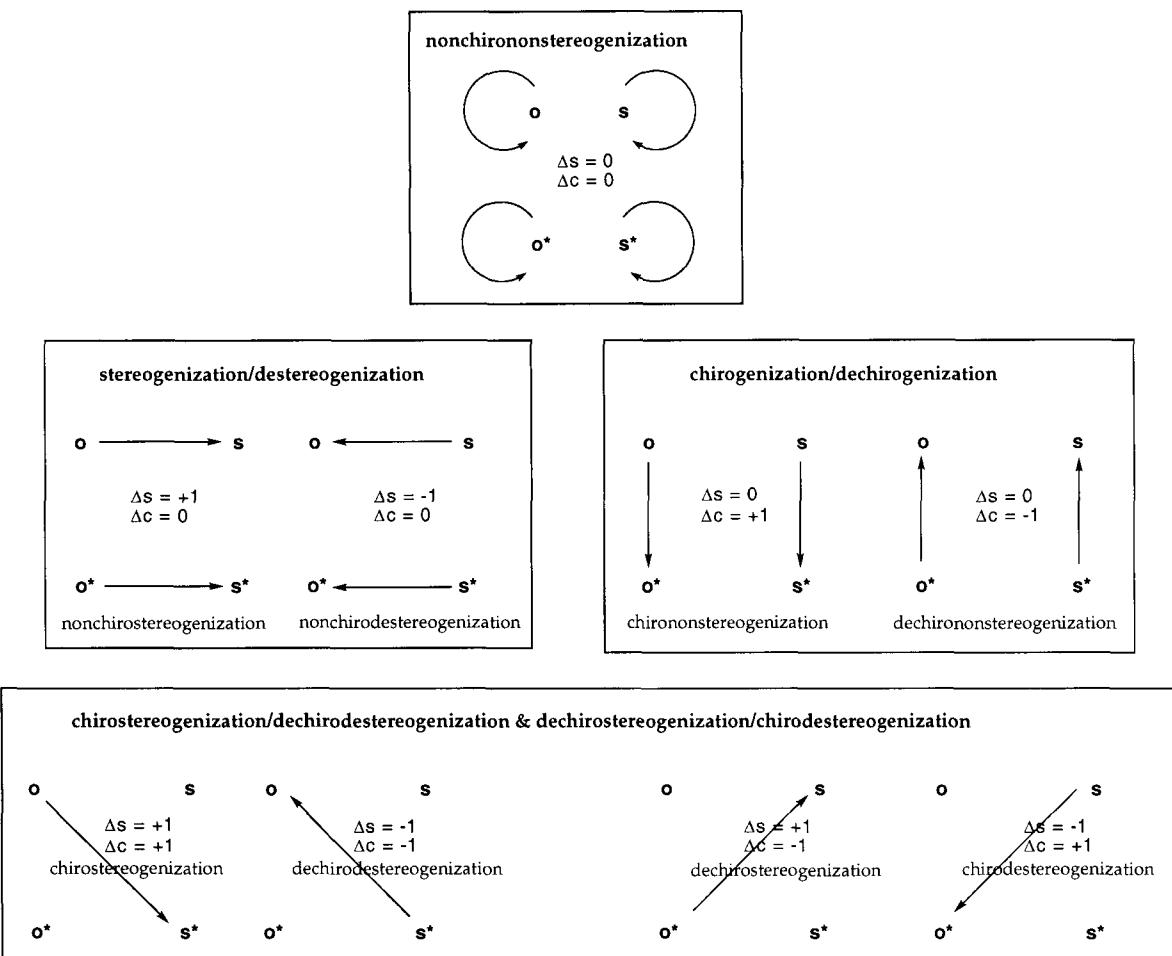
nonchirononstereogenization			
$o \rightarrow o$	0	0	
$o^* \rightarrow o^*$	0	0	
$s \rightarrow s$	0	0	
$s^* \rightarrow s^*$	0	0	

**Table 16.3.** Composite Classification of Destereogenizations/Stereogenizations, Nonstereogenizations and Nonchirononstereogenizations

Figures 16.6 and 16.7 depict the above changes in stereogenicity and chirotopicity, for all types of atom-atom transformations:



**Figure 16.6.**  $\Delta s$  and  $\Delta c$  in Stereogenizations/Destereogenizations and Chirogenizations/Dechirogenizations



**Figure 16.7.**  $\Delta s$  and  $\Delta c$  in All Processes including Chirostereogenizations and Dechirostereogenizations

When each of the transformative terms is linked to the junctive/disjunctive/substitutive aspect, the process becomes clearly defined e.g. substitutive stereogenization, disjunctive dechirogenization, junctive chirostereogenization, etc.

Figure 16.8 portrays a flow-chart of the interrelationships of all the terms we have advanced above. The classification chart in the said figure may be looked at two ways - from top to bottom, or bottom to top. The former classification gives primacy to stereogenization (reflected in changes of  $\Delta s$ ), whereas the latter, emphasizes chirogenization (revealed in changes in  $\Delta c$ ).

From the standpoint of stereogenization, one looks at Figure 16.8 from top to bottom. If  $\Delta s$  is negative, one has a destereogenization, as in  $s \rightarrow o$ ,  $s \rightarrow o^*$ ,  $s^* \rightarrow o$  and  $s^* \rightarrow o^*$  conversions. If  $\Delta s$  is zero, one is dealing with nonstereogenization, as in the following conversions:  $o \rightarrow o^*$ ,  $s \rightarrow s^*$ ,  $o^* \rightarrow o$ ,  $s^* \rightarrow s$ ,  $o \rightarrow o$ ,  $o^* \rightarrow o^*$ ,  $s \rightarrow s$ , and  $s^* \rightarrow s^*$ . If  $\Delta s$  is positive, one is looking at a stereogenization, as in  $o \rightarrow s$ ,  $o^* \rightarrow s$ ,  $o \rightarrow s^*$ ,  $o^* \rightarrow s^*$ . Each of these three classes is subdivided further on the basis of the corresponding  $\Delta c$  values.

For destereogenizations ( $\Delta s=-1$ ), if  $\Delta c = -1$ , one is dealing with dechirodestereogenization, as in  $s^* \rightarrow o$  conversions. On the other hand, if  $\Delta c=0$ , the process is a nonchirodestereogenization (as in  $s \rightarrow o$  and  $s^* \rightarrow o^*$ ); if  $\Delta c=+1$ , the process is a chirodestereogenization, as in  $s \rightarrow o^*$  conversions.

For nonstereogenizations ( $\Delta s=0$ ), if  $\Delta c = -1$ , one has a dechirononstereogenization - as in  $o^* \rightarrow o$  and  $s^* \rightarrow s$  conversions. On the other hand, if  $\Delta c=0$ , the process is a nonchirononstereogenization (as in  $o \rightarrow o$ ,  $o^* \rightarrow o^*$ ,  $s \rightarrow s$ ,  $s^* \rightarrow s^*$  transformations); in the case of  $\Delta c=+1$ , the process is a chirononstereogenization, as in  $o \rightarrow o^*$ ,  $s \rightarrow s^*$ .

Finally, for stereogenizations ( $\Delta s=+1$ ),  $\Delta c=-1$  characterizes a dechirostereogenization, as in  $o^* \rightarrow s$  conversions. On the other hand, if  $\Delta c=0$ , the process is a nonchirostereogenization (as in  $o \rightarrow s$ ,  $o^* \rightarrow s^*$  transformations); and if  $\Delta c=+1$ , the process is a chirostereogenization, as in  $o \rightarrow s^*$  transformations.

From the standpoint of chirogenization, one looks at Figure 16.8 from bottom to top. If  $\Delta c$  is  $-1$ , one has a dechirogenization, if  $\Delta c=0$ , a nonchirogenization, and if  $\Delta c=+1$ , a chirogenization. Here too, each of these processes is subclassified on the basis of the corresponding  $\Delta s$  values.

For dechirogenizations ( $\Delta c=-1$ ), if  $\Delta s$  is  $-1$ , one has a dechirodestereogenization, as in  $s^* \rightarrow o$  conversions. On the other hand, if  $\Delta s=0$ , the process is a dechirononstereogenization (as in  $o^* \rightarrow o$  and  $s^* \rightarrow s$  transformations); and if  $\Delta s=+1$ , the process is a dechirostereogenization as in  $o^* \rightarrow s$  transformations.

For nonchirogenizations ( $\Delta c=0$ ), if  $\Delta s$  is  $-1$ , one has a nonchirodestereogenization, as in  $s \rightarrow o$  and  $s^* \rightarrow o^*$  conversions. On the other hand, if  $\Delta s=0$ , the process is a nonchirononstereogenization (as in  $o \rightarrow o$ ,  $o^* \rightarrow o^*$ ,  $s \rightarrow s$ , and  $s^* \rightarrow s^*$  transformations); and if  $\Delta c=+1$ , the process is a nonchirostereogenization as in  $o \rightarrow s$ ,  $o^* \rightarrow s^*$  transformations.

Finally, for chirogenizations ( $\Delta c=+1$ ), if  $\Delta s$  is  $-1$  one has a chirodestereogenization, as in  $s \rightarrow o^*$  conversions. However, if  $\Delta s=0$ , the process is a chirononstereogenization (as in  $o \rightarrow o^*$  and  $s \rightarrow s^*$  transformations), and if  $\Delta s=+1$ , the process is a chirostereogenization (as in  $o \rightarrow s^*$  transformations).

Figure 16.8 also shows the correlation between stereogenization and chirogenization.

Dechirogenization correlates with dechirodestereogenization, dechirononstereogenization and dechirostereogenization (shown in thin lines, Figure 16.8). Nonchirogenization, on the other hand, correlates with nonchirodestereogenization, nonchirononstereogenization and nonchirostereogenization (shown in medium-intensity lines, Figure 16.8). Finally,

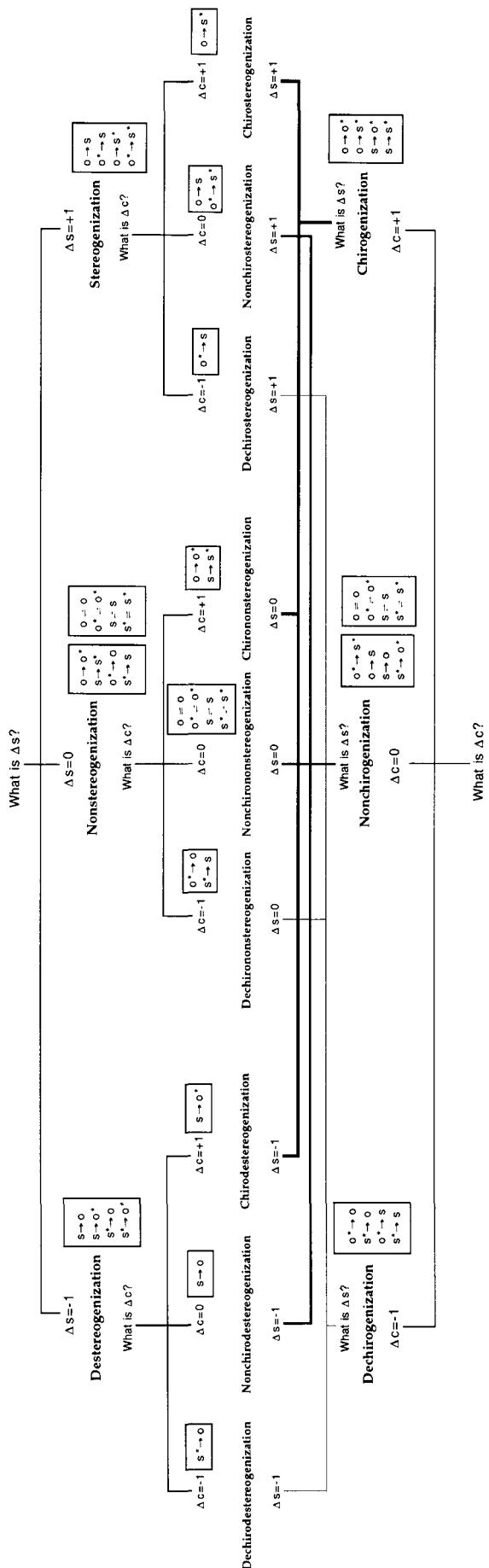


Figure 16.8. Classification of Stereogenization and Chirogenization

chirogenization correlates with chirodestereogenization, chirononstereogenization and chirostereogenization (shown in thick lines, Figure 16.8).

### Summary

We defined and illustrated stereogenization/destereogenization (generation/loss of a stereogenic atom), chirogenization/dechirogenization (generation/loss of a chirotopic atom), and chirostereogenization/dechirodestereogenization (generation/loss of a chirostereogenic atom) in organic reactions. We also defined degree of stereogenicity and degree of chirotopicity of an atom.

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"There is nothing lost by discarding your faults."

*Sophia Bedford-Pierce, The Key to Life.*

# 17

## Stereochemical Classification of Organic Transformations. 1. Stereotopoprocesses

The multitude of terms in the literature, describing the *outcome* of a given chemical transformation, is a result of the need to emphasize a particular characteristic or selective aspect of a given transformation, e.g. stereoselectivity of the process, optical purity of the product(s), the generation or destruction of an asymmetric center during the transformation, etc.. Asymmetric synthesis, chiral synthesis, asymmetric induction, asymmetric destruction, kinetic resolution, asymmetric desymmetrization<sup>6</sup> are such terms – ones that have described well, specific aspects of a wide variety of reactions. To date, there has been no attempt to depict all of these aspects as parts of a "big picture." Indeed, the problem of a systematic universal classification of chemical transformations has remained unsolved.

In Chapter 16 we defined stereogenization/destereogenization, chirogenization/dechirogenization, and chirostereogenization/dechirodestereogenization of an *individual atom* in a molecule engaged in a chemical transformation. We also defined the change in the degree of stereogenicity ( $\Delta s_a$ ) and degree of chirotopicity ( $\Delta c_a$ ) of *that particular reacting atom* in a transformation. In this chapter, we develop a universal classification of stereochemical reactions, on the basis of the net change of the number of stereogenic atoms,  $\Delta s$ , for the *overall* transformation.<sup>7</sup> Further subclassification is carried out on the basis of the dual criteria of rotativity<sup>8</sup> (expected optical activity) and stereoselectivity (preferential formation of one stereoisomer over another). Finally, the concept of stereospecificity is discussed, and the subclasses leading to rotative synthesis ("chiral synthesis"), stereoselective reactions, and asymmetric synthesis are identified. The merits of these classifications are discussed.

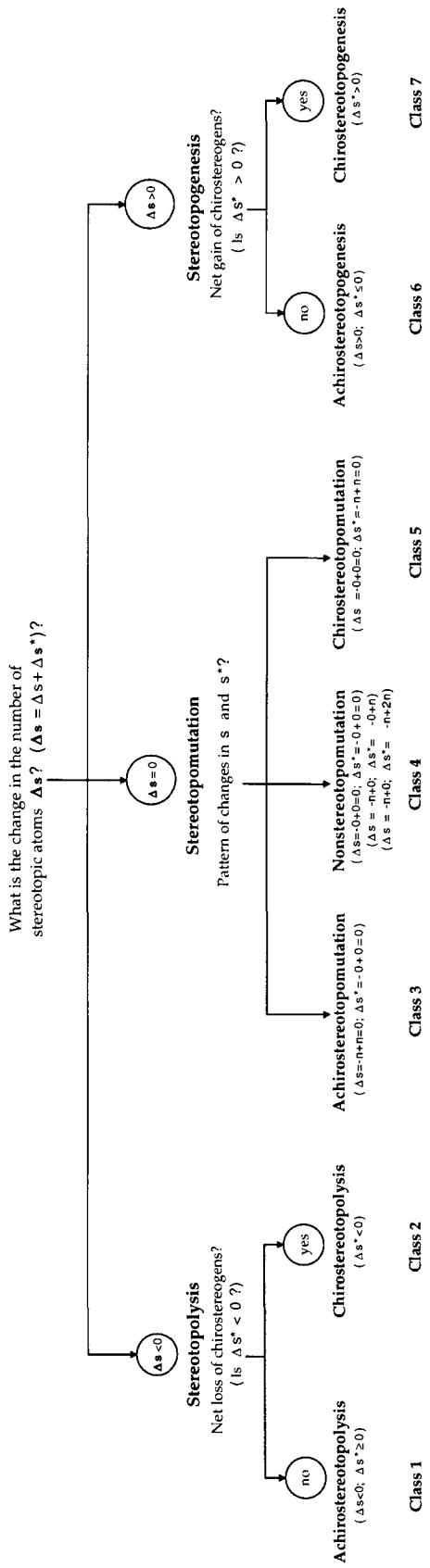


Figure 17.1. Stereochemical Classification of Stereotopoprocesses

## I. Stereopolysis, Stereopomutation, Stereopogenesis

Every atom in a molecule is either stereogenic (types s and s\*) or astereogenic (types o and o\*). The degree of stereogenicity of a given molecule,  $s_m$ , is equal to the sum of the degrees of stereogenicity of all stereogenic atoms of types s and s\*:

$$s_m = n_s \cdot s_a + n_{s^*} \cdot s_a = n_s \cdot (+1) + n_{s^*} \cdot (+1) = n_s + n_{s^*}. \quad (17.1)$$

Here,  $n_s$  and  $n_{s^*}$  are the numbers of achirostereogenic and chirostereogenic atoms, respectively;  $s_a$  is the degree of stereogenicity of a given stereogenic atom, be it of type s or s\*;  $s_a=+1$  (p. 16).

For a given *transformation*, the change in the degree of stereogenicity,  $\Delta s$ , is defined as follows:

$$\Delta s = \sum_{\text{products}} s_m - \sum_{\text{reactants}} s_m = \sum_{\text{products}} (n_s + n_{s^*})_{m_p} - \sum_{\text{reactants}} (n_s + n_{s^*})_{m_r} \quad (17.2)$$

$$= \sum (n_s(\text{reactants}) - n_s(\text{products})) + \sum (n_{s^*}(\text{reactants}) - n_{s^*}(\text{products})) \quad (17.3)$$

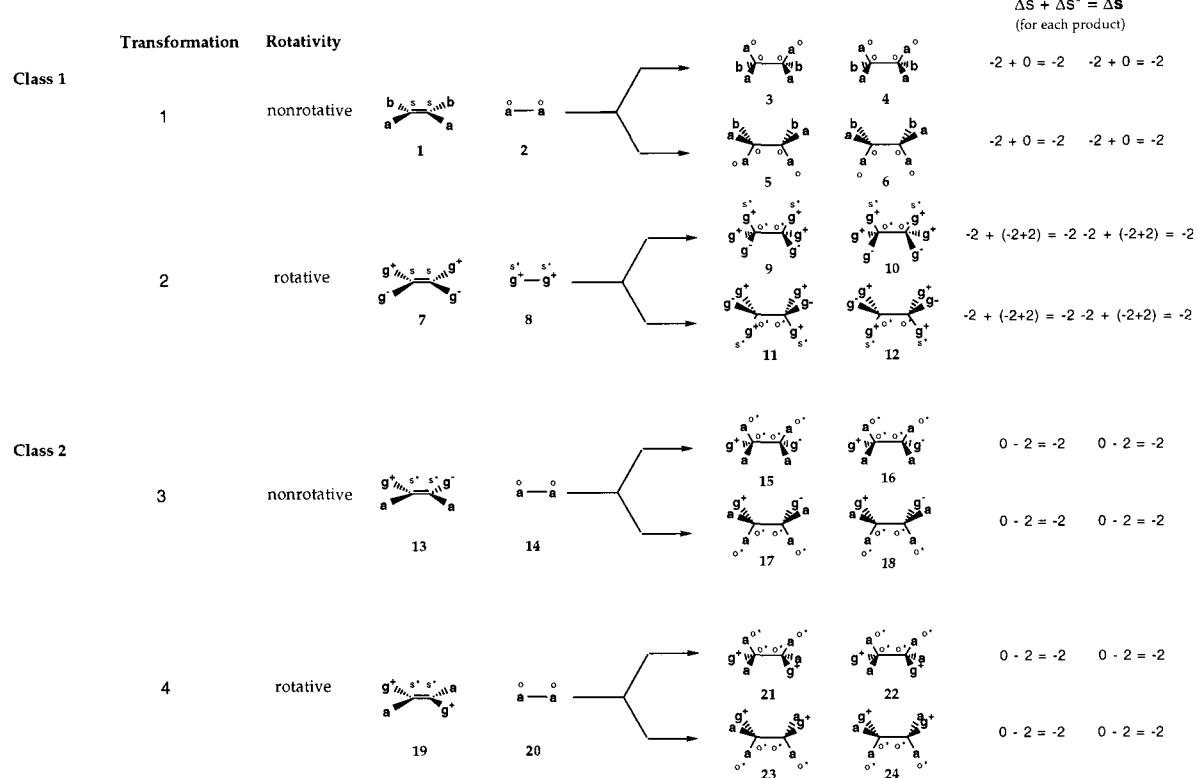
$$= \Delta s + \Delta s^* \quad (17.4)$$

where  $m_p$  and  $m_r$  are the numbers of stereogenic atoms in each product and reactant, respectively. In effect,  $\Delta s$ , for a given transformation, is the change in the number of stereogenic atoms of type s ( $\Delta s$ ), plus the change in the number of stereogenic atoms of type s\* ( $\Delta s^*$ ). A chemical transformation in which there is a net decrease in the number of stereogenic atoms,  $\Delta s < 0$ , is termed a *stereopolysis*. A transformation in which there is a net gain of stereogenic atoms,  $\Delta s > 0$ , is called a *stereopogenesis*. Finally, a transformation in which there is no net gain or loss of stereogenic atoms is referred to as *stereopomutation* ( $\Delta s = 0$ ). Figure 17.1 portrays these three classes of stereopoprocesses, along with their subclasses.

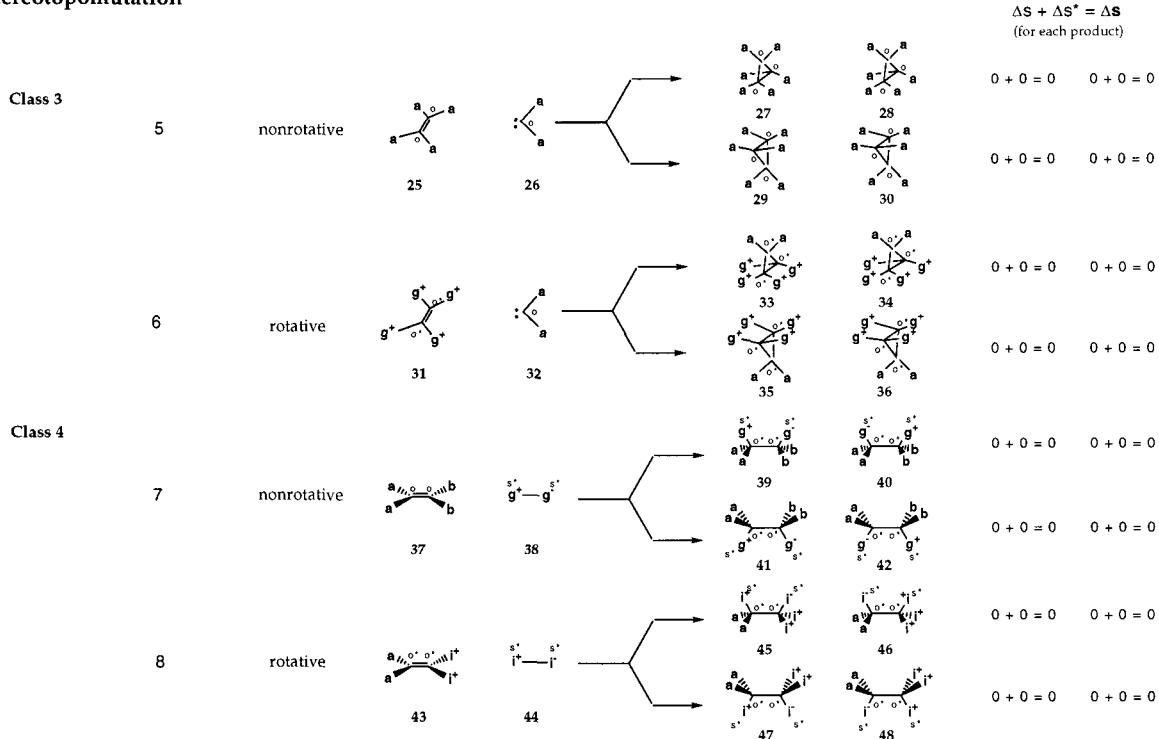
A stereopolysis ( $\Delta s < 0$ ) in which there is a net loss of chirostereogenic atoms s\* ( $\Delta s^* < 0$ ) is termed a *chirostereopolysis* (Class 2); that, in which  $\Delta s^* \geq 0$ , is an *achirostereopolysis* (Class 1). In stereopomutations ( $\Delta s = 0$ ), we discern three subclasses – *achirostereopomutation* - in which equal numbers of only s-type atoms are gained and lost during the transformation (Class 3), *nonstereopomutation* - in which offsetting changes in both s- and s\*-types occur (Class 4), and *chirostereopomutation*, where equal numbers of only s\*-type atoms are gained and lost during the transformation (Class 5). A stereopogenesis ( $\Delta s > 0$ ) in which a net gain of chirostereogenic atoms s\* ( $\Delta s^* > 0$ ) takes place is called *chirostereopogenesis* (Class 7); that in which  $\Delta s^* \leq 0$  is termed an *achirostereopogenesis* (Class 6). The processes of Classes 1-7 are collectively referred to as *stereopoprocesses*, and are presented in Figure 17.1.

Figures 17.2 and 17.3 portray examples of each of the seven classes of stereopoprocesses. The former figure depicts examples of stereopolysis and stereopomutation, while the latter figure shows examples of stereopogenesis. In these figures, each reaction is shown to lead to four possible products, irrespective of the morphic relationship between the members of the quartet; (that is, members within a quartet may be homomorphic, enantiomeric, diastereomeric, astereomeric or nonequimorphic with respect to each other). The two top structures, in the quartet of structures, result from the vectorial reversal (vectoselectivity) of the reagent, relative to substrate, at the *top* face of the substrate. The lower two structures in the quartet are the corresponding products resulting from the reaction of the reactant at the *bottom* face (facioselectivity) of the substrate. For each product, we indicate the values of  $\Delta s$ ,  $\Delta s^*$  and  $\Delta s$ . In the examples shown in Figures 17.2 and 17.3, the numbers are identical for each member of the quartet; this is not always so (*vide infra*). The said figures also indicate the nonrotative and rotative nature of the product mixture, in each of the *transformations* (*vide infra*).

## Stereotopolysis

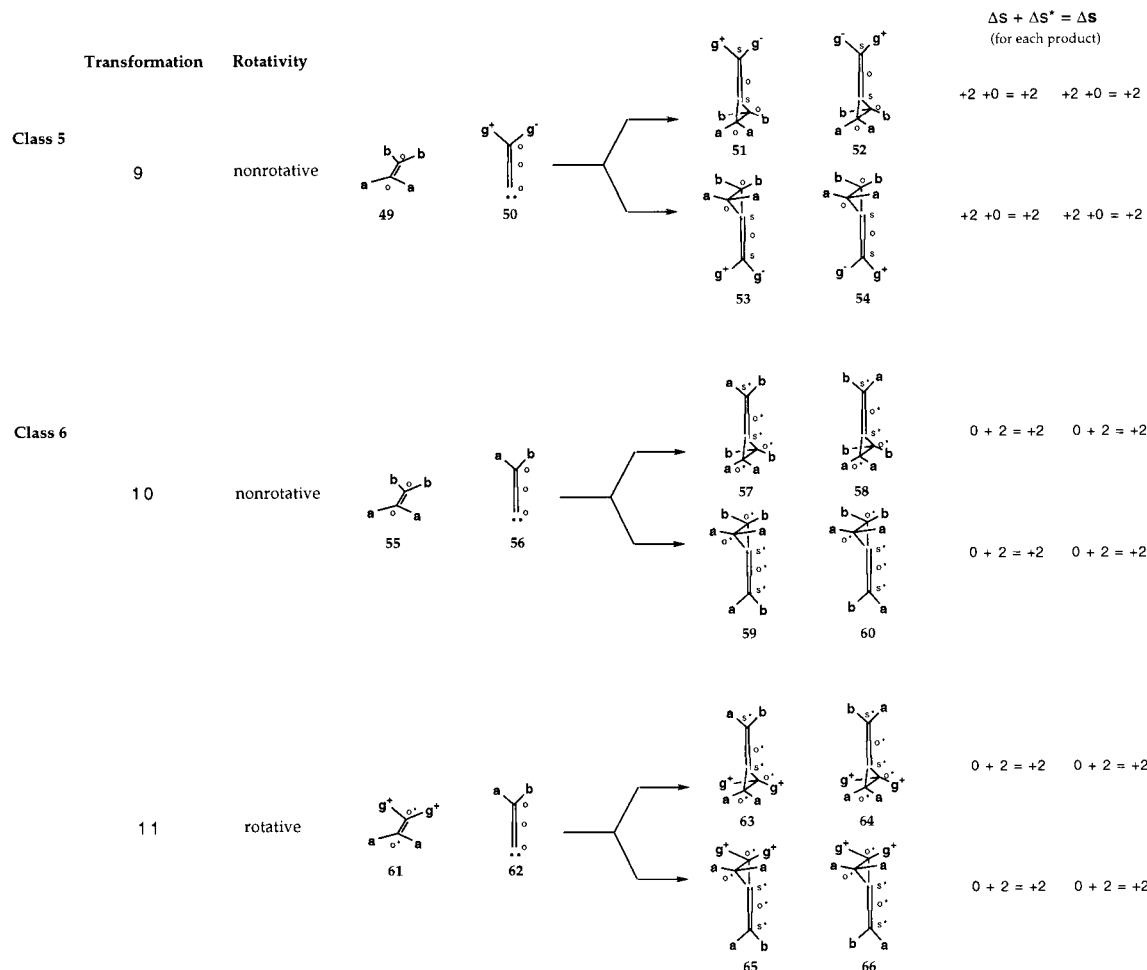


## Stereotopomutation



**Figure 17.2.** Examples of Nonrotative and Rotative Stereotopolysis and Stereotopomutation

## Stereotopogenesis

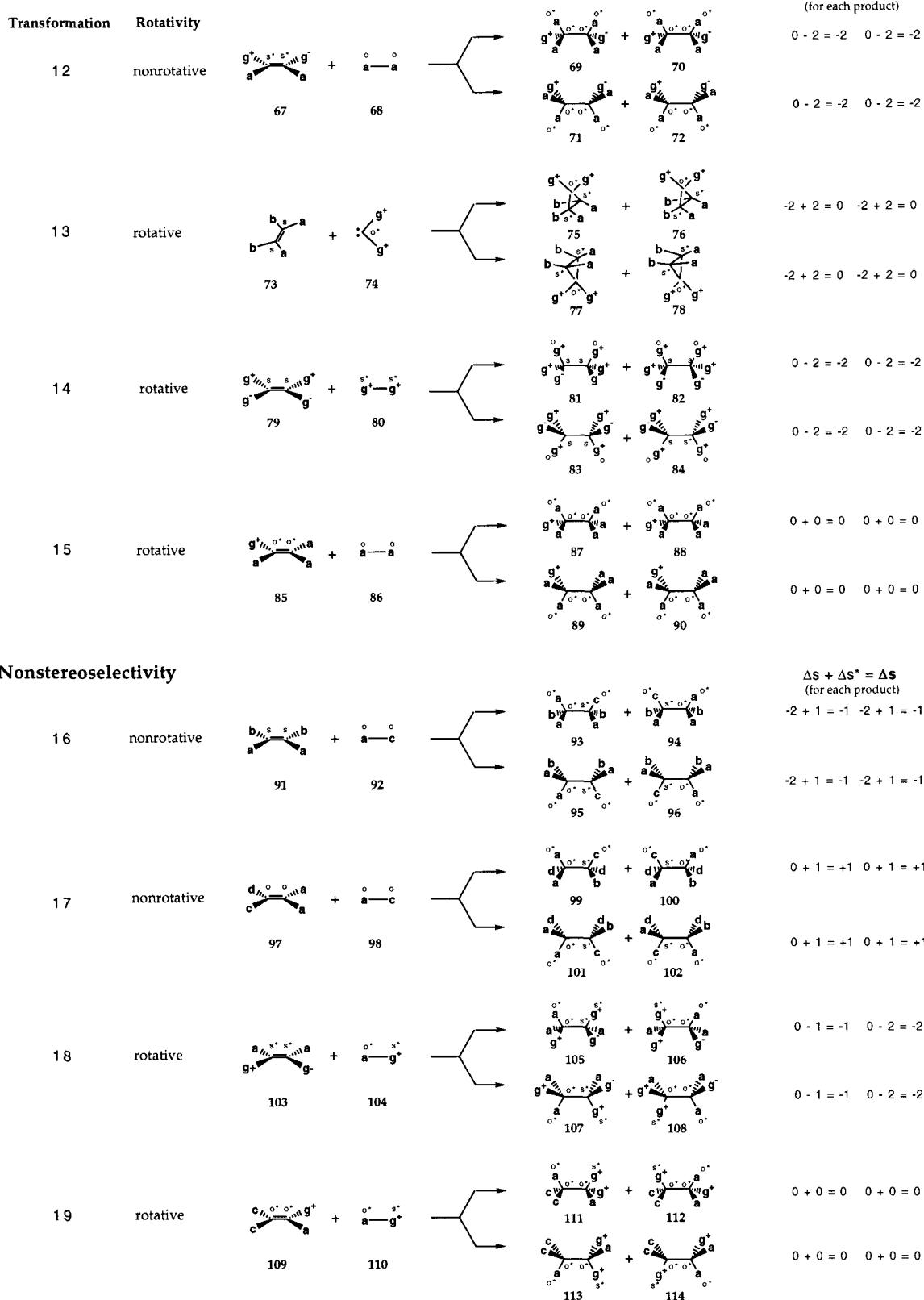


**Figure 17.3.** Examples of Nonrotative and Rotative Stereotopogenesis

## II. Nonrotativity and Rotativity

A substance is said to be *nonrotative*, if it is *expected* to be optically inactive (at any wavelength). A substance is said to be *rotative*, if it is *expected* to be optically active (at any wavelength). We have designated a product/product mixture of a given reaction as nonrotative, if it consists of achiral products and/or enantiomeric product pair(s) in equimolar amounts. In the examples of Figures 17.2 and 17.3 above, reactions  $1+2 \rightarrow 3+4+5+6$  (Class 1),  $13+14 \rightarrow 15+16+17+18$  (Class 2),  $25+26 \rightarrow 27+28+29+30$  (Class 3),  $37+38 \rightarrow 39+40+41+42$  (Class 4),  $49+50 \rightarrow 51+52+53+54$  (Class 5),  $55+56 \rightarrow 57+58+59+60$  (Class 6), are transformations that lead to nonrotative mixtures.

## Stereoaselectivity



**Figure 17.4.** Examples of Nonrotative/Rotative Stereoaselective and Nonstereoselective Transformations

Typically, mixtures that have one of the following compositions are nonrotative :

H	1 achiral substance
E <sup>*</sup> / <sup>E</sup>	2 enantiomers (equimolar amounts)
E <sup>*</sup> / <sup>E,N</sup>	2 enantiomers (equimolar amounts) and an achiral common astereomer
E <sup>*</sup> / <sup>E,D<sup>*</sup>/<sup>D</sup></sup>	2 diastereomeric enantiomeric pairs
D,F	2 achiral diastereomers
D,F,G	3 achiral diastereomers

In the nonrotative examples cited in Figures 17.2 and 17.3 above, transformations 1, 3, and 5 lead to a single achiral substance H; transformations 7 and 10 yield racemic mixtures E<sup>\*</sup>/<sup>E</sup>, whereas transformation 6 leads to two achiral diastereomers D,F.

In contrast, a reaction labelled rotative in Figures 17.2 and 17.3, is one that leads to a product/product mixture containing either one enantiopure substance, or, a mixture of one (or more) enantiomeric product pair(s), such that at least one of the latter pairs is present in unequal amounts of the component enantiomeric forms; there may or may not be accompanying achiral components. In Figures 17.2 and 17.3 above, transformations 7+8→9+10+11+12 (Class 1), 19+20→21+22+23+24 (Class 2), 31+32→33+34+35+36 (Class 3), 43+44→45+46+47+48 (Class 4), and 61+62→63+64+65+66 (Class 6), yield rotative mixtures. There is no transformation in Class 5 that leads to a rotative mixture.

Examples of rotative mixtures include:

H*	1 chiral substance
D*,F*	2 chiral diastereomers
D*,F*,G*	3 chiral diastereomers
D*,F*,G*,J*	4 chiral diastereomers

In the rotative examples of Figures 17.2 and 17.3, each of transformations 2, 4, and 6 leads to a single chiral substance H\*, whereas each of transformations 8 and 11 yields two chiral diastereomers D\*,F\*. Appendix 17.A provides a comprehensive list of nonrotative and rotative 1-, 2-, 3-, and 4-component systems; the quartet modes were defined in Chapter 12, Vol. 2, pp. 84-88.

### III. Stereoaselectivity, Nonstereoselectivity and Stereoselectivity

A *stereoselective* reaction is one in which at least one product/transition state can, in principle, form in two or more stereomeric forms, *and*, one of the stereomeric forms predominates over the other (e.g. one enantiomer over its counterpart, and/or one diastereomer over another).

A *nonstereoselective* reaction is one in which at least one product/transition state can, in principle, form in two or more stereomeric forms, *and* these stereoisomeric forms - enantiomers or diastereomers - are formed in equimolar amounts. Hence, nonstereoselectivity manifests itself either in the formation of racemates, and/or accidentally-equimolar diastereomeric mixtures.

A *stereoaselective* reaction is one in which none of the products/transition *can*, in principle, form in stereomeric forms; additional products, if formed, are nonstereomeric - astereomeric or nonequimolar - with respect to each other.

In Figures 17.4 and 17.5, we provide examples of stereoaselective, nonstereoselective and stereoselective transformations.

## Stereoselectivity

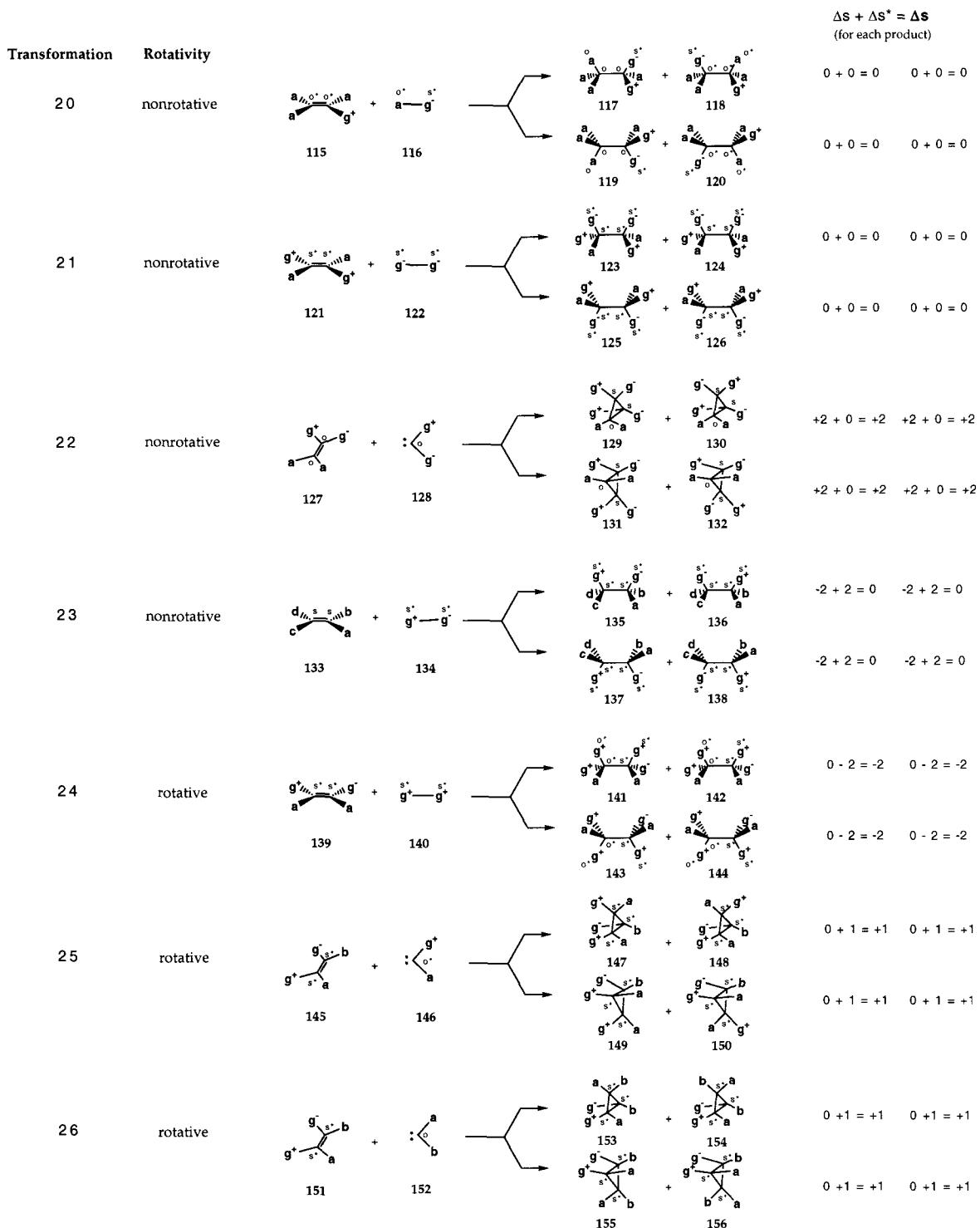


Figure 17.5. Examples of Nonrotative/Rotative Stereoselective Transformations

Typically, stereoaselective transformations result in a single achiral or chiral substance:

H	1 achiral substance
H*	1 chiral substance

Nonstereoselective product mixtures may consist of racemic mixtures, or racemic mixtures along with an achiral common astereomer:

E*/*E	2 enantiomers (equimolar amounts)
E*/*E*, N	2 enantiomers (equimolar amounts) and an achiral common astereomer

Stereoselective mixtures are exemplified by one of the following mixtures:

D*,F*	2 chiral diastereomers (in unequal amounts)
D,F,G	3 achiral diastereomers (in unequal amounts)
D*,F*,G*	3 chiral diastereomers (in unequal amounts)
E*/*E, D*/*D	2 diastereomeric enantiomeric pairs (in unequal amounts)
D*,F*,G*,J*	4 chiral diastereomers (in unequal amounts)

It should be noted that any one of the last five cases above would be considered *nonstereoselective*, if the component diastereomers are formed accidentally in equal amounts (*vide infra*, for stereoselective ones) as shown below:

D*,F*	2 chiral diastereomers (in equal amounts)
D,F,G	3 achiral diastereomers (in equal amounts)
D*,F*,G*	3 chiral diastereomers (in equal amounts)
E*/*E, D*/*D	2 diastereomeric enantiomeric pairs (in equal amounts)
D*,F*,G*,J*	4 chiral diastereomers (in equal amounts)

Appendix 17.B shows compositions of substances (products or transition states) that result from stereoaselective, nonstereoselective and stereoselective transformations.

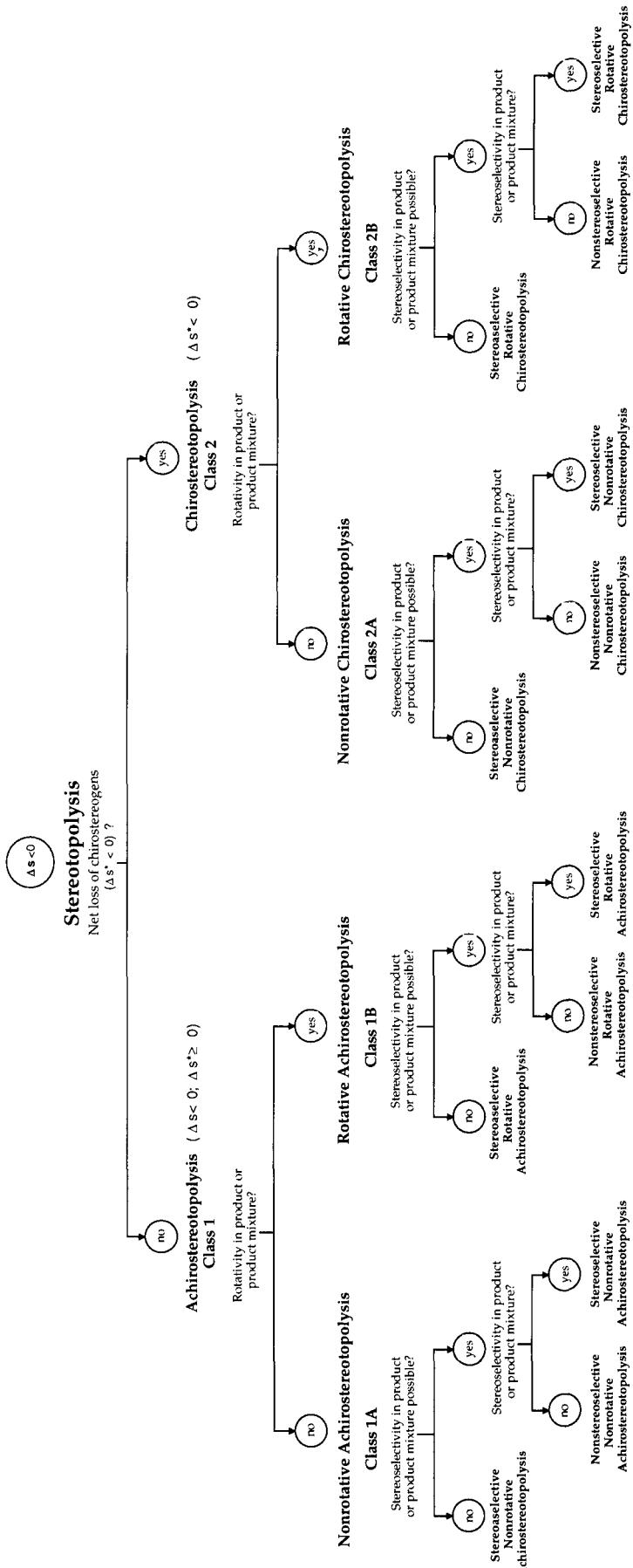
#### IV. Rotativity and Stereoselectivity

In Figure 17.4, stereoaselective transformation 12 yields a nonrotative product (H), whereas each of transformations 13, 14 and 15 leads to a rotative product (H\*). In the case of nonstereoselective transformations 16 (E\*,\*E) and 17 (E\*/\*E,N\*/\*N), one obtains nonrotative mixtures; products obtained in transformations 18 (E\*,F\*) and 19 (A\*,N\*) would be rotative. In Figure 17.5, we find that stereoselective transformations 20 (D,F,M), 21 (D,F), 22 (D,F,G), 23 (E\*/\*E,D\*/\*D) lead to nonrotative mixtures, whereas transformations 24 (D\*,F\*), 25 (D\*,F\*,G\*), 26 (D\*,F\*,G\*,J\*) produce rotative mixtures.

It is clear that when both properties - rotativity and stereoselectivity - of chemical transformations are taken into account, one finds that stereoaselective, nonstereoselective and stereoselective reactions can lead to mixtures that are either nonrotative or rotative. It follows that nonrotative mixtures can result from stereoaselective, nonstereoselective or stereoselective transformations. It turns out that rotative mixtures also are obtainable in transformations that are stereoaselective, nonstereoselective or stereoselective.

#### V. Stereotopology, Rotativity and Stereoselectivity

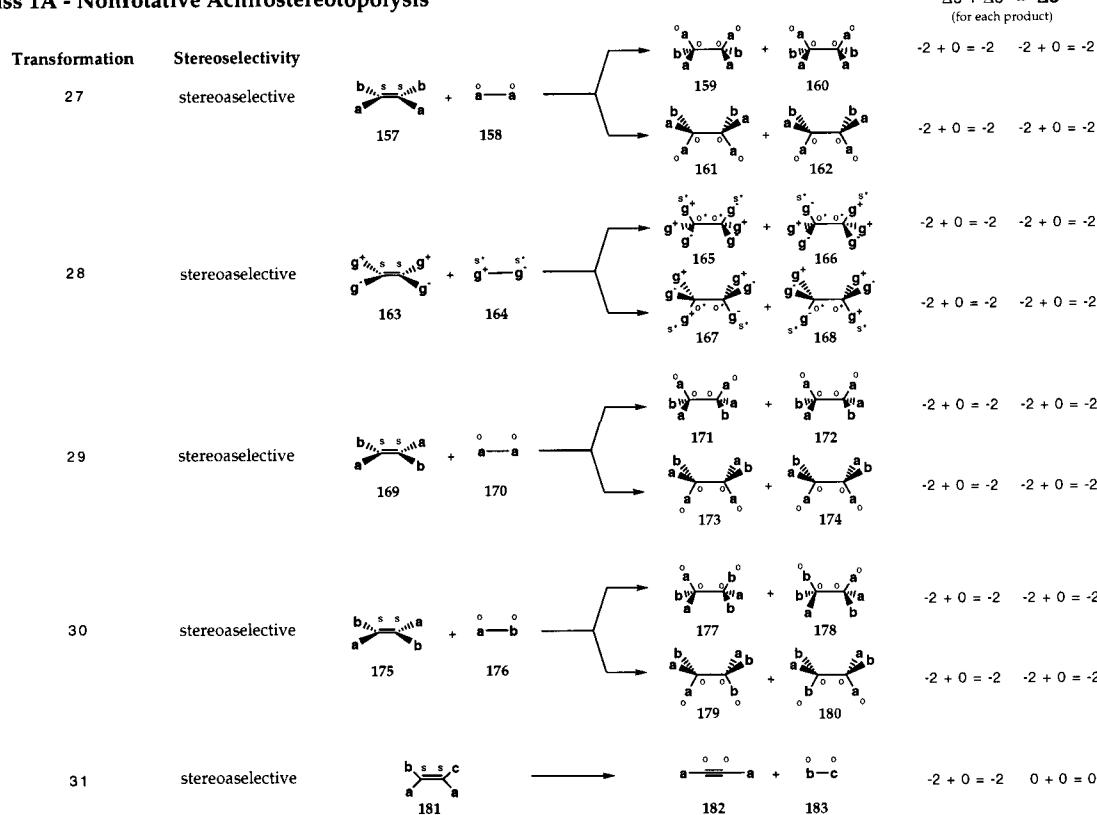
We have already seen that stereotopology is classified into achirostereotopology (Class 1), if



**Figure 17.6.** Classification of Stereotopysis

there is no net loss of chirostereogens, and chirostereotopolysis (Class 2), if indeed there is a net loss of chirostereogens (Figure 17.1). We now turn into the subclassification of Classes 1 and 2 (Figure 17.6). Achirostereotopolysis (Class 1) may be subdivided into nonrotative achirostereotopolysis (Class 1A) and rotative achirostereotopolysis (Class 1B), depending on whether the resulting product mixture is nonrotative or rotative, respectively. As shown in Figure 17.6, each of these subclasses may be stereoaselective, nonstereoselective or stereoselective. Chirostereotopolysis (Class 2), in turn, is subclassified into nonrotative chirostereotopolysis (Class 2A) and rotative chirostereotopolysis (Class 2B), depending on the nonrotativity or rotativity of the corresponding product mixture. Each of these subclasses may, in turn, be stereoaselective, nonstereoselective or stereoselective (Figure 17.6). Figures 17.7 and 17.8 depict examples of all the subclasses mentioned above.

### Class 1A - Nonrotative Achirostereotopolysis



### Class 1B - Rotative Achirostereotopolysis

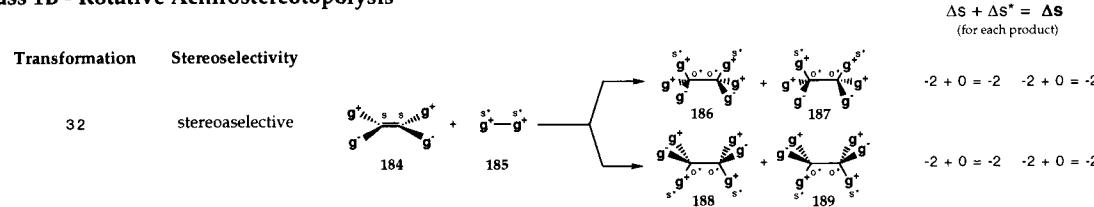
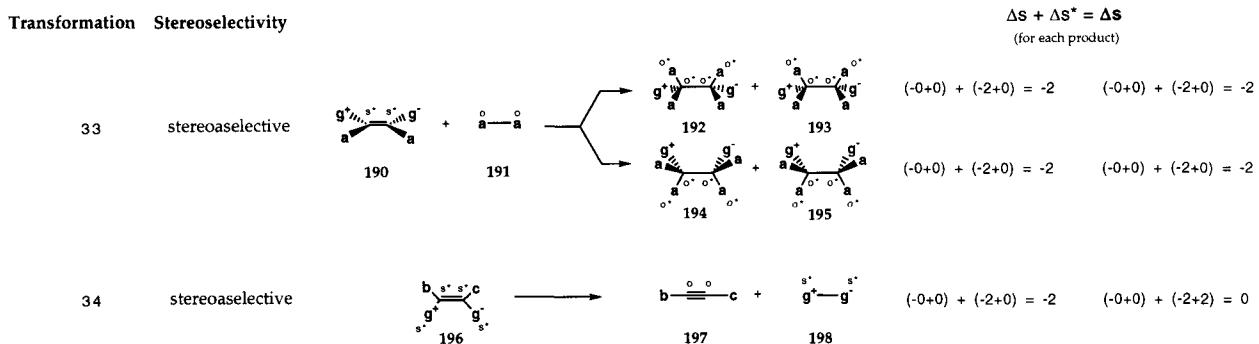


Figure 17.7. Examples of Nonrotative and Rotative Achirostereotopolysis

## Class 2A - Nonrotative Chirostereotopolysis



## Class 2B - Rotative Chirostereotopolysis

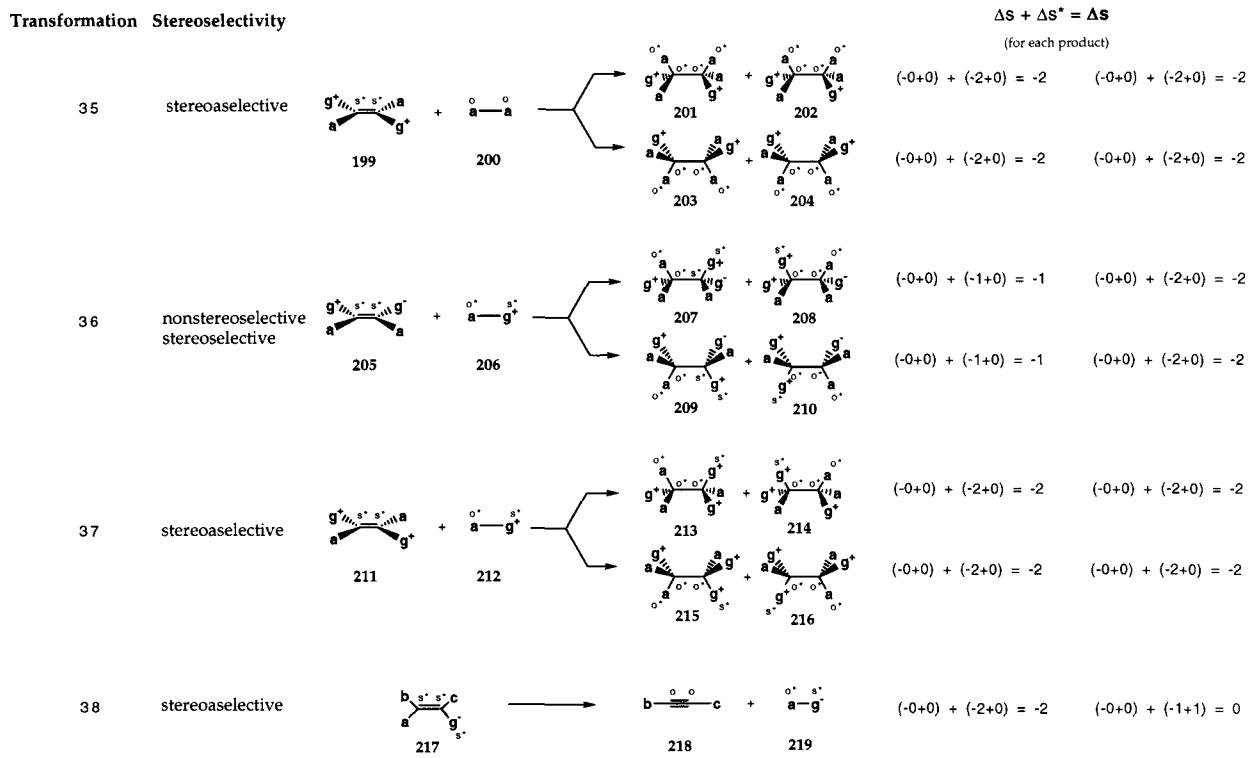


Figure 17.8. Examples of Nonrotative/Rotative Chirostereotopolysis

(Class 1A), while transformation 32 is an example of rotative achirostereotopolysis (Class 1B). In Classes 1A and 1B (Figure 17.7), all transformations are stereoaselective (**159=160=161=162**; **165=166=167=168**; **171=172=173=174**; **177=178=179=180**). In Figure 17.8, transformations 33 and 34 exemplify nonrotative  $sp^3$  and  $sp^2$  chirostereotopolyses, respectively (Class 2A). In this class, transformations 33 and 34 are stereoaselective (**192=193=194=195**). In Class 2B, on the other hand, transformations 35-37 constitute examples of rotative  $sp^3$  chirostereotopolyses, and transformation 38 exemplifies rotative  $sp^2$  chirostereotopolysis. Transformations 35, 37 and 38 are stereoaselective (**201=202=203=204**, **213=214=215=216**), while transformation 36 is either stereoselective (if diastereomers **207**, **208**(=**210**) and **209** are formed in unequal amounts), or nonstereoselective (if the said three diastereomers are formed in equal amounts).

## VI. Stereotopomutation, Rotativity and Stereoselectivity

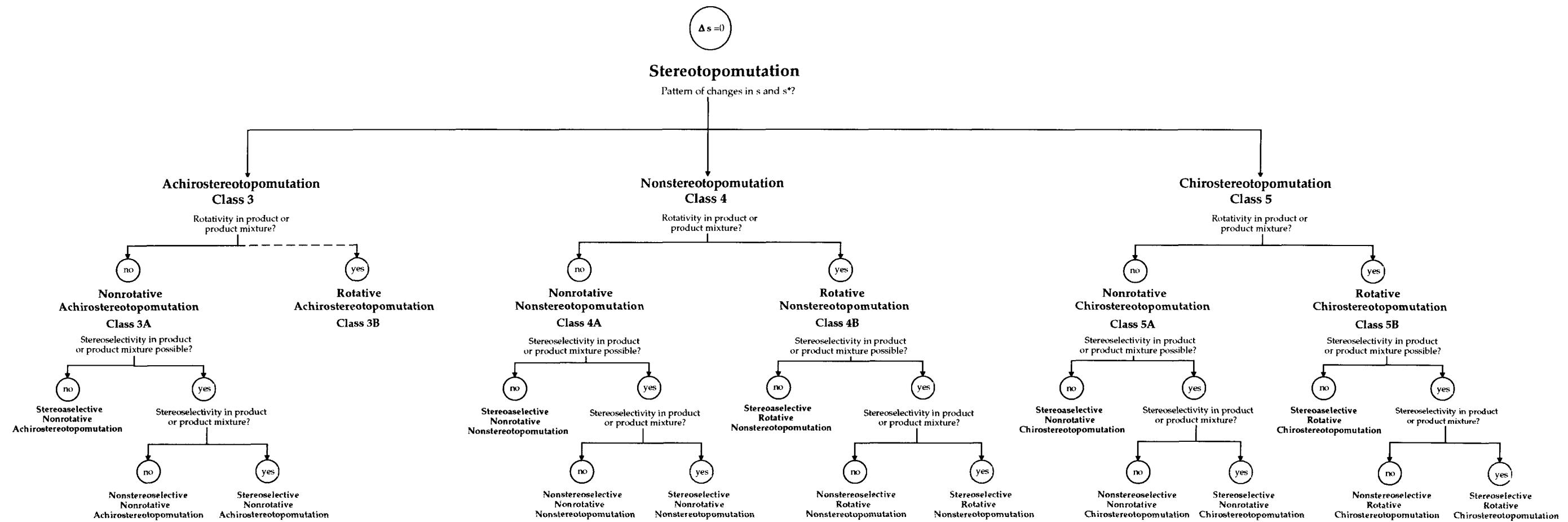
As seen earlier (Figure 17.1, p. 26), stereotopomutation is subclassified into achirostereotopomutation (Class 3), if there is topomutation of stereogenic atoms of only type s), nonstereotopomutation (Class 4), if there is no topomutation of stereogenic atoms of type s/s\* (or offsetting topomutation of stereogenic atoms of both types s/s\*), and chirostereotopomutation (Class 5), if there is topomutation of stereogenic atoms of only type s\*. We now discuss the subclassification of Classes 3, 4 and 5, as portrayed in Figure 17.9.

Achirostereotopomutation (Class 3) is always nonrotative (Class 3A); there is no "rotative achirostereotopomutation" ("Class 3B"). Nonrotative achirostereotopomutation may be stereoaselective, nonstereoselective or stereoselective. In contrast, nonstereotopomutation (Class 4) is subclassified into nonrotative nonstereotopomutation (Class 4A) and rotative nonstereotopomutation (Class 4B). Each of these subclasses may be stereoaselective, nonstereoselective or stereoselective. Finally, chirostereotopomutation (Class 5) is subclassified into nonrotative chirostereotopomutation (Class 5A) and rotative chirostereotopomutation (Class 5B). Each of these subclasses also can be stereoaselective, nonstereoselective or stereoselective. In Figures 17.10 and 17.11, we provide examples of all the above subclasses.

In Figure 17.10, transformation 39 and 40 constitute examples of nonrotative astereotopomutation, (Class 3A); the former example is stereoaselective, while the latter one is nonstereoselective. As indicated in this figure, there is no rotative achirostereotopomutation (Class 3B). In Figure 17.11, transformations 41 and 42 exemplify nonrotative nonstereotopomutation (Class 4A); the former transformation is stereoaselective (**234=235=236=237**); the latter one can be either nonstereoselective (if **240**(=**241**) and **242**(=**243**) are formed in equal amounts) or stereoselective (if **240** and **242** are formed in unequal amounts). Transformations 43 and 44 are examples of rotative nonstereotopomutation (Class 4B). Transformation 43 may be either nonstereoselective (if **246**(=**247**) and **248**(=**249**) are formed in equal amounts) or stereoselective (if **246** and **248** are formed in unequal amounts). Transformation 44 is stereoaselective (**252=253=254=255**).

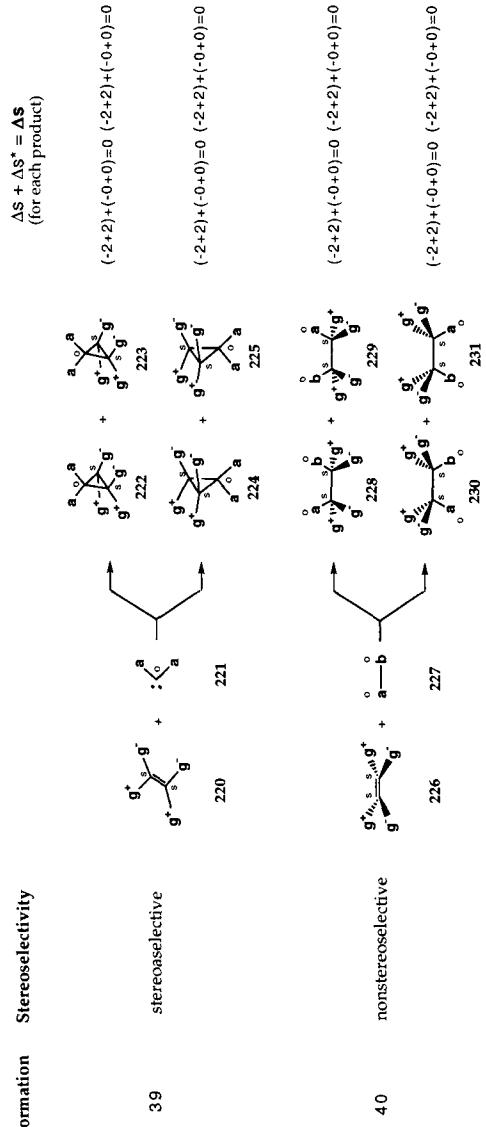
Examples of nonrotative chirostereotopomutation (Class 5A) are embodied in transformations 45 and 46 - the former being stereoaselective (**258=259=260=261**), and the latter being nonstereoselective (**264**(=**266**) is enantiomeric with **265**(=**267**)). Finally, in Figure 17.12, we see transformations 47 and 48 which exemplify rotative chirostereotopomutation (Class 5B) - the former is stereoaselective (**270=271=272=273**), but the latter can be either nonstereoselective (if **277** and **279** are formed in equal amounts) or stereoselective (if **277** and **279** are formed in unequal amounts).

It should be noted that a given transformation may yield several products - some through a stereotopomutation, and others, from a process other than stereotopomutation. For example, in transformation 48, product **276**(=**278**) is the result of stereotopomutation, while **277** and **279** are the result of chirostereotopogenesis ( $\Delta s > 0$ , *vide infra*).



**Figure 17.9.** Classification of Stereotopomutation

### Class 3A - Nonrotative Achirostereotopomutation



### Class 3B - Rotative Achirostereotopomutation

none

**Figure 17.10.** Examples of Nonrotative Achirostereotopomutation

### Class 4A - Nonrotative Nonstereotropomutation

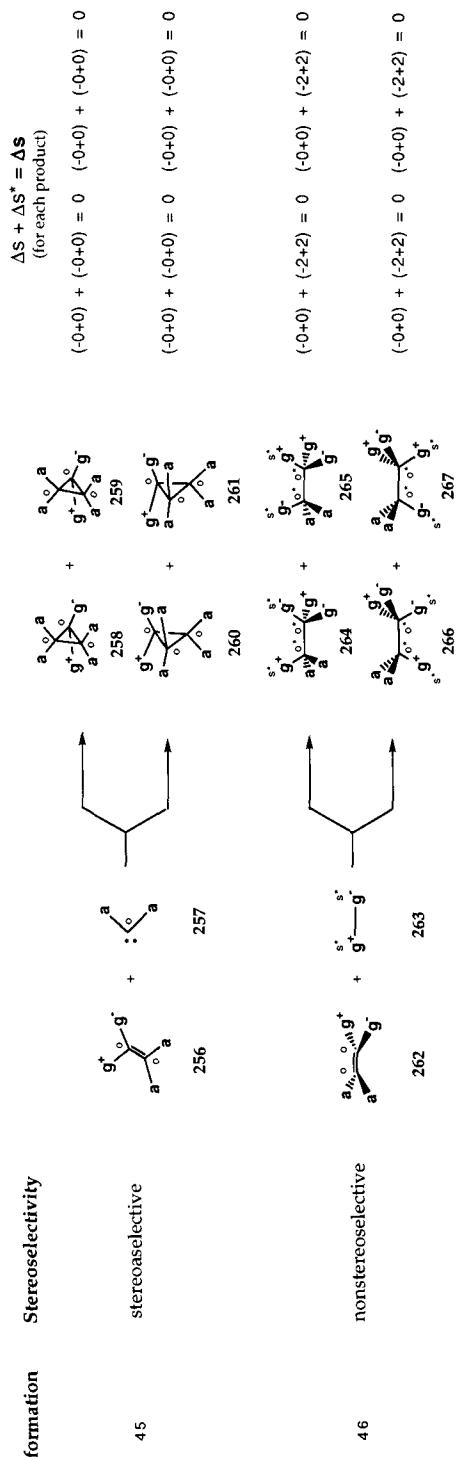
Transformation	Stereoselectivity		$\Delta S + \Delta S^* = \Delta S$ (for each product)
4.1	stereoselective	<p style="text-align: center;">↔</p> <p style="text-align: center;">↔</p>	$(-0+0)+(-0+0)=0$ $(-0+0)+(-0+0)=0$ $(-0+0)+(-0+0)=0$ $(-0+0)+(-0+0)=0$
4.2	nonstereoselective stereoselective	<p style="text-align: center;">↔</p> <p style="text-align: center;">↔</p>	$(-2+0)+(2+0) = 0$ $(-2+0)+(2+0) = 0$ $(-2+0)+(2+0) = 0$ $(-2+0)+(2+0) = 0$

### Class 4B - Rotative Nonstereotropomutation

Transformation	Stereoselectivity		$\Delta S + \Delta S^* = \Delta S$ (for each product)
4.3	nonstereoselective stereoselective	<p style="text-align: center;">↔</p> <p style="text-align: center;">↔</p>	$(-2+2) + (-0+0) = 0$ $(-2+2) + (-0+0) = 0$ $(-2+2) + (-0+0) = 0$ $(-2+2) + (-0+0) = 0$
4.4	stereoselective	<p style="text-align: center;">↔</p> <p style="text-align: center;">↔</p>	$(-0+0)+(-0+0) = 0$ $(-0+0)+(-0+0) = 0$ $(-0+0)+(-0+0) = 0$ $(-0+0)+(-0+0) = 0$

Figure 17.11. Examples of Nonrotative/Rotative Nonstereotropomutation

### Class 5A - Nonrotative Chirostereotopomutation



### Class 5B- Rotative Chirostereotopomutation

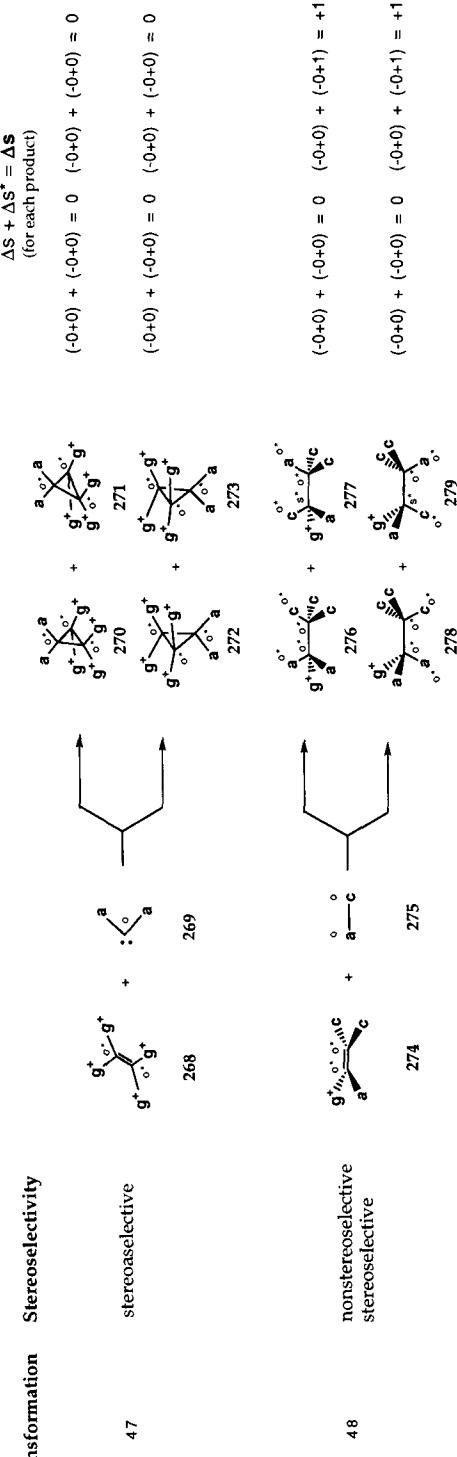


Figure 17.12. Examples of Nonrotative/Rotative Chirostereotopomutation

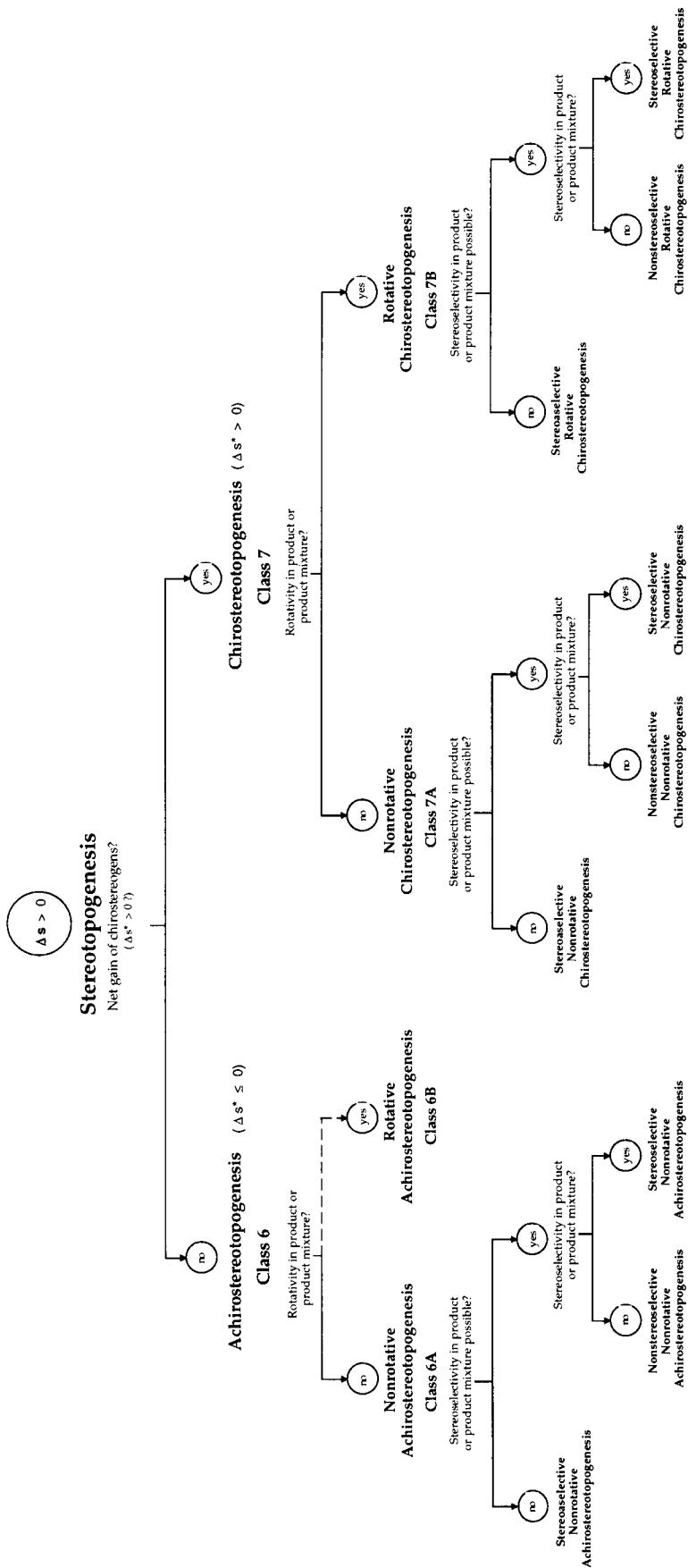


Figure 17.13. Classification of Stereotopogenesis

## VII. Stereotopogenesis, Rotativity and Stereoselectivity

As seen earlier (Figure 17.1, p. 26), stereotopogenesis is subcategorized into achirostereotopogenesis (Class 6), if there is no net gain of stereogenic atoms of type  $s^*$ , and chirostereotopogenesis (Class 7), if there is a gain of stereogenic atoms of type  $s^*$ . We now discuss the complete classification of stereotopogenesis, as portrayed in Figure 17.13.

Achirostereotopogenesis (Class 6) is specified as nonrotative achirostereotopogenesis (Class 6A) since the resulting mixture is nonrotative. It turns out that there is no “rotative achirostereotopogenesis” (“Class 6B”). One finds that Class 6A can be stereoaselective, nonstereoselective or stereoselective. Chirostereotopogenesis (Class 7) can be either nonrotative - Class 7A (nonrotative chirostereotopogenesis), or rotative - Class 7B (rotative chirostereotopogenesis). Each of these subclasses may, in turn, be stereoaselective, nonstereoselective or stereoselective.

In Figures 17.14-17.16, we provide examples of all the above subclasses. In Figure 17.14, transformations 49 and 50 are examples of  $sp^2$  nonrotative achirostereotopogenesis ( $\Delta s=2$  for each member in quartets 282-285 and 288-291). In contradistinction, transformations 51-53 represent  $sp^3$  nonrotative achirostereotopogeneses; ( $\Delta s=1$  for each member in quartets 294-297, 300-303, while  $\Delta s=2$  for each member in quartets 306-309). Each of these transformations may be either nonstereoselective or stereoselective, depending on the relative amounts of the diastereomeric products formed in each case. The products in question are as follows: for transformation 49, 282(=283) is diastereomeric with respect to 284 (=285); in transformation 50, 288/290 and 289/291 constitute diastereomeric pairs. In transformation 51, 294 (=296) is diastereomeric with respect to 295(=297); in transformation 52, 300 (=301) is diastereomeric with respect to 302(=303); finally, in 53, 306(=309) is diastereomeric with respect to 307 (=308).

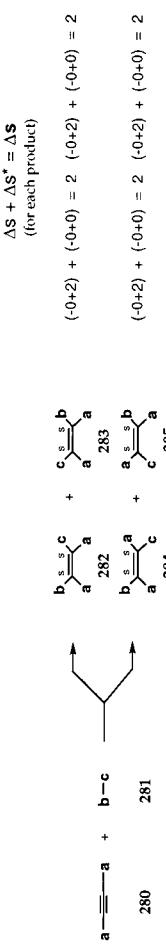
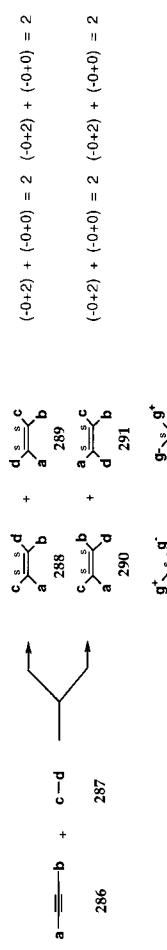
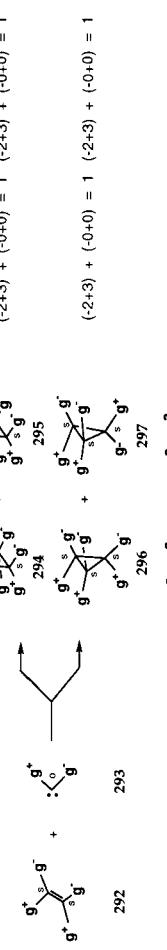
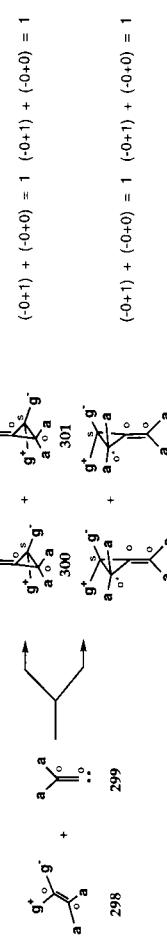
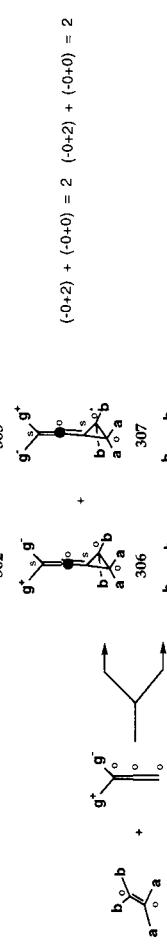
No examples can be provided for “rotative achirostereotopogenesis” (hypothetical “Class 6B”).

All transformations in Figure 17.15 exemplify nonrotative chirostereotopogenesis (Class 7A). Transformations 54 and 55 are cases of  $sp^2$  nonrotative chirostereotopogenesis ( $\Delta s=2$  for each component in quartets 312-315 and 318-321.). The former transformation is nonstereoselective; 312(=314) and 313(=315) are enantiomers, and are formed in equal amounts. Transformation 55 can be stereoselective, if diastereomers 318(=319) and 320(=321) are formed in unequal amounts; if the products are formed in accidentally-equal amounts, the transformation would be considered nonstereoselective.

Transformations 56 and 57 represent  $sp^3$  nonrotative chirostereotopogeneses ( $\Delta s=2$  for each component in quartets 324-327 and 330-330). The former transformation is nonstereoselective, because enantiomers 324(=327) and 325(=326) are formed in equal amounts. Transformation 57 is stereoselective, if diastereomeric racemates 330/331 and 332/333 are formed in unequal amounts; the transformation would be nonstereoselective if the said racemates are formed in accidentally-equal amounts. Finally, transformation 58 is a composite case of  $sp^2+sp^3$  nonrotative chirostereotopogeneses ( $\Delta s=3$  for each component in quartet 336-339). The transformation is stereoselective (if diastereomeric racemates 336/337 and 338/339 are formed in expectedly unequal amounts) or nonstereoselective (if diastereomeric racemates 336/337 and 338/339 are formed in unexpectedly-equal amounts).

In Figure 17.16, all transformations represent examples of rotative chirostereotopogenesis (Class 7B). Transformations 59 and 60 are cases of  $sp^2$  rotative chirostereotopogenesis ( $\Delta s=2$  for each component in quartet 342-345 and 348-351). Either transformation can be nonstereoselective (if diastereomers 342(=345) and 343(=344) are formed in accidentally-equal amounts) or stereoselective (if the said diastereomers are formed in unequal amounts).

## Class 6A - Nonrotative Achirostereotopogenesis

Transformation	Stereoselectivity	$\Delta S + \Delta S^* = \Delta S$ (for each product)
4.9	nonstereoselective stereoselective	 $(-0+2) + (-0+0) = 2 \quad (-0+2) + (-0+0) = 2$
5.0	nonstereoselective stereoselective	 $(-0+2) + (-0+0) = 2 \quad (-0+2) + (-0+0) = 2$
5.1	nonstereoselective stereoselective	 $(-0+2) + (-0+0) = 2 \quad (-0+2) + (-0+0) = 2$
5.2	nonstereoselective stereoselective	 $(-0+1) + (-0+0) = 1 \quad (-0+1) + (-0+0) = 1$
5.3	nonstereoselective stereoselective	 $(-0+2) + (-0+0) = 2 \quad (-0+2) + (-0+0) = 2$

## Class 6B - Rotative Achirostereotopogenesis

none

Figure 17.14. Examples of Nonrotative Achirostereotopogenesis

### Class 7A - Nonrotative Chirostereotopogenesis

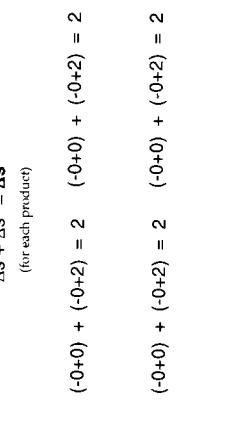
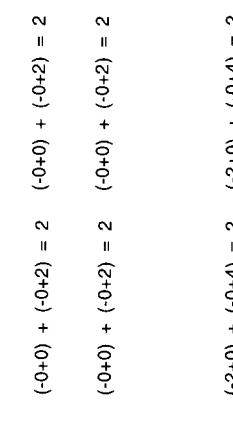
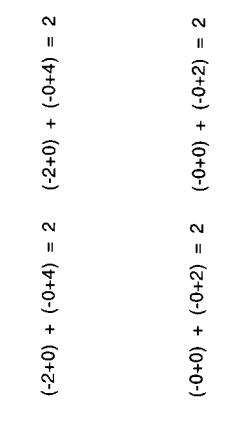
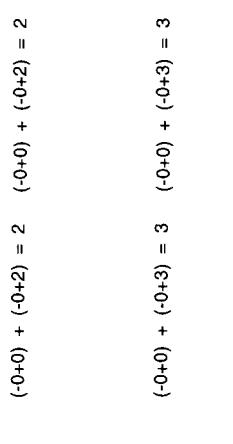
Transformation	Stereoselectivity	$\Delta S + \Delta S^* = \Delta S$ (for each product)
54	nonstereoselective	 <p>(-0+0) + (-0+2) = 2    (-0+0) + (-0+2) = 2</p>
55	nonstereoselective stereoselective	 <p>(-0+0) + (-0+2) = 2    (-0+0) + (-0+2) = 2</p>
56	nonstereoselective	 <p>(-2+0) + (-0+4) = 2    (-2+0) + (-0+4) = 2</p>
57	nonstereoselective stereoselective	 <p>(-0+0) + (-0+2) = 2    (-0+0) + (-0+2) = 2</p>
58	nonstereoselective stereoselective	 <p>(-0+0) + (-0+3) = 3    (-0+0) + (-0+3) = 3</p>

Figure 17.15. Examples of Nonrotative Chirostereotopogenesis

Class 6B - Rotative Chirostereotopogenesis

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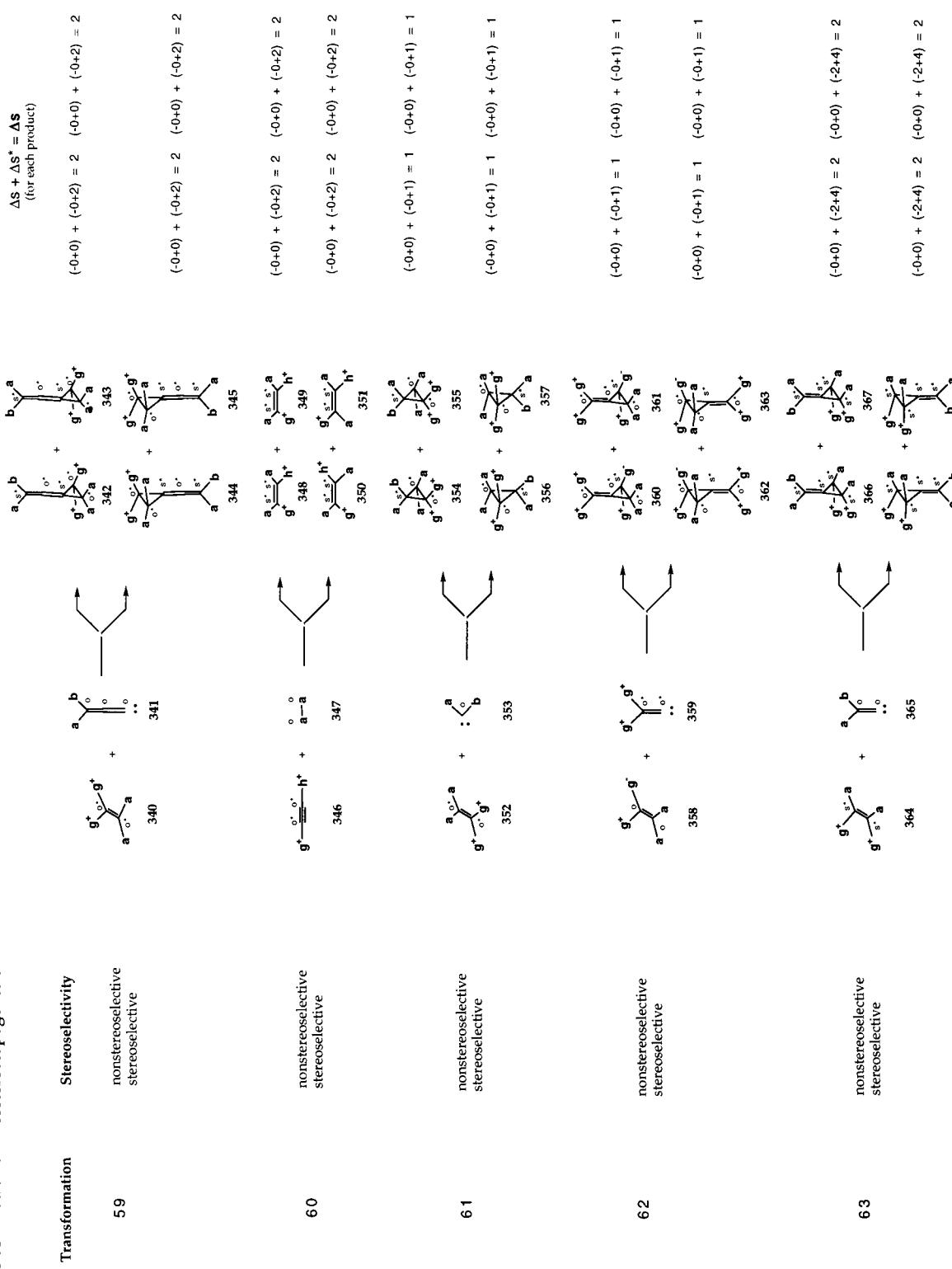


Figure 17.16. Examples of Rotative Chirostereotopogenesis

Transformations 61 and 62 represent  $sp^3$  rotative chirostereotopogeneses ( $\Delta s=1$  for each component in quartets 354-357 and 360-363). Each one of these two transformations can be nonstereoselective (if diastereomers 354(=357) and 355(=356) are formed in equal amounts) or stereoselective (if the latter diastereomers are formed in unequal amounts). Transformation 63 is a composite case of  $sp^2$  and  $sp^3$  rotative chirostereotopogeneses ( $\Delta s=2$  for each component in quartet 366-369). This transformation is nonstereoselective (if diastereomers 366(=369) and 367(=368) are formed in equal amounts) or stereoselective (if the diastereomers in question are formed in unequal amounts).

## VIII. Stereotopoprocesses in Relation to Stereotopic Faces

Tables 17.1-17.3 summarize our findings about the relationship between the subclasses of stereotopoprocesses (stereotopolysis, stereotopomutation and stereotopogenesis), and, each of the different types of homotopic (h1-h6), enantiotopic (e) and diastereotopic (d1-d4) faces.

### A. Homotopic Faces

#### 1. Stereotopolysis

Nonrotative and rotative achirostereotopolyses (Classes 1A and 1B) are possible for h3 faces with achiral and chiral reagents, respectively; neither one is observed for h1, h2, h4, h5 and h6 faces (with achiral or chiral reagents).

Nonrotative chirostereotopolysis (Class 2A) is not seen for any of the h1-h6 classes, but rotative chirostereotopolysis (Class 2B) is found for only h6.

#### 2. Stereotopomutation

Nonrotative achirostereotopomutation (Class 3A) is noted for h3 (achiral reagents); rotative achirostereotopomutation (Class 3B) is not expected for any of the h1-h6 classes.

Nonrotative nonstereotopomutation (Class 4A) is indicated for h1,h2 (achiral reagents), h3 (achiral and chiral reagents), and h5 (chiral reagents); the corresponding rotative mode (Class 4B) is seen for h2,h3 (chiral reagents), h4,h5 (achiral and chiral reagents). Neither mode is observed for h6.

Nonrotative chirostereotopomutation (Class 5A) is expected for h1 and h2 (achiral reagents), while the rotative mode (Class 5B) is anticipated for h2 (chiral reagents) and h4-h6 (achiral and chiral reagents); neither one is apparent for h3.

#### 3. Stereotopogenesis

Nonrotative achirostereotopogenesis (Class 6A) is evident only for h2 and h3, but not for h1, h4, h5 and h6 faces. Strikingly, "rotative achirostereotopogenesis" ("Class 6B") is not possible for any homotopic face; it is a nonexistent subclass.

Both nonrotative and rotative chirostereotopogeneses (Classes 7A and 7B) are observed for h2, h3 faces with achiral and chiral reagents, respectively. Only the rotative mode (Class 7B) is noted for h5 and h6 (achiral and chiral reagents). Neither mode is seen for h1 and h4 faces.

### B. Enantiotopic Faces

#### 1. Stereotopolysis

At enantiotopic faces, nonrotative achirostereotopolysis (Class 1A) is expected with achiral reagents, while rotative achirostereotopolysis (Class 1B) is possible with chiral reagents.

Classification	Nonrotative (nr) or Rotative (r)	Class	h1						h2						h3						h4						h5						h6					
			ac	c	ac	c	ac	c	ac	c	ac	c	ac	c	ac	c	ac	c	ac	c	ac	c	ac	c	ac	c	ac	c	ac	c	ac	c						
achirostereotopolysis	nr	1A							Aa	Nn																												
	r	1B							Aa	Ns																												
chirostereotopolysis	nr	2A																																				
	r	2B																																				
achirostereotopomutation	nr	3A							Aa																													
	r	3B																																				
nonstereotopomutation	nr	4A	Aa						Aa	NsNhe Ns Nn																												
	r	4B							Aa																													
chirostereotopomutation	nr	5A	Aa						Aa	Ns																												
	r	5B								Aa	Ns Nhe																											
achirostereotopogenesis	nr	6A								Ns																												
	r	6B																																				
chirostereotopogenesis	nr	7A									Aa An Nn Ns																											
	r	7B										Ns																										

ac : achiral reagent  
c : chiral reagent

Table 17.1. Stereotopolysis/Stereotopomutation/Stereotopogenesis at Homotopic Faces h1-h6

		e			
Classification		Nonrotative (nr) or Rotative (r)	Class	ac	c
achirostereotopology	nr	1A	Aa Nas Nne		
	r	1B	Sa Sns Sne		
chirostereotopology	nr	2A	Aa Ns		
	r	2B	Ns Ss Ss		
achirostereotopomutation	nr	3A			
	r	3B			
nonstereotopomutation	nr	4A	Na Ns Nas Nne		
	r	4B	Sa Ss Sns Sne		
chirostereotopomutation	nr	5A	Na Ns Ss		
	r	5B	Ns Sa Ss		
achirostereotopogenesis	nr	6A			
	r	6B			
chirostereotopogenesis	nr	7A	Na Ns Nas Nne		
	r	7B	Nas Ss Sns Nne Ss Sne		

ac : achiral reagent  
c : chiral reagent

Table 17.2. Stereotopology/Stereopomutation/Stereotopogenesis at Enantiotopic Faces

				d1		d2		d3		d4	
Classification		Nonrotative (nr) or Rotative (r)	Class	ac	c	ac	c	ac	c	ac	c
STEREOTOPOLYSIS	achirostereotopolysis	nr	1A	Aa		Sn					
		r	1B		Sa		Sa Sas Sne				
	chirostereotopolysis	nr	2A			Aa		Aa Sn Nas Nne		Sa Ss Sas Sne	Sas Sne
		r	2B				Ns Sa Ss		Ns Sa Ss	Aa Nas Nne Sa Ss Sas Sne	Aa Sa Sas Sne
STEREOTOPOMUTATION	achirostereotopomutation	nr	3A	Aa Sa		Sa Sas Sne					
		r	3B								
	nonstereotopomutation	nr	4A	Sa		Aa Sn		Nas Nne		Sas Sne	Sa
		r	4B		Sa		Sa Sas Sne			Aa Ss Sas Sne	Ss Sas Sne
	chirostereotopomutation	nr	5A			Aa		Nas Nne Sa Sn		Nas Nne	Sa Sas Sne
		r	5B				Aa Sa Sas Sne		Sa Ss	Sa Ss Nas Nne Sas Sne	
STEREOTOPGENESIS	achirostereotopogenesis	nr	6A			Sa Ss Sas Sne		Nas Nne		Sa	Sas Sne
		r	6B								
	chirostereotopogenesis	nr	7A			Sn Ss		Nas Nne Sn			
		r	7B				Sa Ss Sas Sne		Ss	Sa Ss Sas Sne	Sa Ss Sas Sne

ac : achiral reagent  
c : chiral reagent

**Table 17.3.** Stereotopolysis/Stereotopomutation/Stereotopogenesis at Diastereotopic Faces d1-d4

Similarly, nonrotative chirostereotopolysis (Class 2A) takes place with achiral reagents, while rotative chirostereotopolysis (Class 2B) is indicated with chiral reagents.

## **2. Stereotopomutation**

Achirostereotopomutation (Classes 3A and 3B) does not take place at enantiotopic faces. However, nonrotative nonstereotopomutation (Class 4A) is observed with achiral reagents, and the rotative mode (Class 4B), with chiral reagents.

Nonrotative chirostereotopomutation (Class 5A) occurs with achiral reagents; the rotative mode (Class 5B) is seen with chiral reagents.

## **3. Stereotopogenesis**

No achirostereotogeneses (Classes 6A and 6B) are possible at enantiotopic faces. However, one does observe nonrotative chirostereotopogenesis (Class 7A) with achiral reagents, and rotative chirostereotopogenesis (Class 7B), with chiral reagents.

## **C. Diastereotopic Faces**

### **1. Stereopolysis**

Nonrotative and rotative chirostereotopolyses (Classes 1A and 1B) are observed for only diastereotopic faces d<sub>1</sub>,d<sub>2</sub>, in the presence of achiral and chiral reagents, respectively.

Chirostereotopolyses (Classes 2A and 2B) are possible for d<sub>2</sub>-d<sub>4</sub>. For d<sub>2</sub> and d<sub>3</sub>, achiral reagents give nonrotative mixtures; chiral reagents give rotative mixtures. For d<sub>4</sub> faces, on the other hand, chirostereotopolyses, with achiral and chiral reagents, yield either nonrotative or rotative mixtures.

### **2. Stereotopomutation**

Nonrotative achirostereotopomutations (Class 3A)) are indicated only for d<sub>1</sub> and d<sub>2</sub> (achiral reagents); the rotative mode ("Class 3B") is nonexistent.

At d<sub>1</sub>-d<sub>4</sub> faces, nonstereotopomutations (Classes 4A and 4B) occur with achiral as well as chiral reagents.

Chirostereotopomutations (Classes 5A and 5B) are not observed for d<sub>1</sub> faces. For d<sub>2</sub> and d<sub>3</sub> faces, the nonrotative mode (Class 5A) is observed with achiral reagents, whereas the rotative mode (Class 5B) is operative with chiral reagents. In contrast, for d<sub>4</sub> faces, nonrotative and rotative modes (Classes 5A and 5B) are both observed with achiral or chiral reagents.

### **3. Stereotopogenesis**

Nonrotative achirostereotopogeneses (Class 6A) are displayed by d<sub>2</sub>-d<sub>4</sub> - d<sub>2</sub>,d<sub>3</sub>, with achiral reagents, and d<sub>4</sub>, with either achiral or chiral reagents. As noted earlier, there is no "rotative achirostereotopogenesis" ("Class 6B").

No stereotopogenesis (Classes 7A and 7B) is possible for d<sub>1</sub>. The nonrotative mode (Class 7A) is observed with d<sub>2</sub>, d<sub>3</sub> (achiral reagents), and the rotative mode (Class 7B), with d<sub>2</sub>,d<sub>3</sub> (chiral reagents). The rotative mode (Class 7B) is expected for d<sub>4</sub> faces, with either achiral or chiral reagents.

## **IX. New Terminology vs. Literature Terminology**

With increasing stereochemical complexity of novel synthetic transformations, terms such as asymmetric transformation, asymmetric synthesis, asymmetric destruction, asymmetric induction, kinetic resolution have been developed chronologically, as dictated by the need for

specifying stereochemical details. The older terms are being gradually replaced by newer terms - terms such as stereoselective synthesis, enantioselective synthesis, diastereoselective synthesis, double stereodifferentiation, stereomutation, etc.

There are several drawbacks to the current set of terms. Firstly and foremost, there is no common conceptual framework - hence, the resultant disharmonious and disordered terminology. Secondly, there is no universal agreement on the use of certain terms - owing to limited applicability, ill-definition and/or controversial interpretation. Thirdly, there is no attempt to relate reactants *and* products in a systematic way; most terms focus on one or the other; further, for reactants, the focus may be on the substrate, rather than *all* reactants - substrate *plus* reagent. Fourthly, fine differences between seemingly similar transformations are inexpressible with the existing terms. Fifthly, the available single terms cannot describe transformations which lead to composite mixtures. We attempt to remedy all five shortcomings.

Our novel theoretical framework for the stereochemical classification of chemical transformations takes into account all changes of stereogenicity and chirotopicity of participating atoms, and for all reactants and products. The universal terms advanced in this chapter encompass all of the literature terms above, accommodate as-yet-undiscovered transformations, and enable one to delineate subtle stereochemical nuances.

We illustrate the new terminology through transformations of four substrates - abC=X, ag<sup>+</sup>C=X, adC=Cbc, and ag<sup>+</sup>C=Cbc - with a variety of achiral and chiral reagents, in the absence and presence of chiral influences (solvent, catalyst, etc.). Substrates abC=X and adC=Cbc represent molecules with enantiotopic faces; ag<sup>+</sup>C=X and ag<sup>+</sup>C=Cbc incorporate diastereotopic faces.

### A. abC=X

The transformations of this molecule are portrayed in Figures 17.17 and 17.18.

In Figure 17.17, transformations 64-70 give rise to seven types of product/product mixtures - H, E\*/ $\bar{E}$  (: equal amounts), D\*,F\*, A\*,X\*, E\*/ $\bar{E}$ ,D\*/ $\bar{D}$  (: equal amounts), E\*/ $\bar{E}$ ,Z\*/ $\bar{\Sigma}$  (: equal amounts), and, D\*,F\*,X\*,Y\*. Transformation 64 leads to a single achiral product H (372=373=374=375), and is best described as a nonrotative nonstereotopomutation, with attendant vectoaselectivity and enantiofacioaselectivity. Transformation 65 gives a racemate E\*/ $\bar{E}$  (378=379/380=381), the transformation being a case of nonrotative chirostereotopogenesis - nonvectoselective and enantiofaciononselective. Transformation 66 generates two chiral diastereomers D\*,F\* (384=385,386=387); it is described as a rotative chirostereotopogenesis - nonvectoselective but enantiofacioselective. Transformation 67 yields two chiral nonequimers A\*,X\* (390=392,391=393); it is a composite case of rotative chirostereotopomutation (formation of 390=392) and rotative chirostereotopogenesis (formation of 391=393) - the result of nonequivectoselectivity and enantiofacioselectivity. Transformation 68 yields two racemic pairs of diastereomers (racemate 396/399 is diastereomeric with respect to racemate 397/398) and is described as a nonrotative sp<sup>3</sup> chirostereotopogenesis - characterized by diastereovectoselectivity and enantiofaciononselectivity. Transformation 69 generates two racemic pairs of nonequimers (racemate 402/404 is nonequimERIC with respect to racemate 403/405); this is a case of nonrotative sp<sup>3</sup> chirostereotopogenesis with attendant nonequivectoselectivity and enantiofaciononselectivity. Finally, transformation 70 is a rotative sp<sup>3</sup> chirostereotopogenesis leading to four chiral diastereostereomers D\*,F\*,X\*,Y\* (408-411); the process is characterized by nonequivectoselectivity, as well as enantiofacioselectivity.

Figure 17.18 (p. 54) depicts transformations 71-72 where account is taken of the chiral influence (chiral solvent, chiral catalyst, "chiral" radiation or other chiral factor). In these transformations, one notes the following changes in relation to those in Figure 17.17. In transformation 71 (the counterpart of 64 where no chiral influence is exerted), there is no overall effect, since all pathways converge onto a single product H. In transformation 72 (the counterpart of transformation 65), the two enantiomers (428=429 and 430=431) are produced in unequal

Transformation	Designation		Product(s)	$\Delta S$	$\Delta S^*$	$\Delta \alpha$
6.4	nonrotative nonstereotopomutation vectoaselectivity enantiofacioselectivity		H	0 0 0	0 0 0	
6.5	nonrotative chirostereotopogenesis (diastereoselective synthesis) nonvectoselectivity enantiofaciononselectivity		E*/H (/ equal amounts)	0 +1 +1	0 +1 +1	
6.6	rotative chirostereotopogenesis nonvectoselectivity enantiofacioselectivity		D*, F*	0 -2+3 +1	0 -2+3 +1	
6.7	rotative chirostereotopomutation and rotative chirostereotopogenesis nonequivvectoselectivity enantiofacioselectivity		A*, X*	0 -1+1 0	0 -1+2 +1	
6.8	nonrotative sp <sup>3</sup> chirostereotopogenesis (diastereoselective synthesis but not enantioselective synthesis) diastereovectoselectivity enantiofaciononselectivity		E*/E,D*/D (/ equal amounts)	0 -2+3 +1	0 -2+3 +1	
6.9	nonrotative sp <sup>3</sup> chirostereotopogenesis nonequivvectoselectivity enantiofaciononselectivity		E*/E,Z*/Z (/ equal amounts)	0 +1 +1	0 +1 +1	
7.0	rotative sp <sup>3</sup> chirostereotopogenesis nonequivvectoselectivity enantiofacioselectivity		D*, F*, X*, Y*	0 -1+2 +1	0 -1+2 +1	

Figure 17.17. Examples of Transformations of abC=X

Transformation	Designation			Products(s)	$\Delta S$ , $\Delta S^*$ , $\Delta S$ (for each product)
7.1	nonrelative nonstereotropomutation nonequivectoselectivity enantiofaceselectivity	$b \xrightarrow{a} X$	$a \xrightarrow{-h^+} a$	homomers 412 413 414 415 416 417 418 419 420 421	0 0 0 0 0 0
7.2	rotative chirosteriotropogenesis (asymmetric synthesis) (enantioselective synthesis) nonequivectoselectivity enantiofaceselectivity	$b \xrightarrow{a} X$	$a \xrightarrow{-h^+} a$	homomers 422 423 424 425 426 427 428 429 430 431	0 -0.1 +1 0 -0.1 +1
7.3	rotative $sp^3$ chiroteriotropogenesis (double asymmetric synthesis) (enantioselective and diastereoselective synthesis) diastereovectoselectivity enantiofaceselectivity	$b \xrightarrow{a} X$	$c \xrightarrow{-h^+} c$	homomers 432 433 434 435 436 437 438 439 440 441	0 -2.3 +1 0 -2.3 +1
7.4	relative $sp^3$ chiroteriotropogenesis (double asymmetric synthesis) (enantioselective and nonequimorphoselective) synthesis) nonequivectoselectivity enantiofaceselectivity	$b \xrightarrow{a} X$	$c \xrightarrow{-h^+} d$	homomers 442 443 444 445 446 447 448 449 450 451	0 +1 +1 0 +1 +1

Figure 17.18. Examples of Transformations of  $abc=X$  (chiral influence)

amounts, from diastereomeric transition states (424=425 and 426=427). This is the classic case of an *asymmetric synthesis*; it is also described as an enantioselective synthesis. The transformation fits the description of a "de novo synthesis of a chiral substance from an achiral precursor such that one enantiomer predominates over the other."<sup>9a</sup> Transformation 73 (the counterpart of transformation 68) yields two enantioenriched pairs of diastereomers - 438,441 and 439,440 – owing to the intervening diastereomeric/nonequimERIC sets of transition states 434-437. This is a case of a *double asymmetric synthesis*, or, a diastereoselective synthesis with concomitant enantioselective synthesis. Transformation 74 (the counterpart of transformation 69) yields two enantioenriched pairs of nonequimers (448,450 and 449,451), owing to the involvement of nonequimERIC and diastereomERIC transition states (444-447) - a dual manifestation of nonequivectoselectivity and enantiofacioselectivity.

### B. $\text{ag}^+\text{C=X}$

The transformations of this molecule are presented in Figures 17.19 and 17.20. Additionally, Figure 17.21 incorporates the effect of chiral perturbations ("chiral influence").

In Figures 17.19 and 17.20, transformations 75-85 generate seven types of product(s) -  $\text{H}^*$ ,  $\text{A}^*,\text{X}^*$ ,  $\text{D}^*,\text{F}^*$ ,  $\text{D},\text{F},\text{X}^*$ ,  $\text{D}^*,\text{F}^*,\text{G}^*$ ,  $\text{D}^*,\text{F}^*,\text{X},\text{Y}$ , and  $\text{D}^*,\text{F}^*,\text{X}^*,\text{Y}^*$ . Transformations 75 and 76 lead to the corresponding single chiral products  $\text{H}^*$  (454=455=456=457 and 460=461=462=463, respectively). The former transformation is described as a rotative nonstereotopomutation, with attendant vectoaselectivity and diastereofacioaselectivity; the latter transformation is a rotative chirostereotopomutation also with attendant vectoaselectivity and diastereofacioaselectivity. Transformation 77 gives rise to two chiral nonequimers,  $\text{A}^*,\text{X}^*$  (466=468 and 467=469); it is a case of rotative chirostereotopomutation - nonequivectoselective and diastereofaciononselective. Transformations 78 and 79 produce the corresponding pairs of chiral diastereomers  $\text{D}^*,\text{F}^*$  (472=473, 474=475 and 478=479 and 480=481, respectively). They are both described as rotative  $\text{sp}^3$  chirostereotopogeneses. The former is a classic example of an *asymmetric induction*. The last two transformations are vectoaselective and diastereofacioselective.

In Figure 17.20, transformation 80 yields three diastereomers - two achiral and one chiral -  $\text{D},\text{F},\text{X}^*$  (484=486, 485, 487, respectively). The transformation is a composite case – a rotative chirostereotopomutation (484=486) and a nonrotative  $\text{sp}^3$  achirostereotopogenesis (485 and 487) - characterized by nonequivectoselectivity and diastereofacioselectivity. The next transformation, 81, yields three chiral diastereomers  $\text{D}^*,\text{F}^*,\text{G}^*$  (490=492,491,493) and represents the composite case of a rotative chirostereotopomutation (490=492) and a rotative  $\text{sp}^3$  chirostereotopogenesis (491 and 493); it is diastereovectoselective as well as diastereofacioselective. Transformations 82 and 83 yield two diastereomers and one nonequimer ( $\text{D}^*,\text{F}^*,\text{X}^*$ ) - all three being chiral. In the former transformation, one observes a rotative nonstereotopomutation (496=498), as well as a rotative chirotopogenesis (497 and 499). Transformation 83 is a composite case of  $\text{sp}^3$  chirotopogenesis (502 and 504) and chirostereotopomutation (503=505). Both transformations are nonequivectoselective and diastereofacioselective. In transformation 84 one obtains two chiral diastereomers, and two additional diastereomers that are astereomeric with respect to the first two -  $\text{D}^*,\text{F}^*,\text{X},\text{Y}$ . The transformation represents a composite case of a rotative  $\text{sp}^3$  chirostereotopogenesis (508 and 510) and a nonrotative  $\text{sp}^3$  achirostereotopogenesis (509 and 511), with attendant nonequivectoselectivity and diastereofacioselectivity. Finally, transformation 85 leads to two pairs of chiral astereomeric diastereostereomers ( $\text{D}^*,\text{F}^*,\text{X}^*,\text{Y}^*$ ), and, in turn, is characterized by nonequivectoselectivity as well as diastereofacioselectivity. The latter transformation is a case of a rotative  $\text{sp}^3$  chirostereogenesis (514, 515, 516 and 517). Figure 17.21 portrays transformations 86-89 which bring forth the changes engendered by the chiral influence. In transformation 86 (the counterpart of 75 where no chiral additional chiral influence is exerted), there is no overall effect, since all pathways converge onto a single product  $\text{H}^*$  (524=525=526=527); it remains a case of rotative nonstereotopomutation. In transformation 87 (the counterpart of transformation 78), two chiral diastereomers  $\text{D}^*,\text{F}^*$  (534=535 and 536=537) are expected to form, since the

Transformation	Designation		Products(s)	$\Delta S \Delta S^* \Delta s$ (for each product)
75	rotative nonstereotopomutation vectoselectivity diastereofacioselectivity	$g^* \xrightarrow{a} X$ + $a \rightarrow g^*$	homomers 454 + 455 456 + 457	0 0 0 0 0 0
76	rotative chirostereotopomutation vectoselectivity diastereofacioselectivity	$g^* \xrightarrow{a} X$ + $g^* \xrightarrow{a} g^*$	homomers 460 + 461 462 + 463	0 -2+2 0 0 -2+2 0
77	rotative chirostereotopomutation nonequivalentoselectivity diastereofacioselectivity	$g^* \xrightarrow{a} X$ + $a \xrightarrow{a} g^*$	nonenamers 464 + 465 466 + 467 468 + 469	0 -1+1 0 0 -1+1 0 0 -2+2 0 0 -2+2 0
78	rotative $sp^3$ chirostereotopogenesis (asymmetric induction) (diastereoselective synthesis) vectoselectivity diastereofacioselectivity	$g^* \xrightarrow{a} X$ + $b \rightarrow b$	homomers 472 + 473 474 + 475	0 -1+1 0 0 -1+1 0 0 -1+1 0 0 -1+1 0
79	rotative $sp^3$ chirostereotopogenesis (diastereoselective synthesis) vectoselectivity diastereofacioselectivity	$g^* \xrightarrow{a} X$ + $w^* \xrightarrow{w^*} w^*$	homomers 476 + 477 478 + 479 480 + 481	0 -2+3 +1 0 -2+3 +1 0 -2+3 +1 0 -2+3 +1

Figure 17.19. Examples of Transformations of  $ag^+C=X$

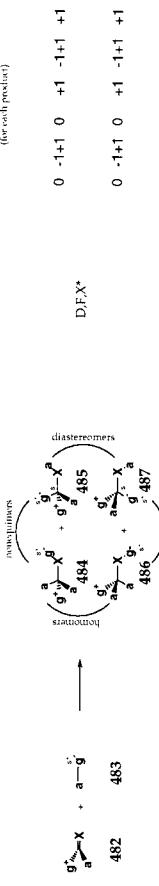
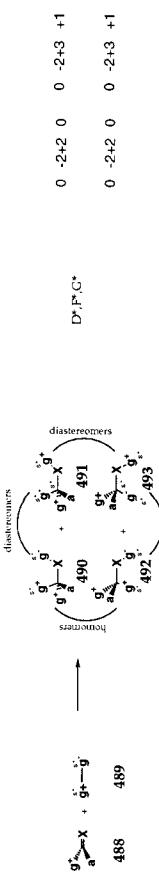
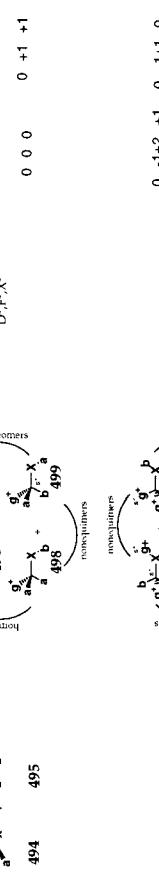
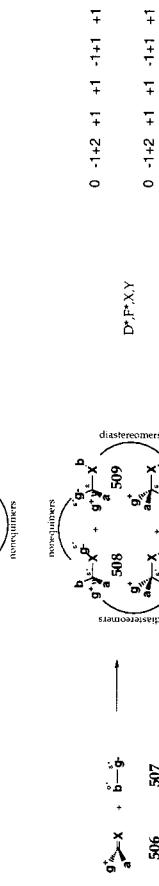
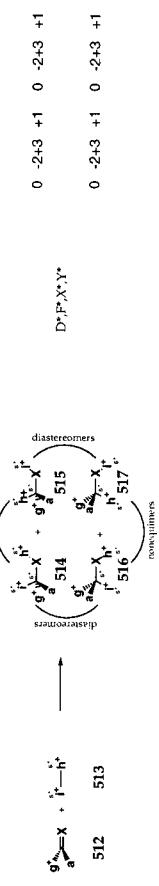
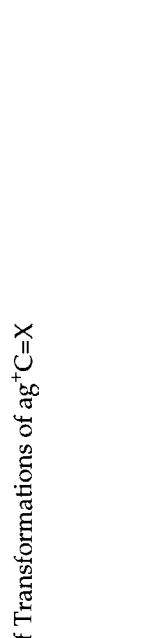
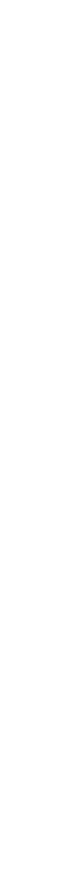
Transformation	Designation		Products	$\Delta S$	$\Delta S^*$	$\Delta S$ (for each product)
80		nonchiral monomers	diastereomers 	0 -1+1 0	+1 -1+1 +1	D,F,X*
81		nonchiral monomers	diastereomers 	0 -2+2 0	0 -2+3 +1	D*,F*,C*
82		nonchiral monomers	diastereomers 	0 0 0	0 +1 +1	D*,F*,X*
83		nonchiral monomers	homomers 	0 0 0	0 +1 +1	D*,F*,Y*
84		nonchiral monomers	diastereomers 	0 -1+2 +1	0 -1+1 0	D*,F*,X,Y*
85		nonchiral monomers	diastereomers 	0 -1+2 +1	+1 -1+1 +1	D*,F*,X*,Y*

Figure 17.20. Examples of Transformations of  $\text{ag}^+\text{C}=\text{X}$

Transformation	Designation		$\Delta S$	$\Delta S^*$	$\Delta S$	Product(s)
		(for each product)				
86	rotative nonstereotropomutation vectoselectivity diastereofacoselectivity	518      519			0 0 0    0 0 0	$H^*$
87	rotative $sp^3$ chirostereotropogenesis (asymmetric induction) (diastereoselective synthesis) vectoselectivity diastereofacoselectivity	528      529			0 -0+1 +1    0 -0+1 +1	$D^*, F^*$
88	rotative chirostereotropomutation and rotative $sp^3$ chirostereotropogenesis (double diastereoselective synthesis) diastereovectoselectivity diastereofacoselectivity	538      539			0 -2+2 0    0 -2+3 +1	$D^*, F^*, G^*$
89	rotative nonstereotropomutation and rotative $sp^3$ chirostereotropogenesis (diastereoselective synthesis) (and nonequimorphoselective synthesis) nonequivectoselectivity diastereofacoselectivity	548      549			0 0 0    0 -0+1 +1	$D^*, F^*, X^*$

Figure 17.21. Examples of Transformations of  $ag^+C=X$  (chiral influence)

transformation is characterized by vectoaselectivity and diastereofacioselectivity; it is still a case of  $sp^3$  chirostereotopogenesis. The next transformation, 88, yields three chiral diastereomers D\*,F\*,G\* (**544=546,545,547**) in unequal amounts - the result of diastereovectoselective-and-diastereofacioselective rotative chirostereotopomutation (**544=546**), and rotative  $sp^3$  chirostereotopogenesis (**545** and **547**). Finally, transformation 89 yields two chiral diastereomers and a chiral nonequimer - D\*,F\*,X\* (**555, 557** and **554=556**). The process is a composite case of rotative nonstereotopomutation (**554=556**) and rotative  $sp^3$  chirostereotopogenesis (**555** and **557**) - nonequivvectoselective and diastereofacioselective.

### C. adC=Cbc

The transformations of this molecule are represented in Figures 17.22 and 17.23. In Figure 17.24 we include the chiral influence on the course of the transformations. Transformations 90-98 lead to nine types of product mixtures - E\*,E, D\*,F\*, E\*,E,D, E\*,E,N, E\*,E,D\*,D, E\*,E,N\*,N, D\*,F\*,G\*,J\*, D\*,F\*,M\*,N\*, and D\*,F\*,M\*,N.

Transformation 90 generates a racemic mixture (**560=561/562=563**); the process is a nonrotative achirostereotopolysis - avectoselective and enantiofaciononselective. Transformation 91 is a rotative nonstereotopomutation that is avectoselective but enantiofacioselective; it leads to two chiral diastereomers (**566=567** and **568=569**). Transformation 92 gives a racemate (**573/575**) and an achiral diastereomer (**572=574**); it is a case of nonrotative nonstereotopomutation and nonrotative  $sp^3$  chirostereotopogenesis - the result of diastereovectoselectivity, enantiofacioaselectivity (**572=574**) as well as enantiofaciononselectivity (**573** is the enantiomer of **575**). Transformation 93 yields a racemate (**579/581**) and an achiral astereomer (**578=580**) - the composite result of nonrotative achirostereotopolysis and nonrotative nonstereotopomutation - with attendant astereovectoselectivity and, again, a simultaneous case of enantiofaciononselectivity and enantiofacioaselectivity. The next transformation, 94, represents a rotative  $sp^3$  chirostereotopogenesis and produces two diastereomeric racemates (**584/587** and **585/586**); here, one observes diastereovectoselectivity but enantiofacioaselectivity with respect to both sets of products. Transformation 95 is similar; we have a nonrotative achirostereotopolysis along with a nonrotative nonstereotopomutation - characterized by astereovectoselectivity and enantiofaciononselectivity - that yield two astereomeric racemates (**590/592** and **591/593**).

In Figure 17.23, transformation 96 constitutes a rotative  $sp^3$  chirostereogenesis that is diastereovectoselective and enantiofacioselective - manifested in the formation of four chiral diastereomers (**596, 597, 598, and 599**). The process may be considered a case of double diastereoselective synthesis. Finally, each of transformations 97 and 98 yields two astereomeric sets of diastereomeric pairs; in the former case, all four components (**602-605**) are chiral; in the latter transformation, one of the components (**608**) is achiral, the other three are chiral (**609-611**). The former transformation represents a composite case of rotative achirostereotopolysis and rotative nonstereotopomutation; in contradistinction, the latter transformation is a composite case of nonrotative achirostereotopolysis and rotative nonstereotopomutation. Both transformations are subject to astereovectoselectivity and enantiofacioselectivity.

Figure 17.24 illustrates transformations 99-104 which are subject to the chiral influence. In transformation 99 (the counterpart of 90 where no chiral additional chiral influence is exerted), one obtains an enantioenriched mixture of two enantiomers (**618=619** and **620=621** are enantiomers that are formed in unequal amounts). This process, traditionally considered an enantioselective synthesis, is a rotative achirostereotopolysis (there is a net loss of one stereogenic atom with concomitant generation of a rotative substance). Transformation 100 (the counterpart of transformation 92) is a nonrotative nonstereotopomutation (formation of homomeric **628** and **630**) and a rotative  $sp^3$  chirostereotopogenesis (unequal amounts of enantiomers **629** and **631** are generated) - enantiofacioselective-and-enantiofacioaselective. It is interesting to note that **628** and **630**, which are homomers, would be formed at different rates as they arise from diastereomeric transition states - a fact that is experimentally undetectable. Transformation 101

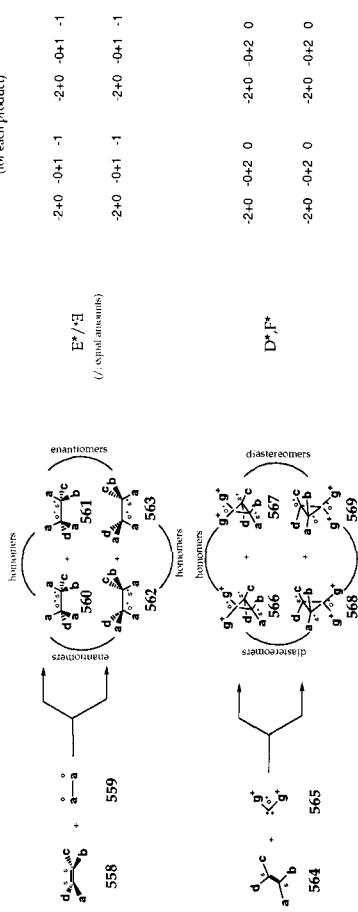
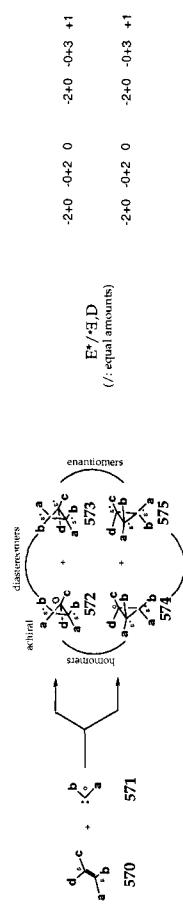
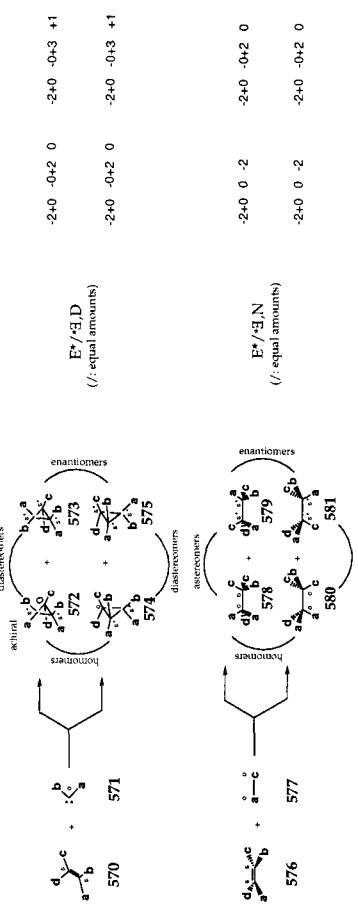
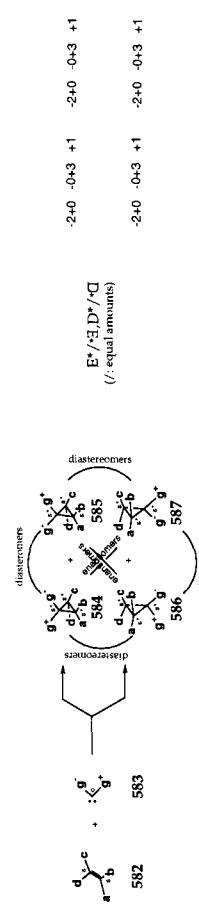
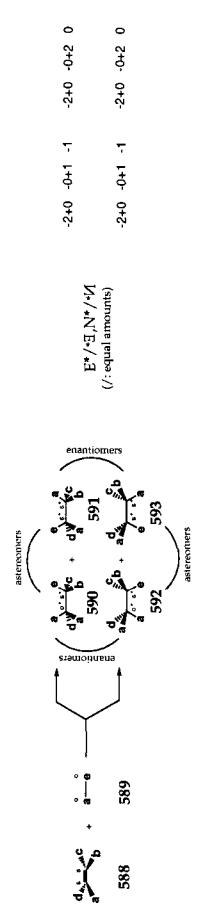
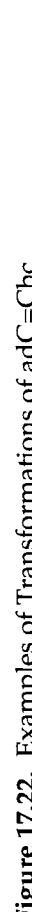
Transformation	Designation		Products	$\Delta S$	$\Delta S^*$	$\Delta S$ (for each product)
90	nonrotative achirostereotopology avectoselectivity enantiofacioselectivity		enantiomers 	-2+0 -0+1 -1	-2+0 -0+1 -1	
91	rotative nonstereotopomutation (diastereoselective synthesis) avectoselectivity enantiofacioselectivity		enantiomers 	-2+0 -0+2 0	-2+0 -0+2 0	
92	nonrotative nonstereotopomutation and nonrotative sp <sup>3</sup> chirostereotopogenesis diastereovectoselectivity enantiofacieselectivity and enantiofacioselectivity		enantiomers 	-2+0 -0+2 0	-2+0 -0+2 0	
93	nonrotative achirostereotopology and nonrotative nonstereotopomutation diastereovectoselectivity enantiofacieselectivity and enantiofacioselectivity		enantiomers 	-2+0 0 -2	-2+0 -0+2 0	
94	nonrotative sp <sup>3</sup> chirostereotopogenesis diastereovectoselectivity enantiofacioselectivity		enantiomers 	-2+0 0 -2	-2+0 -0+2 0	
95	nonrotative achirostereotopology and nonrotative nonstereotopomutation diastereovectoselectivity enantiofacioselectivity		enantiomers 	-2+0 -0+1 -1	-2+0 -0+2 0	

Figure 17.22. Examples of Transformations of adC=Cbc

Transformation	Designation	Products	$\Delta S$	$\Delta S^*$	$\Delta S$ (for each product)
96	rotative sp <sup>3</sup> chirostereotopogenesis (triple diastereoselective synthesis) diastereovectoselectivity enantiofacioselectivity	<p>diastereomers</p> <p>diastereomers</p> <p>diastereomers</p> <p>diastereomers</p> <p>diastereomers</p> <p>diastereomers</p> <p>stereomers</p>	-2+0	-0+3	+1
97	rotative achirostereotopopolysis and rotative nonstereotopomutation (double diastereoselective (and astereomorphoselective) synthesis) astereovectoselectivity enantiofacioselectivity	<p>diastereomers</p> <p>diastereomers</p> <p>diastereomers</p> <p>diastereomers</p> <p>stereomers</p>	-2+0	-0+1	-1
98	nonrotative achirostereotopopolysis and rotative nonstereotopomutation (double diastereoselective (and astereomorphoselective) synthesis) astereovectoselectivity enantiofacioselectivity	<p>achiral</p> <p>diastereomers</p> <p>diastereomers</p> <p>diastereomers</p> <p>stereomers</p>	-2+0	-0+1	-1

Figure 17.23. Examples of Transformations of adC=Cbc

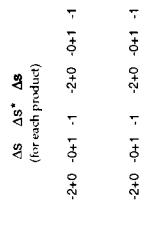
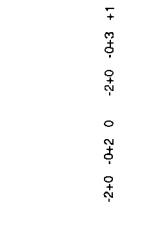
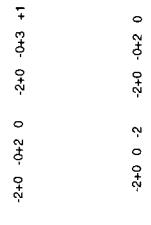
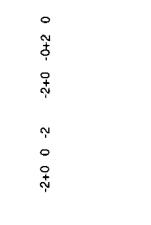
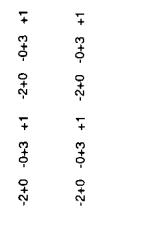
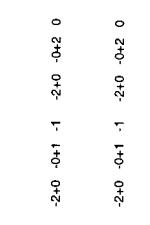
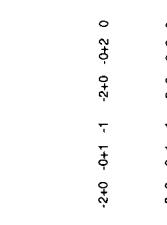
Transformation	Designation			Products	$\Delta S$ , $\Delta S^*$ , $\Delta S$ (for each product)
9.9	rotative achirostereotopology (enantioselective synthesis) enantioselectivity enantiofaceselectivity			E*, E'	-2ΔS -0.1 ΔS <sup>*</sup> -1 ΔS
9.10	nonrotative nonstereotopomutation and rotative sp <sup>3</sup> chirostereotopogenesis (enantioselective and diastereoselective synthesis) nonvectoselectivity enantiofacieselectivity and enantiofaceselectivity			E*, E'	-2ΔS -0.1 ΔS <sup>*</sup> -1 ΔS
10.0	nonrotative achirostereotopology and rotative sp <sup>3</sup> chirostereotopogenesis (enantioselective (and asteroselective) synthesis) nonvectoselectivity enantiofacieselectivity and enantiofaceselectivity			E*, E', D	-2ΔS -0.1 ΔS <sup>*</sup> -1 ΔS
10.1	nonrotative achirostereotopology and rotative nonstereotopomutation (enantioselective (and asteroselective) synthesis) asteroselectivity enantiofacieselectivity and enantiofaceselectivity			E*, E', D*, D'	-2ΔS -0.1 ΔS <sup>*</sup> -1 ΔS
10.2	rotative sp <sup>3</sup> chirostereotopogenesis ((double) asymmetric synthesis) diastereovectoselectivity enantiofaceselectivity			E*, E', N*, N'	-2ΔS -0.1 ΔS <sup>*</sup> -1 ΔS
10.3	rotative achirostereotopology and rotative nonstereotopomutation ((double) enantioselective (and asteroselective) synthesis) asteroselectivity enantiofaceselectivity			D*, F*, M*, N	-2ΔS -0.1 ΔS <sup>*</sup> -1 ΔS
10.4	nonrotative achirostereotopology and rotative nonstereotopomutation ((double) diastereoselective (and asteroselective) synthesis) asteroselectivity enantiofaceselectivity			D*, F*, M*, N	-2ΔS -0.1 ΔS <sup>*</sup> -1 ΔS

Figure 17.24. Examples of Transformations of adC=Cbc (chiral influence)

(the counterpart of 93) yields an enantioenriched mixture of two enantiomers (**639,641**) and an achiral astereomer (**638=640**). This would be described as a composite case of a nonrotative achirostereotopolysis (**638=640**) and a rotative nonstereotopomutation (formation of **639** and **641**) – astereovectoselective, enantiofacioselective and also enantiofacioaselective (the homomers **638** and **640**, again, being formed in unequal amounts). The next transformation, 102 (the counterpart of 94), yields two enantioenriched mixture of diastereomers (**648,651** and **649,650**) - a case of double asymmetric synthesis (double diastereoselective synthesis). This is representative of a rotative  $sp^3$  chirostereotogenesis that is diastereovectoselective and, simultaneously, enantiofacioselective. Transformation 103 (the counterpart of 95) yields two enantioenriched mixtures of astereomers (**658,660** and **659,661**) - also a case of double asymmetric synthesis (astereomorphoselective and diastereoselective synthesis) - the consequence of astereovectoselectivity as well as enantiofacioselectivity. Finally, transformation 104 presents an interesting and unique instance where one obtains two chiral diastereomers (**669** and **671**), and two astereomers (one chiral (**670**), and the other one achiral (**668!**)). This transformation is a composite case - a nonrotative achirostereotopolysis (**668** and **670**) and a rotative nonstereotopomutation (**669** and **671**), with attendant astereovectoselectivity and enantiofacioselectivity.

#### D. $ag^+C=Cbc$

Transformations of this fourth molecule are presented in Figures 17.25-17.27; the chiral influence is explored through corresponding transformations in Figures 17.28-17.30. Transformations 105-119 yield four types of product mixtures - **D\*,F\***, **D\*,F\*,N\***, **D\*,F\*,G\*,J\***, and **D\*,F\*,M\*,N\***.

In Figure 17.25, transformations 105-107 produce two chiral diastereomers **D\*,F\***. These transformations would be described as diastereoselective syntheses. However, the subtle differences in the changes incurred at the stereogenic atoms can be distinguished as follows - the first two (105 and 106) are rotative chirostereotopolyses, but the third one (107) is a rotative chirostereotopomutation - all three being vectoaselective and diastereofacioselective. Transformation 108 is a composite case of a rotative chirostereotopolysis and a rotative chirostereotopomutation - astereovectoselective, diastereofacioselective and also diastereofacioselective.

Each of transformations 109-113 (Figure 17.26) yields four chiral diastereomers **D\*,F\*,G\*,J\***. All five transformations would be described, using previous terminology, as (double) diastereoselective syntheses. In our new terminology, transformation 109 is a composite case of rotative chirostereotopolysis/chirostereotopomutation. Transformation 110 is a composite case of rotative  $sp^3$  chirostereotogenesis/chirostereotopomutation, whereas transformations 111-113 are rotative  $sp^3$  chirostereotogeneses. All five transformations are diastereovectoselective and diastereofacioselective.

In Figure 17.27, each of the six transformations is astereovectoselective and diastereofacioselective, and yields two pairs of astereomeric diastereomers - **D\*,F\*,M\*,N\***. Transformations 114 and 115 represent rotative chirostereotopolyses; 116-118 are chirostereotopolysis/chirostereotopomutation composite cases; transformation 119 is a chirostereotopomutation.

The alterations brought about by the chiral influence are seen through transformations 120-130 in Figures 17.28-17.30. In Figure 17.28, each of transformations 120-122 (the counterparts of 105-107 where no external chiral influence is exerted) generates two chiral diastereomers - **D\*,F\*** (**768=769** and **770=771**, **778=779** and **780=781**, and **788=789**, **790=791**). All three transformations would be generally described as diastereoselective syntheses. However, with the new terminology advanced here, the first two are rotative achirostereotopolyses, whereas the third one is a rotative nonstereotopomutation; all three transformations are vectoaselective and diastereofacioselective. Transformation 123 (the counterpart of 108) yields two chiral

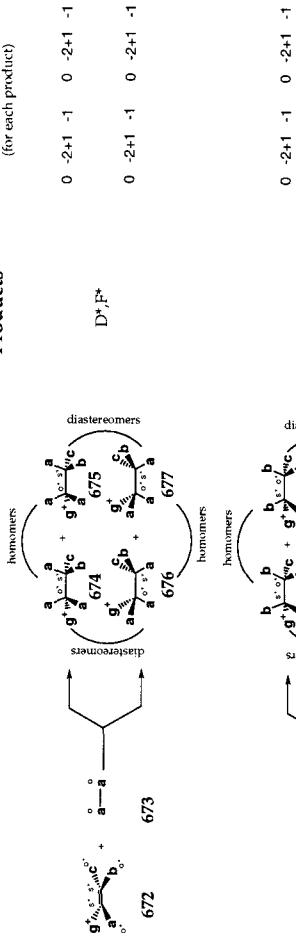
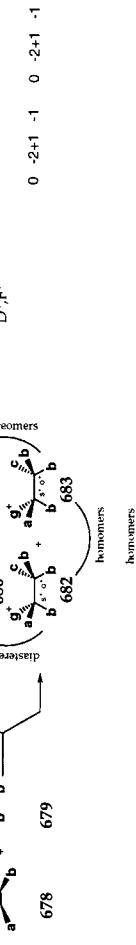
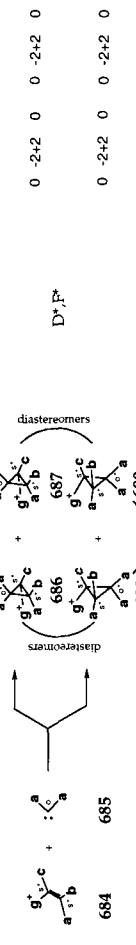
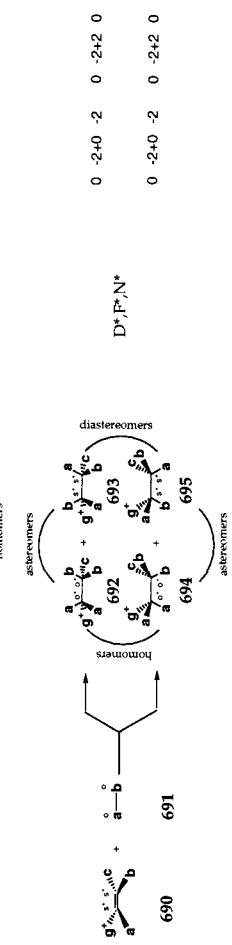
Transformation	Designation	Products	$\Delta s \Delta s' \Delta s$ (for each product)
105	rotative chirostereotopology (diastereoselective synthesis) vectoaselectivity diastereofacioselectivity		0 -2+1 -1 0 -2+1 -1
106	rotative chirostereotopology (diastereoselective synthesis) vectoaselectivity diastereofacioselectivity		0 -2+1 -1 0 -2+1 -1
107	rotative chirostereotopomutation (diastereoselective synthesis) vectoaselectivity diastereofacioselectivity		0 -2+2 0 0 -2+2 0
108	rotative chirostereotopology and rotative chirostereotopomutation (diastereoselective (and astereoselective) synthesis) astereovectoselectivity diastereofacioselectivity and diastereofacioselectivity		0 -2+0 -2 0 -2+2 0 0 -2+0 -2 0 -2+2 0

Figure 17.25. Examples of Transformations of  $ag^+C=Cbc$

Transformation	Designation		Products (for each product)	$\Delta S \Delta S^*$
109	rotative chirostereotopology & rotative chirostereotopomutation ((triple) diastereoselective synthesis) diastereovectoselectivity diastereofacioselectivity		D*, F*, G*, J* D*, F*, G*, J*	0 -2+1 -1 0 -2+2 0 0 -2+1 -1 0 -2+2 0
110	rotative $sp^3$ chirrostereotopogenesis & rotative chirostereotopomutation ((triple) diastereoselective synthesis) diastereovectoselectivity diastereofacioselectivity		D*, F*, G*, J*	0 -2+2 0 0 -2+3 +1 0 -2+2 0 0 -2+3 +1
111	rotative $sp^3$ chirrostereotopogenesis ((triple) diastereoselective synthesis) diastereovectoselectivity diastereofacioselectivity		D*, F*, G*, J*	0 -2+3 +1 0 -2+3 +1 0 -2+3 +1 0 -2+3 +1
112	rotative $sp^3$ chirrostereotopogenesis ((triple) diastereoselective synthesis) diastereovectoselectivity diastereofacioselectivity		D*, F*, G*, J*	0 -2+3 +1 0 -2+3 +1 0 -2+3 +1 0 -2+3 +1
113	rotative $sp^3$ chirrostereotopogenesis ((triple) diastereoselective synthesis) diastereovectoselectivity diastereofacioselectivity		D*, F*, G*, J*	0 -2+3 +1 0 -2+3 +1 0 -2+3 +1 0 -2+3 +1

Figure 17.26. Examples of Transformations of  $ag^+C=CbC$

Transformation	Designation	Products (for each product)	$\Delta S$	$\Delta S^*$	$\Delta S$
114	rotative chirostereotopolysis (double diastereoselective & astereoselective) synthesis astereovectoselectivity diastereofacoselectivity	 Diastereomers 728 729 730 731	0 -2+1 -1	0 -2+1 -1	0 -2+1 -1
115	rotative chirostereotopolysis (double diastereoselective & astereoselective) synthesis astereovectoselectivity diastereofacoselectivity	 Diastereomers 732 733 734 735	0 -2+1 -1	0 -2+1 -1	0 -2+1 -1
116	rotative chirostereotopolysis & rotative chirostereotopomutation (double diastereoselective & astereoselective) synthesis astereovectoselectivity diastereofacoselectivity	 Diastereomers 738 739 740 741	0 -2+1 -1	0 -2+2 0	0 -2+1 -1
117	rotative chirostereotopolysis & rotative chirostereotopomutation (double diastereoselective & astereoselective) synthesis astereovectoselectivity diastereofacoselectivity	 Diastereomers 744 745 746 747	0 -2+2 0	0 -2+1 -1	0 -2+1 -1
118	rotative chirostereotopolysis & rotative chirostereotopomutation (double diastereoselective & astereoselective) synthesis astereovectoselectivity diastereofacoselectivity	 Diastereomers 750 751 752 753	0 -2+2 0	0 -2+1 -1	0 -2+2 0
119	rotative chirostereotopolysis (double diastereoselective & astereoselective) synthesis astereovectoselectivity diastereofacoselectivity	 Diastereomers 756 757 758 759	0 -2+2 0	0 -2+2 0	0 -2+2 0

Figure 17.27. Examples of Transformations of  $ag^+C=Cbc$

Transformation	Designation	Products	$\Delta S$	$\Delta S^*$	$\Delta S$ (for each product)
120	rotative achirostereotopology (diastereoselective synthesis) vectoselectivity diastereofacieselectivity		-2+0	-0+1	-1
121	rotative achirostereotopology (diastereoselective synthesis) vectoselectivity diastereofacieselectivity		-2+0	-0+1	-1
122	rotative nonstereotopomutation (diastereoselective synthesis) vectoselectivity diastereofacieselectivity		-2+0	-0+2	0
123	rotative chirostereotopology & rotative chirostereotopomutation (diastereoselective & astereoselective synthesis) astereovectoselectivity diastereofaciaselectivity		0	-2+0	-2

Figure 17.28. Examples of Transformations of  $ag^+C=Cbc$  (chiral influence)

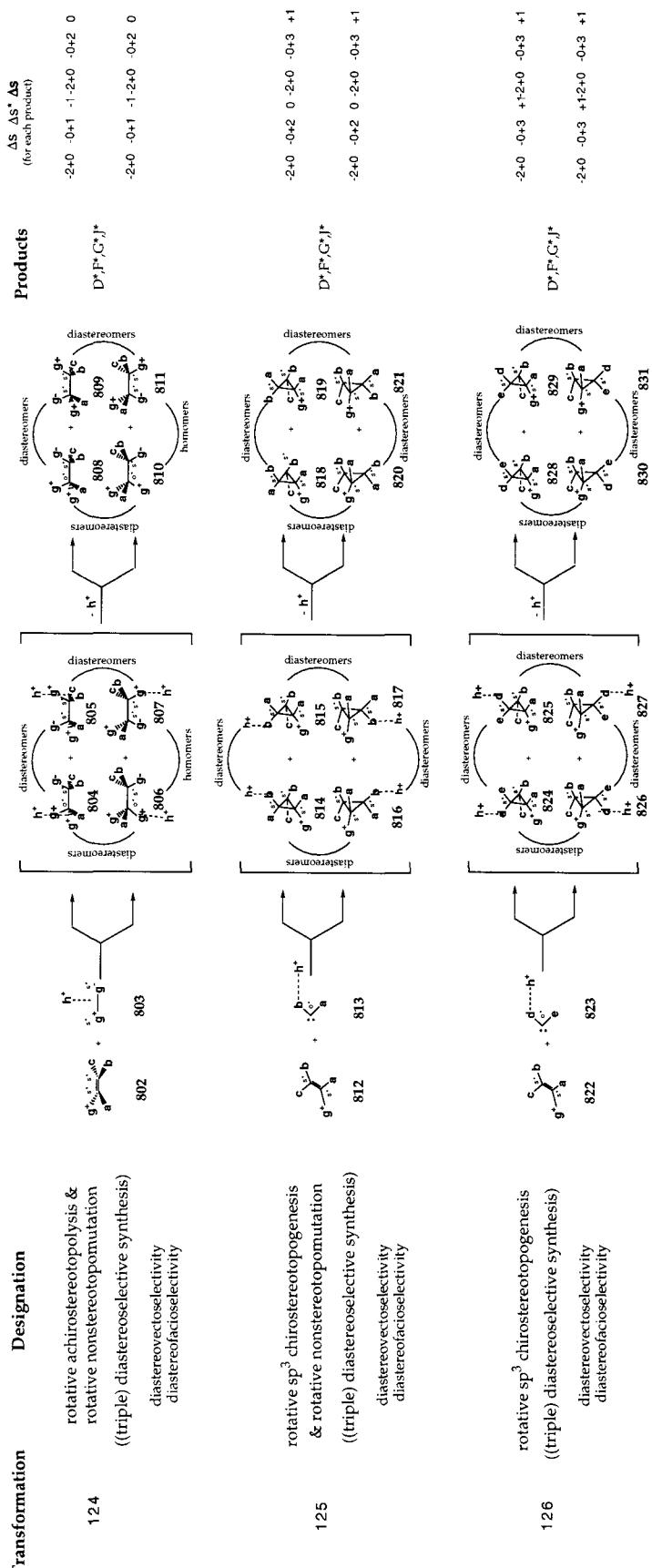


Figure 17.29. Examples of Transformations of  $ag^+C=Cbc$  (chiral influence)

Transformation	Designation		$\Delta S^*$ , $\Delta S^*$ , $\Delta S$ (for each product)
127	rotative chirostereotopolymerization & ((double) diastereoselective (and stereoselective) synthesis) astereovectoselectivity, diastereofacoselectivity		$D^*, F^*, M^*, N^*$ $D^*, F^*, M^*, N^*$ $D^*, F^*, M^*, N^*$ $D^*, F^*, M^*, N^*$
128	rotative chirostereotopolymerization & ((double) diastereoselective (and stereoselective) synthesis) astereovectoselectivity, diastereofacoselectivity		$D^*, F^*, M^*, N^*$ $D^*, F^*, M^*, N^*$ $D^*, F^*, M^*, N^*$ $D^*, F^*, M^*, N^*$
129	rotative chirostereotopolymerization & ((double) diastereoselective (and stereoselective) synthesis) astereovectoselectivity, diastereofacoselectivity		$D^*, F^*, M^*, N^*$ $D^*, F^*, M^*, N^*$ $D^*, F^*, M^*, N^*$ $D^*, F^*, M^*, N^*$
130	rotative chirostereotopolymerization & ((double) diastereoselective (and stereoselective) synthesis) astereovectoselectivity, diastereofacoselectivity		$D^*, F^*, M^*, N^*$ $D^*, F^*, M^*, N^*$ $D^*, F^*, M^*, N^*$ $D^*, F^*, M^*, N^*$

Figure 17.30. Examples of Transformations of  $ag^+C=Cbc$  (chiral influence)

diastereomers (799, 801) and a chiral astereomer (798=800) - D\*,F\*,N\*. In effect, the transformation constitutes a composite case of rotative chirostereotopolysis (798=800) and rotative chirosteropomutation (799, 801) - with attendant astereovectoselectivity, diastereofacioselectivity, and diastereofaciocoselectivity.

Each of the three transformations (124-126 - the counterparts of 109-111) in Figure 17.29 yields four chiral diastereomers - D\*,F\*,G\*,J\*. Transformations 124-126 would be considered as (triple) dikhae syntheses. More detailed scrutiny reveals that transformation 124 is a composite case of rotative achirostereotopolysis and rotative nonstereotopomutation; 125 is a composite case of rotative sp<sup>3</sup> chirostereotopogenesis and rotative nonstereotopomutation, and, 126 is, simply, a rotative sp<sup>3</sup> chirostereotopogenesis.

In Figure 17.30, each of the remaining transformations (127-130 - the counterparts of 114, 116, 117, and 119, respectively) produces two astereomeric sets of diastereomers - all chiral - D\*,F\*,M\*,N\*. In the older terminology, transformations 127-130 would be considered as (double) diastereoselective (and astereomorphoselective) syntheses. With the new terminology, the first three transformations are composite rotative chirostereotopolyses/chirostereotopomutations; the last one is a rotative chirostereopomutation; all four transformations are astereovectoselective and diastereofaciocoselective.

Using the currently available terms in the literature, of all the examples in Figures 17.17-17.30 (transformations 64-130), transformation 72 (Figure 17.18) would be the only example of "asymmetric synthesis" - a case of "*de novo* synthesis of a chiral substance from an achiral precursor such that one enantiomer predominates over the other."<sup>9a</sup> Transformations 72 and 99 would be considered "enantioselective syntheses," since they "produce the two enantiomers of a chiral product in unequal amounts."<sup>9b</sup> Transformations 65,68,79,91,105-107, and 120-122 are "diastereoselective syntheses" because they are "reactions in which a new stereogenic element is introduced in such a way that diastereomers are produced in unequal amounts."<sup>9c</sup> The literature lacks terms to describe selective formation of one astereomer over another e.g. transformation 50 (Figure 17.14), or, of one nonequimer over another e.g. transformations 67 (Figure 17.17) and 77 (Figure 17.19). By analogy with "enantioselective synthesis" and "diastereoselective synthesis," one could designate transformation 50 as an "astereoselective synthesis", and transformations 67 (Figure 17.17) and 77 (Figure 17.19) as "nonequiselective syntheses".

Designations of Type of Synthesis	Transformation
<b>Three-Component</b>	
enantioselective and diastereoselective synthesis	100
enantioselective and astereoselective synthesis	101
diastereoselective and enantiononselective synthesis	92
double diastereoselective synthesis	81,88
diastereoselective and astereoselective synthesis	108,123
diastereoselective and nonequiselective synthesis	89
astereoselective and enantiononselective synthesis	93
<b>Four-Component</b>	
double enantioselective and diastereoselective synthesis	73,102
double enantioselective and astereoselective synthesis	103
double enantioselective and nonequiselective synthesis	74
diastereoselective and double enantiononselective synthesis	68
double diastereoselective and astereoselective synthesis	97,98,104,114-119,127-130
double diastereoselective and nonequiselective synthesis	70,84,85
diastereoselective and double enantiononselective synthesis	94
astereoselective and double enantiononselective synthesis	95
triple diastereoselective synthesis	96,109-113,124-126

However, these terms, along with "enantioselective synthesis" and "diastereoselective synthesis," lack the desired clarity; for example, nonequiselective synthesis would apply to transformation 67 (non-racemate) as well as transformation 69 (racemate case) (Figure 17.17).

Additionally, the literature lacks terms to describe selectivity in reactions leading to three, four (or more) products; selective morphogenesis in such transformations was discussed in Chapter 10 (Volume 2). In the absence of concise terminology in this regard, selectivity differences in the various examples of Figures 17.17-17.30 may be delineated through composite, albeit vague and confusing designations shown below:

In contrast, the universal and comprehensive scheme we have presented is unambiguous and clear; the numerous examples we have presented in the cited figures attest to the fact that our scheme provides a designation of the stereochemical changes - to the desired degree of detail - in any transformation leading to 1-, 2-, 3- and 4-component systems.

## X. Stereospecificity and Nonstereospecificity

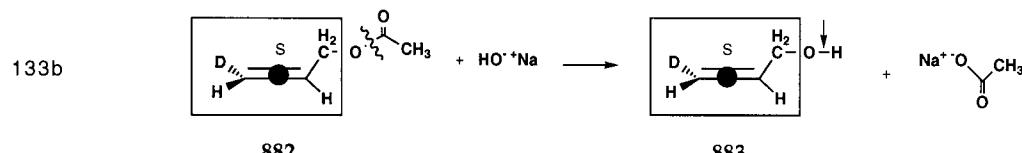
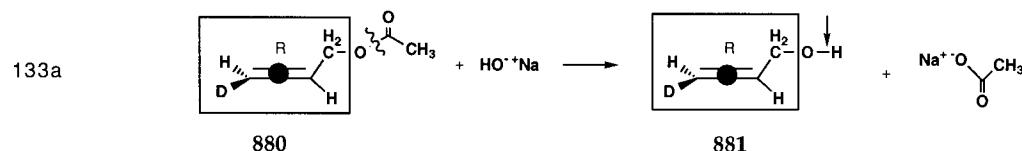
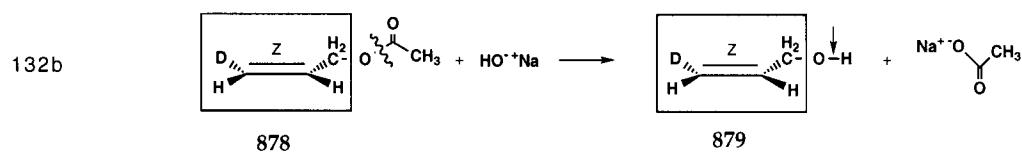
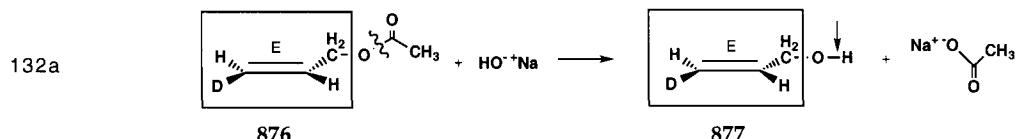
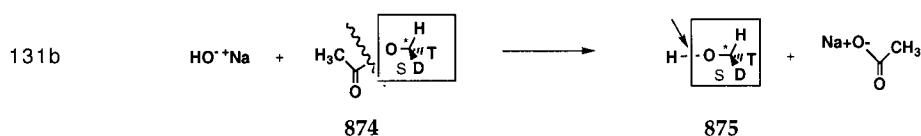
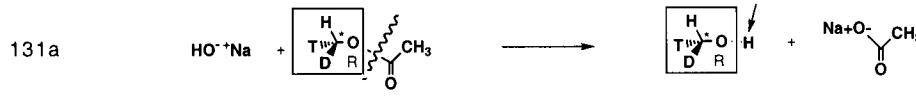
The discussion given above brings forth the need to refine the concept of *stereospecificity*. The term has been used, in distinct connotations, by chemists representing two principal schools of thought. According to the first school, a reaction in which one stereomeric product is formed, to the total exclusion of other stereomeric products, is stereospecific; that is, stereoselectivity is 100%. In the latter case, one would question: what would be the acceptable margin of error -  $\pm 0.01\%$ ? If so, would a reaction that displays 99.98% stereoselectivity not to be considered as stereospecific? Where does one draw the line? As our analytical techniques are refined, a reaction deemed stereospecific today by the above definition, may not be so tomorrow. This can be confusing, since stereospecificity becomes a function of the sensitivity of the analytical method. The use of *stereospecificity* in this manner should be abandoned.

According to the second school of thought - first proposed by Zimmerman and coworkers<sup>10</sup> and strongly advocated by Eliel<sup>11</sup> - a reaction is stereospecific if stereomerically-distinct reactants yield stereomerically-distinct products. The wording of this definition is troublesome - with respect to enantiomers, as well as diastereomers. The following examples demonstrate the inadequacy of this definition.

In Figure 17.31, we depict three examples of saponification *viz.* transformations 131-133. In the first case, (*R*)-2-octyl acetate (872) is hydrolyzed to give (*R*)-2-octyl alcohol (873); the enantiomeric (*S*)-2-octyl acetate (874) yields (*S*)-2-octyl alcohol (875). In the next example, (*E*)-3-deuteriopropenyl acetate (876) is saponified to (*E*)-3-deuteriopropenol (877), while the diastereomeric (*Z*)-3-deuteriopropenyl acetate (878) is hydrolyzed to (*Z*)-3-deuteriopropenol (879). In the third example, (*R*)-4-deutero-2,3-butadienyl acetate (880) is cleaved to yield (*R*)-4-deutero-2,3-butadienol (881), and the enantiomeric (*S*)-4-deutero-2,3-butadienyl acetate (882) leads to (*S*)-4-deutero-2,3-butadienol (883). Thus, in transformations 131a/b and 133a/b, enantiomerically-distinct reactants yields enantiomerically-distinct products, and in 132a/b, diastereomerically-distinct reactants yield diastereomerically-distinct products. In sum, since, stereomerically-distinct reactants yield stereomerically-distinct products, the saponifications of these esters (transformations 131a/b-133a/b), by the Zimmerman definition, must be considered as stereospecific. This is illogical and untrue; the saponification reaction *per se* has no stereochemical attribute. The Zimmerman definition has the right notion, but leaves something to be desired.

Figure 17.32 portrays transformations 134a/b-136a/b. In 134a, (*R*)-deuteriotritiomethyl acetate (884) is subjected to an  $S_N2$  inversion to give (*S*)-deuterioiodotritiomethane (885); the

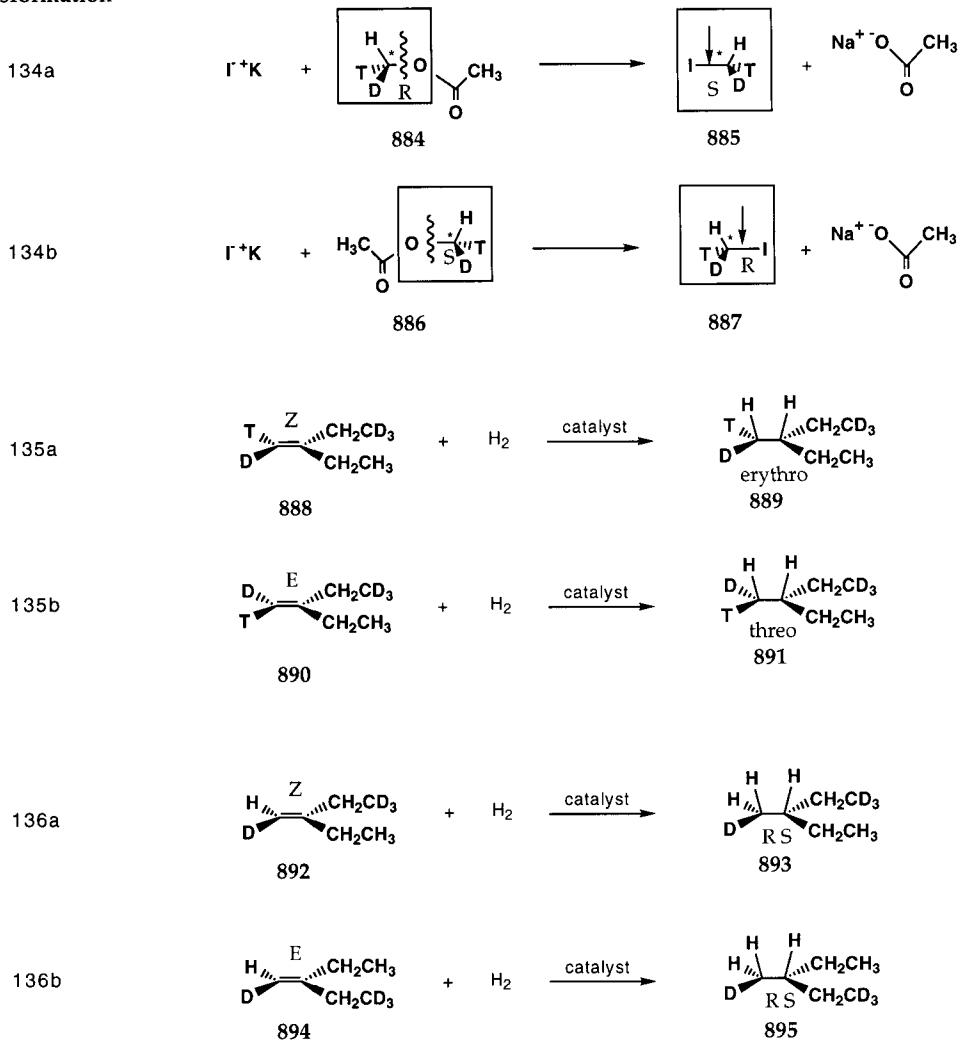
**Transformation**



**Figure 17.31.** Examples of Transformations with no Stereospecificity

enantiomeric (*S*)-deuteriotritiomethyl acetate, in transformation 134b, is transformed to (*R*)-deuterioiodotritiomethane (887). In cases 135a/b, (*Z*)-2-ethyl-1,4,4,4-tetradeutero-1-tritiobutene (888) is reduced to *erythro*-1,1,4-tetradeutero-3-ethyl-4-tritiobutane (889), and the diastereomeric (*E*)-2-ethyl-1,4,4,4-tetradeutero-1-tritiobutene (890) is reduced to *threo*-1,1,1,4-tetradeutero-3-ethyl-4-tritiobutane (891). Here too, stereomerically-distinct reactants yield stereomerically-distinct products. These would also be deemed stereospecific, by the

**Transformation**



**Figure 17.32.** Examples of Stereospecific Transformations

Zimmerman definition. This designation, in sharp contrast to that of 131-133, is logical and true. The principal difference between the sets of examples is that in the former three examples (Figure 17.31), the stereogens remain intact, the reactions do not involve the stereogenic elements in the reactants. In contrast, in the examples of Figure 17.32, because the stereogenic atoms are actually involved in the chemical transformations; the stereogens of the reactants are transformed into new stereogens in the products.

In the light of these examples, we hereby provide a different definition of stereospecificity and nonstereospecificity – one that is applicable only to kinetically-controlled transformations.

In the light of these examples, we hereby provide a different definition of stereospecificity and nonstereospecificity – one that is applicable only to kinetically-controlled transformations.

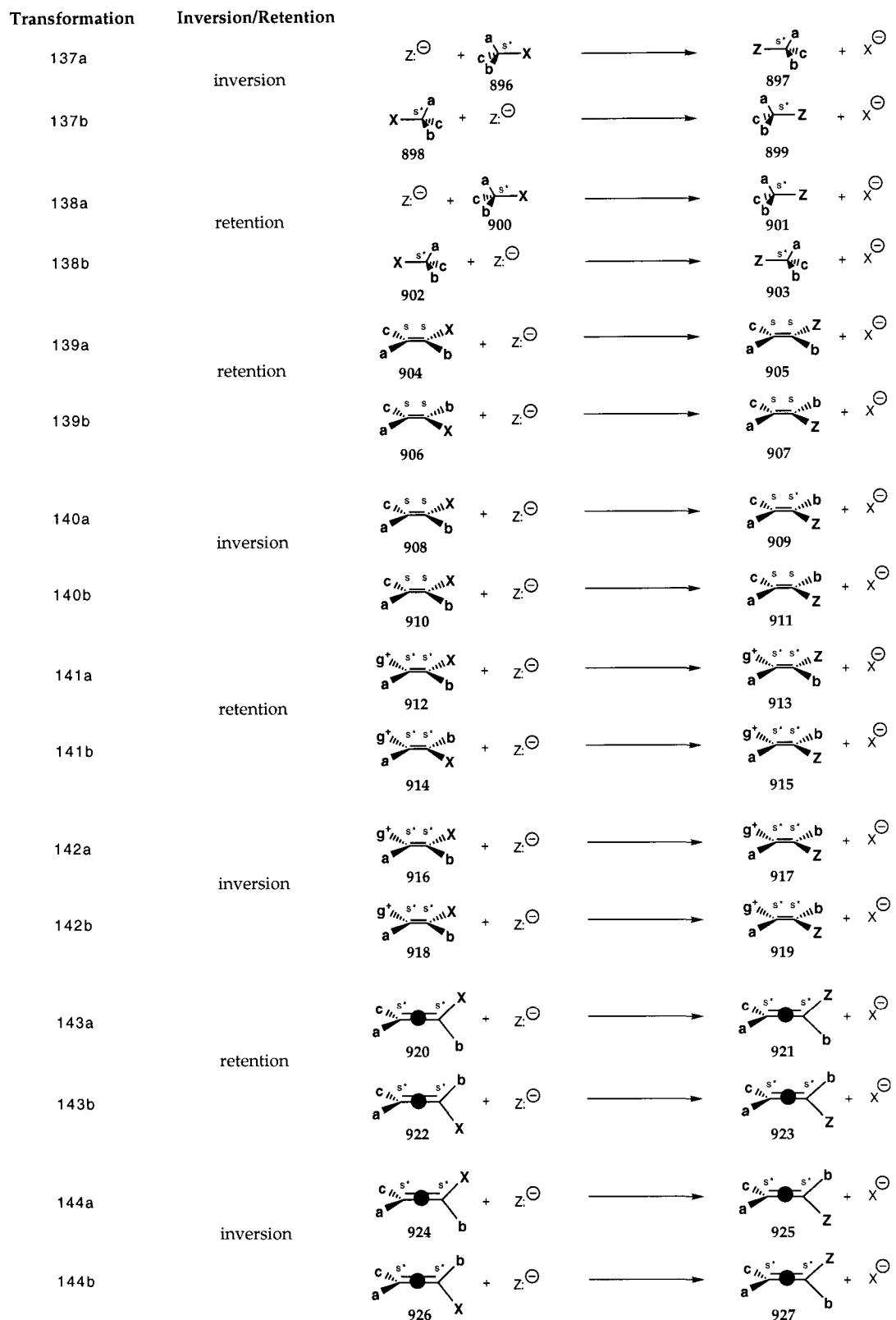
The reaction of a reagent R with substrate S is said to be *stereospecific* (or *partially stereospecific*<sup>10</sup>) if either or both configurationally-distinct stereomeric form(s) of S - S<sub>1</sub> or/and S<sub>2</sub> - is(are) transformed into configurationally distinct stereomeric products P<sub>1</sub>, P<sub>2</sub> (or *non-equimolar* mixtures of P<sub>1</sub> and P<sub>2</sub> ( $[P_1] \neq [P_2]$ )) containing one (or more) *de novo* stereogenic element(s).<sup>12</sup> This means that whereas a stereomeric (real) substrate S<sub>1</sub> yields a product P<sub>1</sub> (or mixture of P<sub>1</sub> and P<sub>2</sub> ( $[P_1] \neq [P_2]$ )), the corresponding stereospecific transformation of stereomeric substrate S<sub>2</sub> (real or *hypothetical*) would/might yield product P<sub>2</sub> (or nonequimolar mixture of P<sub>1</sub> and P<sub>2</sub> ( $[P_1] \neq [P_2]$ )). Thus, there is, *in principle*, an inverse configurational correlation between reactants S<sub>1</sub> and S<sub>2</sub>, on the one hand, and between products from S<sub>1</sub>, and those from S<sub>2</sub>, on the other. Nevertheless, stereospecificity characterizes a *single* transformation, and the reactions of reagent R with substrate S<sub>1</sub> and S<sub>2</sub> may exhibit different stereospecificities (*vide infra*).

A *nonstereospecific* reaction is one in which two stereopure stereomeric substrates S<sub>1</sub> and S<sub>2</sub>, with distinct configurations of a common stereogenic element, are transformed into identical 50:50 mixtures of the two sets of products P<sub>1</sub> and P<sub>2</sub> ( $[P_1] = [P_2]$ ).<sup>13</sup> It is not unreasonable to expect that the reaction of reagent R with substrate S<sub>1</sub> may exhibit stereospecificity, whereas that with stereomeric substrate S<sub>2</sub> may be nonstereospecific.

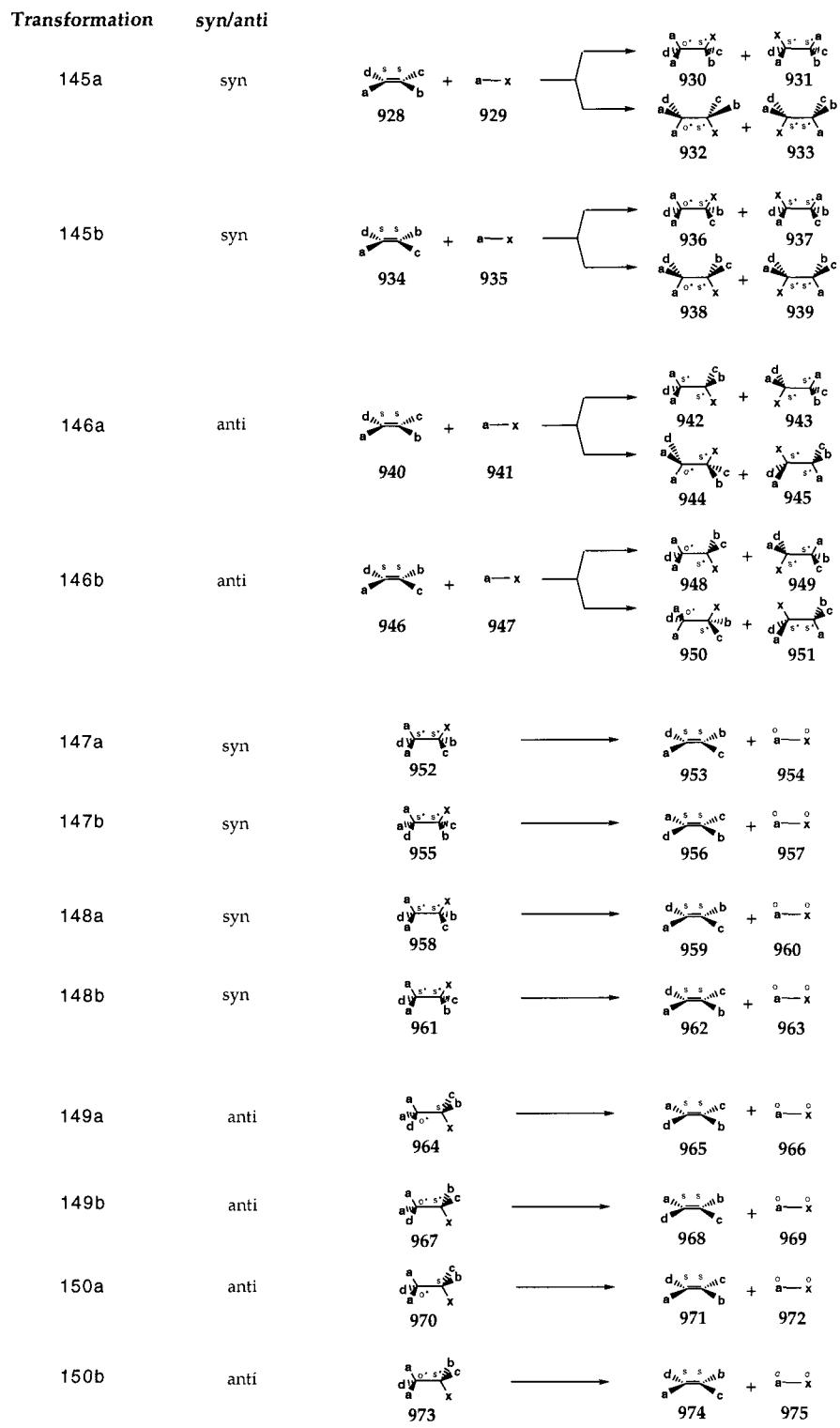
The degree of stereospecificity of a given transformation can be expressed quantitatively in terms of % stereospecificity (*vide infra*); % stereospecificity varies from 0 to 100%. The stereospecificity of a nonstereospecific reaction is exactly 0%. In the above example of the dibromination of norbornene, the reaction would be called nonstereospecific *only if* it leads to a product mixture consisting of a 50:50 *trans:cis* adducts; % stereospecificity in that case would be 0. For the dibromination of norbornene, the % stereospecificity is given by the difference in % *trans* adduct and % *cis* adduct.

Stereospecificity, just like stereoselectivity, regioselectivity, and facioselectivity, becomes non-transparent and experimentally determinable only with the proper substrates. The stereospecificity of an S<sub>N</sub>2 process cannot be established using CH<sub>3</sub>I or iodocyclohexane; both substrates lack stereogenic elements, and stereospecificity is irrelevant. The stereospecificity of the S<sub>N</sub>2 process above becomes experimentally nontransparent if one were to use (S)- or (R)-2-octyl iodide or *cis*- or *trans*-4-*t*-butyliodocyclohexane. The Walden inversions do occur with CH<sub>3</sub>I or iodocyclohexane as well, despite the fact that they are experimentally unverifiable - experimentally transparent. Similarly, the stereospecificity of the addition of Br<sub>2</sub> (*anti*) to an alkene cannot be established using ethylene or propene as substrates; however, the stereospecificity is established experimentally using cyclohexene and *trans*-stilbene as the proper substrates. All four alkenes mentioned are presumed to follow the *anti* addition of Br<sub>2</sub> - for stereoelectronic reasons. From a stereochemical viewpoint, in the case of eliminations of type E2, bromoethane and bromocyclohexane are useless as substrates - however, *meso*-dibromostilbene and *dl*-dibromostilbene would be useful. Similarly, regioselectivity of the addition of HBr to an alkene cannot be established using ethylene or cyclohexene as substrates; one needs dissymmetric alkenes such as 1-propene, or 1-methylcyclohexene as the proper substrates. In the case of facioselectivity, ethylene and cyclohexene are not stereochemically useful substrates; proper substrates for establishing *syn*-deuteration would be norbornene and limonene.

To establish stereospecificity of a given reaction, it is not necessary to carry out reactions on both stereomeric substrates S<sub>1</sub> and S<sub>2</sub>, nor is it necessary to have *at hand* both configurationally-distinct starting materials (S<sub>1</sub> and S<sub>2</sub>) and/or their corresponding configurationally-distinct products.<sup>14</sup> However, in order to establish % stereospecificity of a transformation, it is necessary to have (a) at least one starting material S<sub>1</sub> (or S<sub>2</sub>) with a stereogenic element, (b) product(s)



**Figure 17.33.** Examples of Stereospecific Substitutions at  $sp^3$  and  $sp^2$  C



**Figure 17.34.** Examples of Stereospecific Additions and Eliminations

with stereogenic element(s), and (c) a transformation of stereogenic elements – from that in the stereopure starting material to that(those) of product(s). Thus, conversion of (isolable) norbornene (with inherent *cis* double bond) into exclusively (racemic) *trans*-dibromo adduct (with no contamination by the *cis*-dibromo adduct) is considered 100% stereospecific, despite the fact that one does not/cannot carry out the parallel bromination reaction on the (unisolable-at-room-temperature) hypothetical “*trans*-norbornene” possessing a highly strained bicyclic ring system.

In this example, % stereospecificity can be determined for “*cis*”-norbornene, even though (a) both stereomeric starting materials are not available physically, and (b) the reaction is carried out only on one of them (“*cis*”-norbornene). In general, a product mixture may consist of 1-4 components, as shown later; that is why one has to consider one or more stereogenic elements in the products. Figure 17.33 depicts examples of stereospecific nucleophilic substitutions at  $sp^3$  and  $sp^2$  C. Figure 17.34 portrays examples of stereospecific additions and eliminations.

As shown in Figure 17.33, the stereospecificity of a reaction stems from a stereoelectronic bias for the transformation - inversion vs. retention in substitution reactions at  $sp^3$  and  $sp^2$  (alkenic or allenic) atoms. Transformations 137a/b and 138a/b represent the classic  $S_N2$  inversion and retention of configurations at  $sp^3$  C; transformations 139a/b-142a/b exemplify retention and retention of configurations at alkenic  $sp^2$  C, and, transformations 143a/b-144a/b typify retention and retention of configurations at allenic  $sp^2$  C.

The two opposing modes are *syn* vs. *anti* addition, or *syn* vs. *anti* elimination (Figure 17.34). The stereospecificity stems from a stereoelectronic bias for the transformation - *syn* vs. *anti* additions to alkenes, and *syn* vs. *anti* eliminations to yield alkenes. In Figure 17.34, transformations 145a/b-146a/b constitute examples of addition, while 147a/b-150a/b represent cases of elimination. In Figure 17.35, we illustrate what should be considered as *astereospecific* reactions. In the four examples of Figure 17.35, either reactants or products lack the requisite stereogenic elements. In transformations 151 and 153, it is the reactants (976 and 984) that are devoid of a stereogenic element; in the case of transformations 152a/b, 154a/b, it is the reactants that lack a stereogenic element. Therefore, for all four cases, no correlation can be established between stereogenic elements of reactants, on the one hand, and those of products, on the other. The stereogenic element  $g^+$  in each of transformations 151 and 152a/b does not qualify as a requisite stereogenic element, since it is not part of a stereogenic element that partakes in the transformations. It follows that the issue of stereospecificity for all four cases is irrelevant, and the transformations are said to be *astereospecific*. An *astereospecific* transformation is not to be confused with a nonstereospecific one. In the latter case, % stereospecificity drops to zero (*vide infra*), while in the former, the concept of stereospecificity is irrelevant. In *astereospecific* reactions 151 and 153, stereoselectivity is still relevant since one obtains stereomeric products (978/979, 986/987) (*vide infra*).

## XI. Quantitation of Stereospecificity

In general, for a given transformation of  $S_1$ , stereospecificity can be expressed quantitatively as the difference between the amounts of products/transition states from stereospecific route for substrate  $S_1$ , and those of products from the corresponding stereospecific route for substrate  $S_2$  (see p. 74). In Figure 17.36-17.40, we provide examples of transformations that can range the gamut from 0 to 100% stereospecificity; we define the quantitative expressions for stereospecificity, and contrast them with the corresponding definitions of stereoselectivity.

### A. One- and Two-Component Systems

Figures 17.36-17.38 portray transformation pairs 155a/b, 156a/b, 157a/b, 158a/b and 159a/b, each of which leads to either 1- or 2-component product mixtures, at the highest degree

Transformation

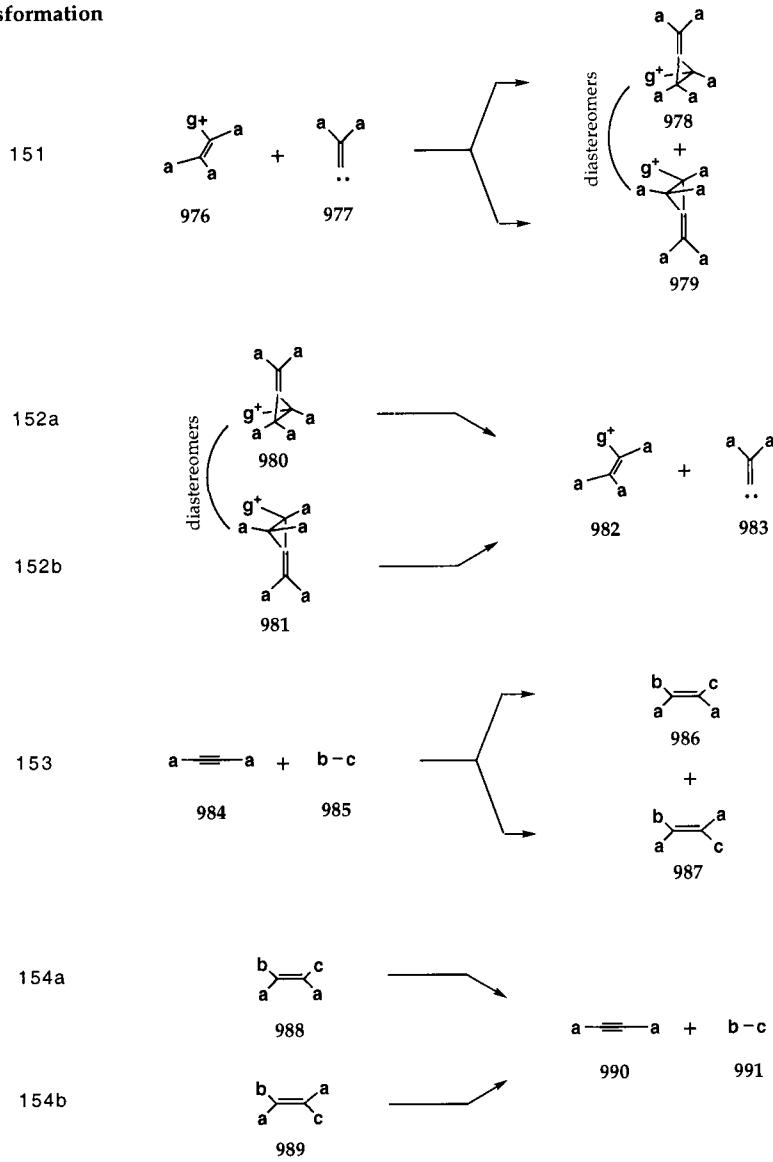


Figure 17.35. Examples of Astereospecific Transformations

of stereospecificity. In Figure 17.36, the stereospecific  $\text{S}_{\text{N}}2$  substitution of substrate 993 generates product 994. For this substitution, the stereospecificity is given by the difference in the amounts of the inverted (major) product (994,  $\text{E}^*$ ) and any (minor) enantiomeric product (998,  ${}^*\text{E}$ ). For 155b, the stereospecificity would be the difference in the amounts of the inverted (major) product (998,  ${}^*\text{E}$ ) and any (minor) enantiomeric product (994,  $\text{E}^*$ ). Here, the two stereospecificities are expected to be numerically identical, since the pathways are enantiometric, and hence, isoenergetic. Similar considerations apply to transformations 156a/b, and the corresponding stereospecificities are given by the expression shown in Figure 17.36.

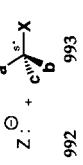
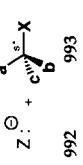
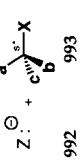
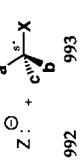
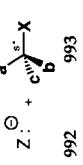
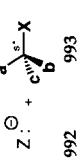
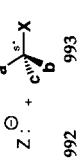
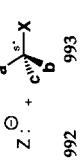
Transformation	Composition of Product		Stereospecificity	Stereoselectivity	
	ee	es			
155a	 + 	992 993	 + 	E*	$  \%E^* - \%E^{*'}  $
155b	 + 	996 997	 + 	E*	$  \%E^* - \%E^{*'}  $
156a	 + 	1000 1001	 + 	D	$  \%D - \%F  $
156b	 + 	1004 1005	 + 	F	$  \%F - \%D  $

Figure 17.36. Comparison of Stereospecificity and Stereoselectivity

In Figure 17.37, the stereospecific *syn* addition of **1009** to **1008** would yield a single chiral product **E\*** (**1010=1011=1012=1013**); the corresponding diastereomer, **1014**, would yield a pair of chiral diastereomers **D\*,F\*** (**1016=1017,1018=1019**). The stereospecificity of the former reaction would be equal to  $|(\%E^* - (\%D^* + \%F^*))|$ ; that, of the latter transformation, would be  $|(\%D^* + \%F^*) - \%E^*|$ . Here, the two stereospecificities are not expected to be numerically identical, since the pathways are diastereometric, and hence, nonisoenergetic. In the limit, if the reaction of diastereomer **1008** proceeds to give exclusively **1010** ( $=1011=1012=1013$ ), with no cross-contamination by **1016**( $=1017$ ) and **1018**( $=1019$ ), the stereospecificity of the reaction would be  $|(\%E^* - (\%D^* + \%F^*))| = |100 - (0 + 0)| = 100\%$ . Similarly, if **1014** leads exclusively to **1016**( $=1017$ ) and **1018**( $=1019$ ) (with no cross contamination by **1010**( $=1011=1012=1013$ ), the stereospecificity of the reaction would be  $|(\%D^* + \%F^*) - \%E^*| = |100 - (0 + 0)| = 100\%$ . In contradistinction, if either reaction proceeds to give a 50:50 mixture of **E\*/(D\*+F\*)**, the stereospecificity would be  $|(\%E^* - (\%D^* + \%F^*))| = |50 - (50)| = 0\%$  (note the ratio of **D\*** to **F\*** is not necessarily 1:1).

Similar considerations apply to transformations **158a/b**. In Figure 17.37, the stereospecific *syn* addition of **1021** to substrate **1020** would yield a racemic product **E\*/ $\text{*\mathbb{E}}$**  (**1022=1024**)/(**1023=1025**); the corresponding diastereomer, **1026**, would yield a diastereomeric racemic product **D\*/ $\text{*\mathbb{D}}$**  (**1028=1030**)/(**1029=1031**). The stereospecificity of the former reaction would be equal to  $|(\%E^* + \%*\mathbb{E}) - (\%D^* + \%*\mathbb{D})|$ ; that of the latter transformation would be  $|(\%D^* + \%*\mathbb{D}) - (\%E^* + \%*\mathbb{E})|$ . Here too, the two stereospecificities are not expected to be numerically identical, since the pathways are diastereometric, and hence, nonisoenergetic. In the limit, if the reaction of **1020** proceeds to give exclusively **(1022=1024)/(1023=1025)**, with no cross-contamination by **1028**( $=1030$ ) and **1029**( $=1031$ ), the stereospecificity of the reaction would be  $|(\%E^* + \%*\mathbb{E}) - (\%D^* + \%*\mathbb{D})| = |100 - (0 + 0)| = 100\%$ . Similarly, if **1026** leads exclusively to **1028**( $=1030$ ) and **1029**( $=1031$ ) (with none of **1022**( $=1024$ ) and **1023**( $=1025$ )), the stereospecificity of the reaction would be  $|(\%D^* + \%*\mathbb{D}) - (\%E^* + \%*\mathbb{E})| = |100 - (0 + 0)| = 100\%$ . In contradistinction, if either reaction proceeds to give a 50:50 mixture of **E\*/ $\text{*\mathbb{E}}$**  and **D\*/ $\text{*\mathbb{D}}$** , the stereospecificity would be  $|(\%E^* + \%*\mathbb{E}) - (\%D^* + \%*\mathbb{D})| = |(50) - (50)| = 0\%$ .

## B. Three-Component Systems

We extend the above definition of stereospecificity to cases where routes from the two configurationally related substrates may lead separately to product mixtures that contain three or more products. In Figures 17.38 and 17.39, we show four cases.

Transformations **159a** and **159b** lead to  $(E^* + \mathbb{E}^* + D)_a$  and  $(E^* + \mathbb{E}^* + D)_b$  mixtures, respectively. In this case, enantiomeric products **E\*** and  **$\mathbb{E}^*$**  (for each of pathways **a** and **b**) stem from the reactions of two enantiotopic ligands "a" and "a'"; furthermore, one expects  $[E^*]_a \neq [E^*]_b$ ,  $[\mathbb{E}^*]_a \neq [\mathbb{E}^*]_b$ , and  $[D]_a \neq [D]_b$ . The stereospecificity of **159a** would be given by  $|(\%E^* + \%*\mathbb{E} + \%D)_a - (\%E^* + \%*\mathbb{E} + \%D)_b|$ ; that of **159b** would be equal to  $|(\%E^* + \%*\mathbb{E} + \%D)_b - (\%E^* + \%*\mathbb{E} + \%D)_a|$ .

Transformation **160a** (Fig. 17.38) yields  $[(E^*/\mathbb{E}) + D]_a$ , and transformation **160b** gives  $[(E^*/\mathbb{E}) + F]_b$ ; thus, **E\*** and  **$\mathbb{E}^*$**  are products in common. The stereospecificity of **160a** is given by  $|[(\%E^* + \%*\mathbb{E})_a + \%D] - [(\%E^* + \%*\mathbb{E})_b + \%F]|$ ; that of **160b** is equal to  $|[(\%E^* + \%*\mathbb{E})_b + \%F] - [(\%E^* + \%*\mathbb{E})_a + \%D]|$ .

In Figure 17.39, transformation **161a** generates  $D_a^*, F_a^*, G^*$ , while transformation **161b** produces  $D_b^*, F_b^*, J^*$ ; thus, **D\*,F\*** are products in common. The stereospecificity of **161a** is given by the expression  $|(\%D_a^* + \%F_a^* + \%G^*) - (\%D_b^* + \%F_b^* + \%J^*)|$ ; that of **161b** is equal to  $|(\%D_b^* + \%F_b^* + \%J^*) - (\%D_a^* + \%F_a^* + \%G^*)|$ .

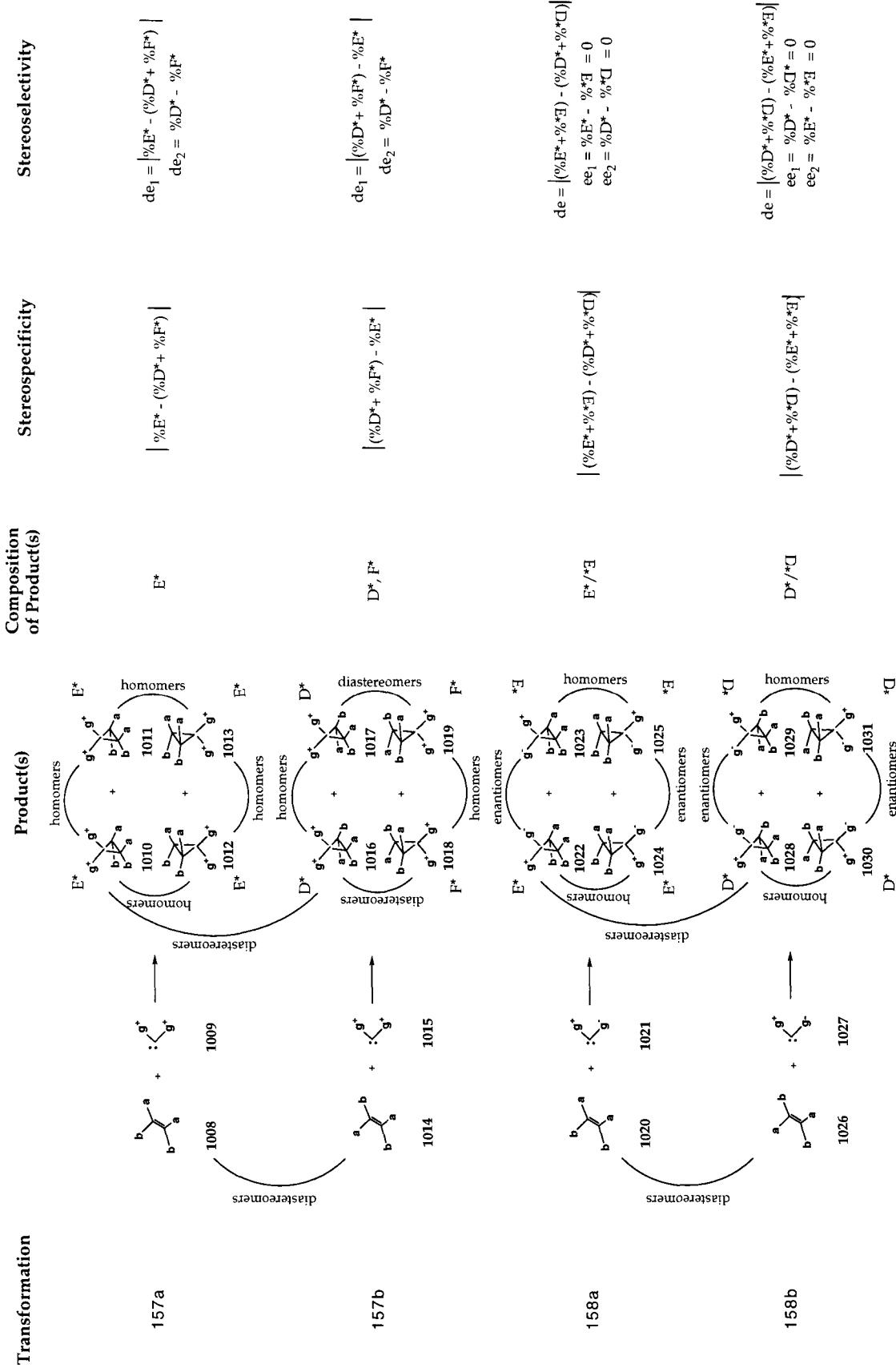


Figure 17.37. Comparison of Stereospecificity and Stereoselectivity of Transformations Yielding One(-to-Three)- and Two(-to-Four)-Component Product Mixtures

$D_b^*, K, L$ ;  $D^*$  is the product in common. The stereospecificity of 162a is given by  $|[\%D_a^* + \%F + \%G] - [\%D_b^* + \%K + \%L]|$ ; that of 162b is equal to  $|[(\%D_b^* + \%K + \%L) - (\%D_a^* + \%F + \%G)]|$ .

### C. Four-Component Systems

In the first case of Figure 17.40, transformation 163a produces  $(E^*/\bar{E})(D^*/\bar{D})$ , while transformation 163b generates  $(F^*/\bar{F})(G^*/\bar{G})$ ; there are no products in common. The stereospecificity of 163a is given by  $|[(\%E^* + \%E) + (\%D^* + \%D)] - [(\%F^* + \%F) + (\%G^* + \%G)]|$ ; that of 163b is equal to  $|[(\%F^* + \%F) + (\%G^* + \%G)] - [(\%E^* + \%E) + (\%D^* + \%D)]|$ .

Transformations 164a and 164b give rise to  $D^*, F^*, M_a^*, N_a$  and  $G^*, J^*, M_b^*, N_b$ , respectively; here, there are two products in common -  $M^*$  and  $N$ . The stereospecificity of 164a is given by  $|[(\%D^* + \%F^*) + (\%M_a^* + \%N_a)] - [(\%G^* + \%J^*) + (\%M_b^* + \%N_b)]|$ ; that of 164b is equal to  $|[(\%G^* + \%J^*) + (\%M_b^* + \%N_b)] - [(\%D^* + \%F^*) + (\%M_a^* + \%N_a)]|$ .

## XII. Stereospecificity vs. Stereoselectivity

Stereospecificity is a measure of the mechanistic purity of a kinetically-controlled transformation (inversion vs. retention, *syn*- vs. *anti*-addition, *anti*- vs. *syn*-elimination). In all of the examples of Figures 17.37-17.40, the outcome of a *syn* addition to a *transoid* alkene is considered to be equivalent to an *anti* addition to a *cisoid* alkene. Stereoselectivity characterizes the relative proportions of the stereomeric products in any given transformation, regardless of the mechanistic purity of the transformations.

Figures 17.36-17.40 show the stereoselectivities in each of transformations 155-164, along with the corresponding stereospecificities. % Stereospecificity and % stereoselectivity may or may not be numerically identical (*vide infra*).

In Figure 17.36, for transformations 155a/b and 156a/b, % stereoselectivity and % stereospecificity are numerically identical; for these cases, n% stereospecificity corresponds to n% stereoselectivity.

For transformation 157a (Figure 17.37), % stereoselectivity is revealed at two levels -  $de_1 = |\%E^* - (\%D^* + \%F^*)|$  and  $de_2 = (\%D^* - \%F^*)$ ; for transformation 157b, these expressions are reversed -  $de_1 = |(\%D^* + \%F^*) - \%E^*|$ ;  $de_2 = (\%D^* - \%F^*)$ . In the case of 157a, % stereospecificity and  $de_1$  are numerically identical;  $de_2$  reveals the excess of  $D^*$  over  $F^*$ , and if the transformation is 100% stereospecific (no  $D^*$  and  $F^*$  are formed),  $de_2$  would vanish. Similar considerations apply to transformation 157b. Here, % stereospecificity and  $de_1$  are numerically identical;  $de_2$  may have any value in the range of 0-100%. If transformation 157b is 100% stereospecific (no  $E^*$  is formed),  $de_1$  would be also 100%, and  $de_2$  would vanish.

Similarly, for 158a/b, there is % stereospecificity,  $(\%E^* + \%E) - (\%D^* + \%D)$ , on the one hand, and three levels of % stereoselectivity -  $de = |(\%E^* + \%E) - (\%D^* + \%D)|$ ,  $ee_1 = \%E^* - \%E$ , and  $ee_2 = \%D^* - \%D$ , on the other. If 158a is 100% stereospecific (no  $D^*/\bar{D}$  are formed), the first level of % stereoselectivity,  $de$ , is numerically identical with % stereospecificity; however,  $ee_1 (= \%E^* - \%E)$  and  $ee_2 = \%D^* - \%D$  would both be equal to zero, since  $E^*/\bar{E}$  and  $D^*/\bar{D}$  are racemates. If 158a is n% stereospecific ( $n < 100\%$ ), stereoselectivity  $de$  is also n%;  $ee_1$  and  $ee_2$  both remain zero. Similarly, if 158b is 100% stereospecific (no  $E^*/\bar{E}$  are formed), the first level of % stereoselectivity,  $de$ , is also 100%; as before,  $ee_1 = (\%D^* - \%D)$  and  $ee_2 = (\%E^* - \%E)$  would vanish. If 158b is n% stereospecific ( $n < 100\%$ ), stereoselectivity  $de$  is n%;  $ee_1$  and  $ee_2$  remain both zero, since  $D^*/\bar{D}$  (158b) and  $E^*/\bar{E}$  (in 158a) would still be racemic mixtures.

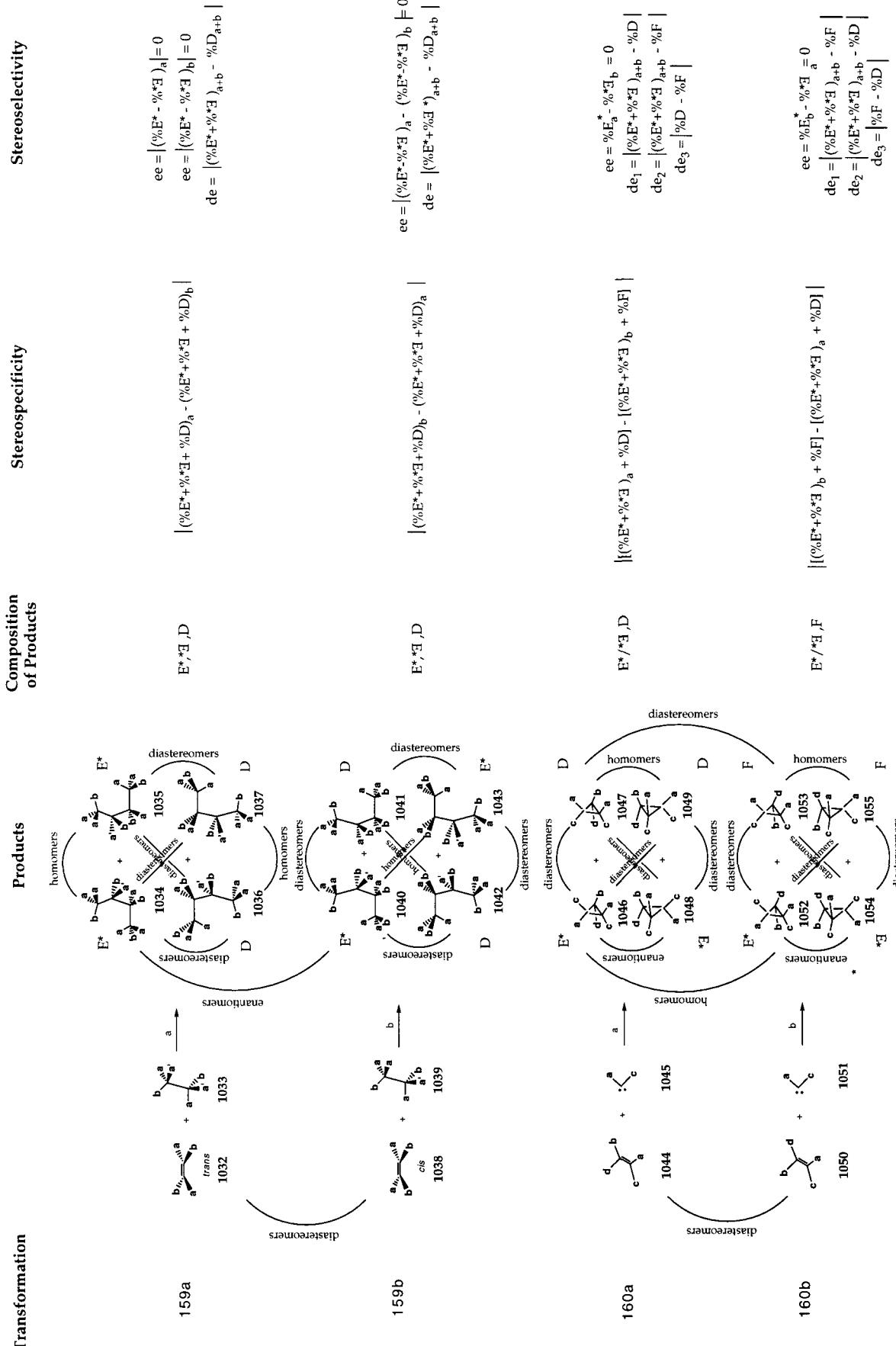


Figure 17.38. Comparison of Stereospecificity and Stereoselectivity of Transformations Yielding Three-(to-Four)-Component Product Mixtures

Transformation      Products      Composition of Products      Stereospecificity

Stereoselectivity

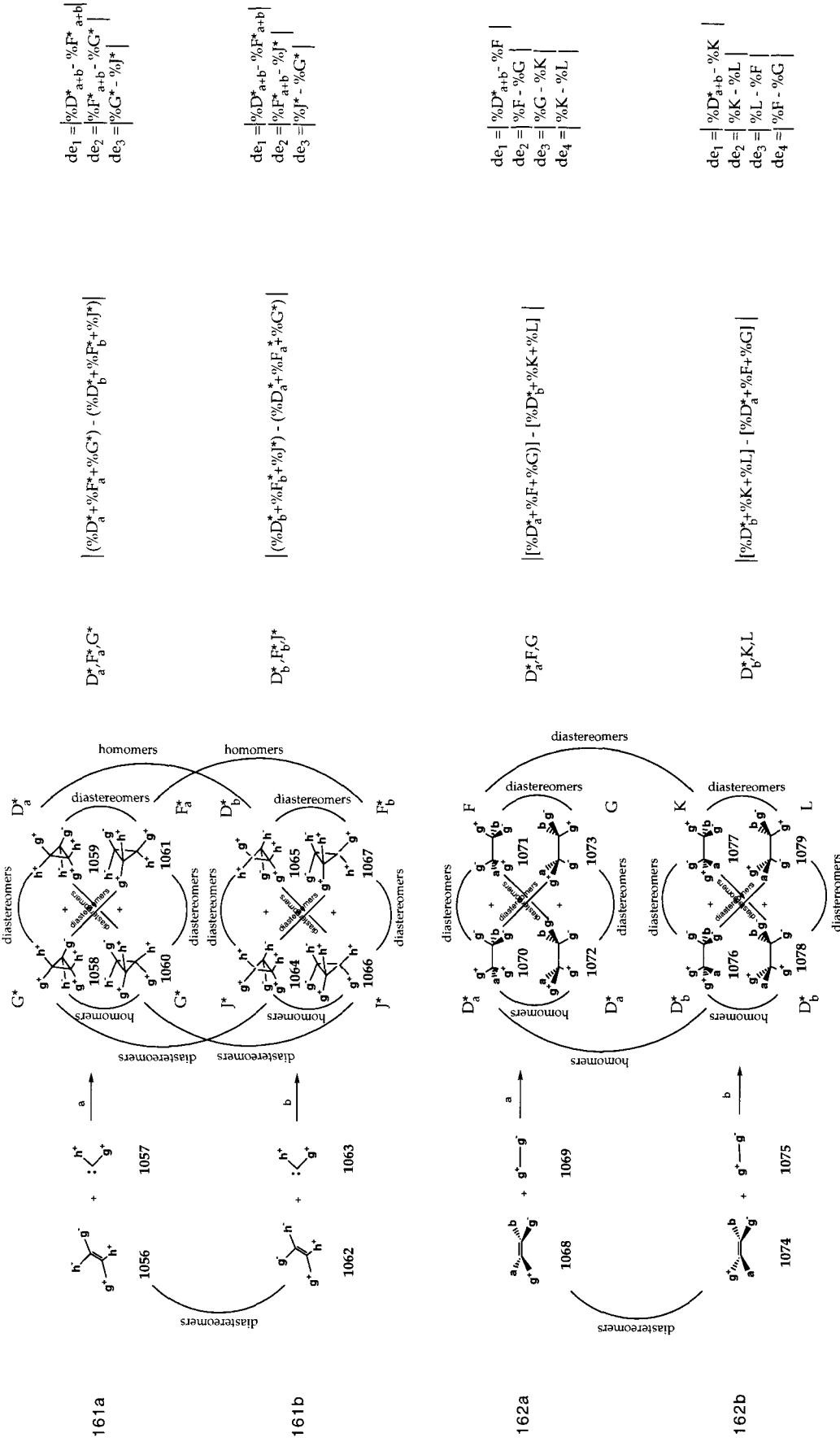


Figure 17.39. Comparison of Stereospecificity and Stereoselectivity of Transformations Yielding Three-(to-Five)-Component Product Mixtures

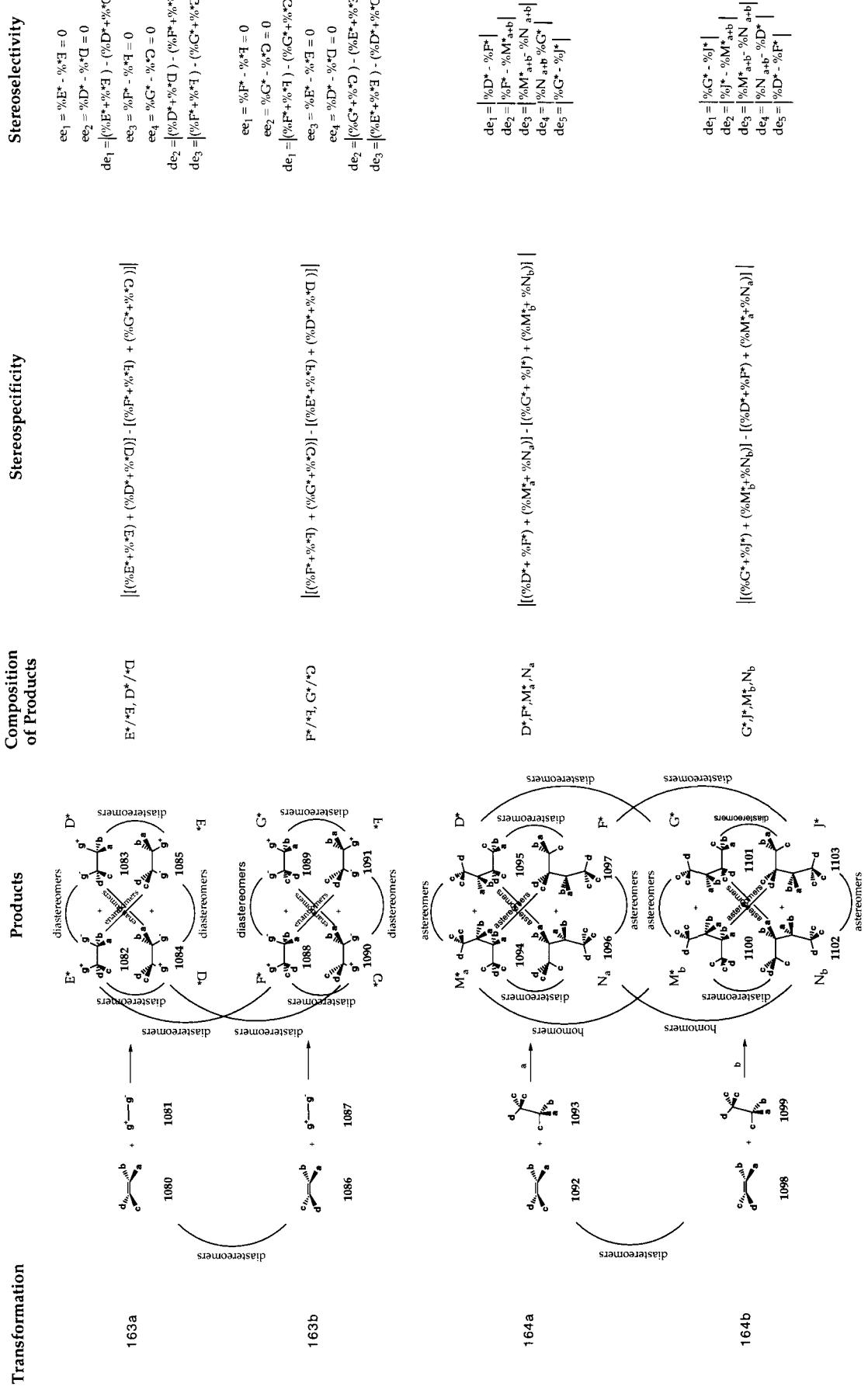


Figure 17.40. Comparison of Stereospecificity and Stereoselectivity of Transformations Yielding Four(-to-Eight)-Component Product Mixtures

As we examine transformations 159,160 (Figure 17.38), 161,162 (Fig. 17.39) and 163,164 (Figure 17.40), we notice that stereoselectivity manifests itself at several levels – two levels for 159, four levels for 160, three levels for 161, four levels for 162, three levels for 163, and, five levels for 164. In none of these cases, is numerical identity between % stereospecificity and % stereoselectivity expected (except by accident). It is interesting to note that, in transformation 160, one may also define a *racemate excess* (*re*),  $re = (\%E^* + \%*\bar{E})_a - (\%E^* + \%*\bar{E})_b$  - as a measure of the excess of the (same) racemate formed in pathway "a" over that formed through pathway "b". The quantitative experimental determination of "re" would require judicious isotopic labelling.

We now consider the relationship of stereospecificity to stereoselectivity through the examples given in the figures above.

Following our definition of stereospecificity given above, it follows that both stereoselective reactions (transformations (155-163a/b) *and* nonstereoselective ones (transformations 157a/b-163a/b) can be stereospecific. Therefore, the first part of the statement "*all stereospecific processes are stereoselective, but all stereoselective processes are stereospecific*"<sup>11</sup> is not true. By our definition, *all stereospecific processes are not stereoselective*; for example, stereospecific transformations 157a/b-163a/b *can be nonstereoselective*.

It turns out that nonstereospecific transformations, in turn, can be either stereoselective (transformations 157a/b-163a/b) or nonstereoselective (transformations 155-163a/b). In contradistinction, astereospecific transformations may be stereoaselective (transformations 152,154), stereoselective (66,72,74,78,79,87,151,153), or nonstereoselective (66,72,74,78,79,87,151, 153).

Furthermore, we note that stereoselective reactions can be astereospecific (transformations 66,72,74,78,79,87,151,153), stereospecific (transformations 157a/b-163a/b) or nonstereospecific (transformations 157a/b-163a/b). Clearly, all stereoselective reactions are *not* stereospecific. Hence, the second part of the above generalization *viz.* "... all stereoselective are stereospecific" is also not true.

We also wish to point out that nonstereoselective transformations, in turn, can be astereospecific (transformations 66,72,74,78,79,87,151,153), stereospecific (transformations 157a/b-163a/b), or nonstereospecific (transformations 155-163a/b).

Finally, we note that stereoaselective transformations can only be astereospecific (152a/b, 154a/b).

The following Table illustrates the correlation between stereoselectivity and stereospecificity with cited examples.

	Stereoaselective	Stereoselective	Nonstereoselective
<b>Astereospecific</b>	152a/b, 154a/b	66, 72, 74, 78, 79, 87 151, 153	66, 72, 74, 78, 79, 87 151,153
<b>Stereospecific</b>		155 -163a/b	157a/b -163a/b
<b>Nonstereospecific*</b>		157a/b -163a/b	155 -163a/b

\* accidental 0% stereospecificity

**Table 17.4.** Correlation between Stereoselectivity and Stereospecificity

## **Summary**

In this Chapter we developed a universal, systematic stereochemical classification of chemical transformations based on the overall changes in stereogenicity of the atoms involved during a given transformation. Three types of stereotopoprocesses were discerned – *viz.* those that are accompanied by (a) overall loss, (b) no gain/loss, and (c) overall gain of *stereogenic* atoms; we labelled these transformations as stereopolysis, stereopomutation, and stereotogenesis, respectively. Further subclassification of stereotopoprocesses was effected using the joint criteria of rotativity (expected optical activity) and stereoselectivity (preferential formation of one stereoisomers over another). Lastly, we provided a novel definition of stereospecificity for reactions leading multiple products, and established the correlations between stereospecificity and stereoselectivity.

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## Appendix 17.A

### Nonrotative and Rotative Quartet Modes,<sup>15</sup> Product Compositions and Composition Description

(E\*/\*E, D\*/\*D, N\*/\*N and Z\*/\*Z are racemates)

Quartet Mode	Product Composition	Composition Description
<b>Nonrotative</b>		
q1	H	1 achiral substance
q4	E*/*E	2 enantiomers (racemate)
q5	E*/*E	2 enantiomers (racemate)
q3	E*/*E	2 enantiomers (racemate)
q6	D,F	2 achiral diastereomers
q7	D,F	2 achiral diastereomers
q22	D,F	2 achiral diastereomers
q13	A,N	2 achiral astereomers
q14	A,X	2 achiral nonequimers
q12	E*/*E,D	2 enantiomers and an achiral diastereomer
q15	E*/*E,N	2 enantiomers and an achiral common astereomer
q16	E*/*E, X	2 enantiomers and a common achiral nonequimer
q28	D,F,G	3 achiral diastereomers
q44	D,F,M	2 achiral diastereomers and 1 achiral astereomer
q45	D,F,X	2 achiral diastereomers and 1 achiral nonequimer
q10	E*/*E, D*/*D	2 diastereomeric enantiomeric pairs
q25	E*/*E, D*/*D	2 diastereomeric enantiomeric pairs
q11	E*/*E, D*/*D	2 diastereomeric enantiomeric pairs
q18	E*/*E, N*/*N	2 astereomeric enantiomeric pairs
q19	E*/*E, Z*/*Z	2 nonequimERIC enantiomERIC pairs
q26	D,F,G,J	4 achiral diastereomers
q35	D,F,M,N	2 astereomERIC achiral diastereomERIC pairs
q36	D,F,X,Y	2 nonequimERIC achiral diastereomERIC pairs

<b>Rotative</b>		
<b>q2</b>	H*	1 chiral substance
<b>q8</b>	D*,F*	2 chiral diastereomers
<b>q23</b>	D*,F*	2 chiral diastereomers
<b>q9</b>	D*,F*	2 chiral diastereomers
<b>q30</b>	D*,F	2 diastereomers - 1 chiral, 1 achiral
<b>q20</b>	A*,N*	2 chiral astereomers
<b>q21</b>	A*,X*	2 chiral nonequimers
<b>q24</b>	D*,F*,G*	3 chiral diastereomers
<b>q29</b>	D*,F,G	3 diastereomers - 1 chiral and 2 achiral
<b>q31</b>	D*,F*,N*	2 chiral diastereomers and a common chiral astereomer
<b>q32</b>	D*,F*,X*	2 chiral diastereomers and a common chiral nonequimer
<b>q42</b>	D,F,N*	2 achiral diastereomers and a common chiral astereomer
<b>q43</b>	D,F,X*	2 achiral diastereomers and a common chiral nonequimer
<b>q17</b>	E*/*E, N*	2 enantiomers and a chiral common astereome
<b>q33</b>	D*,F*,N*	2 chiral diastereomers and a common achiral astereomer
<b>q34</b>	D*,F*,X	2 chiral diastereomers and a common achiral nonequimer
<b>q27</b>	D*,F*,G*,J*	4 chiral diastereomers
<b>q37</b>	D*,F*,M*,N*	2 astereomeric chiral diastereomeric pairs
<b>q38</b>	D*,F*,X*,Y*	2 nonequimERIC chiral diastereomeric pairs
<b>q39</b>	D*,F*,M,N	2 astereomERIC diastereomeric pairs (1 pair chiral, 1 pair achiral)
<b>q40</b>	D*,F*,X,Y	2 nonequimERIC chiral diastereomeric pairs (1 pair chiral, 1 pair achiral)
<b>q41</b>	D*,F*,M*,N	2 astereomERIC diastereomeric pairs (1 pair chiral, 1 pair mixed achiral/chiral).

## Appendix 17.B

### Stereooselective, Nonstereoselective and Stereoselective Quartet Modes, Product Compositions and Composition Description

(E<sup>\*</sup>/<sup>\*</sup>E, D<sup>\*</sup>/<sup>\*</sup>D, N<sup>\*</sup>/<sup>\*</sup>N and Z<sup>\*</sup>/<sup>\*</sup>Z are racemates)

#### Stereooselective

Quartet Mode	Product Composition	Composition Description
<b>Nonrotative</b>		
q1	H	1 achiral substance
q13	A,N	2 achiral astereomers
q14	A,X	2 achiral nonequimers
<b>Rotative</b>		
q2	H*	1 chiral substance
q20	A*,N*	2 chiral astereomers
q21	A*,X*	2 chiral nonequimers

#### Nonstereoselective (all enantiomeric pairs are in equimolar amounts)

<b>Nonrotative</b>		
q3	E <sup>*</sup> / <sup>*</sup> E	2 enantiomers
q4	E <sup>*</sup> / <sup>*</sup> E	2 enantiomers
q5	E <sup>*</sup> / <sup>*</sup> E	2 enantiomers
q15	E <sup>*</sup> / <sup>*</sup> E,N	2 enantiomers and an achiral common astereomer
q16	E <sup>*</sup> / <sup>*</sup> E,X	2 enantiomers and a common achiral nonequimer
q18	E <sup>*</sup> / <sup>*</sup> E, N <sup>*</sup> / <sup>*</sup> N	2 astereomeric enantiomeric pairs
q19	E <sup>*</sup> / <sup>*</sup> E, Z <sup>*</sup> / <sup>*</sup> Z	2 nonequimERIC enantiomeric pairs

**Nonstereoselective** (all diastereomers are formed in accidentally equimolar amounts)

**Nonrotative**

q <sub>6</sub>	D,F	2 achiral diastereomers
q <sub>7</sub>	D,F	2 achiral diastereomers
q <sub>22</sub>	D,F	2 achiral diastereomers
q <sub>28</sub>	D,F,G	3 achiral diastereomers
q <sub>12</sub>	E <sup>*</sup> / <sup>*</sup> E,D	2 enantiomers and an achiral diastereomer
q <sub>44</sub>	D,F,M	2 achiral diastereomers and 1 achiral astereomer
q <sub>45</sub>	D,F,X	2 achiral diastereomers and 1 achiral nonequimer
q <sub>10</sub>	E <sup>*</sup> / <sup>*</sup> E, D <sup>*</sup> / <sup>*</sup> D	2 diastereomeric enantiomeric pairs
q <sub>11</sub>	E <sup>*</sup> / <sup>*</sup> E, D <sup>*</sup> / <sup>*</sup> D	2 diastereomeric enantiomeric pairs
q <sub>25</sub>	E <sup>*</sup> / <sup>*</sup> E, D <sup>*</sup> / <sup>*</sup> D	2 diastereomeric enantiomeric pairs
q <sub>26</sub>	D,F,G,J	4 achiral diastereomers
q <sub>35</sub>	D,F,M,N	2 astereomeric achiral diastereomeric pairs
q <sub>36</sub>	D,F,X,Y	2 nonequimERIC achiral diastereomeric pairs

**Rotative**

q <sub>8</sub>	D <sup>*</sup> ,F <sup>*</sup>	2 chiral diastereomers
q <sub>9</sub>	D <sup>*</sup> ,F <sup>*</sup>	2 chiral diastereomers
q <sub>23</sub>	D <sup>*</sup> ,F <sup>*</sup>	2 chiral diastereomers
q <sub>30</sub>	D <sup>*</sup> ,F	2 diastereomers - 1 chiral, 1 achiral
q <sub>24</sub>	D <sup>*</sup> ,F <sup>*</sup> ,G <sup>*</sup>	3 chiral diastereomers
q <sub>31</sub>	D <sup>*</sup> ,F <sup>*</sup> ,N <sup>*</sup>	2 chiral diastereomers and a common chiral astereomer
q <sub>32</sub>	D <sup>*</sup> ,F <sup>*</sup> ,X <sup>*</sup>	2 chiral diastereomers and a common chiral nonequimer
q <sub>42</sub>	D,F,N <sup>*</sup>	2 achiral diastereomers and a common chiral astereomer
q <sub>43</sub>	D,F,X <sup>*</sup>	2 achiral diastereomers and a common chiral nonequimer
q <sub>27</sub>	D <sup>*</sup> ,F <sup>*</sup> ,G <sup>*</sup> ,J <sup>*</sup>	4 chiral diastereomers
q <sub>37</sub>	D <sup>*</sup> ,F <sup>*</sup> ,M <sup>*</sup> ,N <sup>*</sup>	2 astereomeric chiral diastereomeric pairs
q <sub>38</sub>	D <sup>*</sup> ,F <sup>*</sup> ,X <sup>*</sup> ,Y <sup>*</sup>	2 nonequimERIC chiral diastereomeric pairs
q <sub>39</sub>	D <sup>*</sup> ,F <sup>*</sup> ,M,N	2 astereomERIC diastereomeric pairs (1 pair chiral, 1 pair achiral)
q <sub>40</sub>	D <sup>*</sup> ,F <sup>*</sup> ,X,Y	2 nonequimERIC chiral diastereomeric pairs (1 pair chiral, 1 pair achiral)
q <sub>41</sub>	D <sup>*</sup> ,F <sup>*</sup> ,M <sup>*</sup> ,N	2 astereomERIC diastereomeric pairs (1 pair chiral, 1 pair achiral/chiral)

**Stereoselective** (all enantiomeric pairs are in nonequimolar amounts resulting from corresponding diastereomeric transition states)

**Nonrotative**

q <sub>3</sub>	E*,*E	2 enantiomers
q <sub>4</sub>	E*,*E	2 enantiomers
q <sub>5</sub>	E*,*E	2 enantiomers
q <sub>15</sub>	E*,*E,N	2 enantiomers and an achiral common astereomer
q <sub>16</sub>	E*,*E,X	2 enantiomers and a common achiral nonequimer
q <sub>18</sub>	E*,*E,N*,*N	2 astereomeric enantiomeric pairs
q <sub>19</sub>	E*,*E,Z*,*Z	2 nonequimERIC enantiomeric pairs

**Stereoselective (all diastereomers pairs are in nonequimolar amounts)**

**Nonrotative**

q <sub>6</sub>	D,F	2 achiral diastereomers
q <sub>7</sub>	D,F	2 achiral diastereomers
q <sub>22</sub>	D,F	2 achiral diastereomers
q <sub>12</sub>	E*/*E,D	2 enantiomers and an achiral diastereomer
q <sub>28</sub>	D,F,G	3 achiral diastereomers
q <sub>44</sub>	D,F,M	2 achiral diastereomers and 1 achiral astereomer
q <sub>45</sub>	D,F,X	2 achiral diastereomers and 1 achiral nonequimer
q <sub>10</sub>	E*/*E,D*/*D	2 diastereomeric enantiomeric pairs
q <sub>11</sub>	E*/*E*,D*/*D	2 diastereomeric enantiomeric pairs
q <sub>25</sub>	E*/*E*,D*/*D	2 diastereomeric enantiomeric pairs
q <sub>26</sub>	D,F,G,J	4 achiral diastereomers
q <sub>35</sub>	D,F,M,N	2 astereomeric achiral diastereomeric pairs
q <sub>36</sub>	D,F,X,Y	2 nonequimERIC achiral diastereomeric pairs

**Rotative**

q <sub>8</sub>	D*,F*	2 chiral diastereomers
q <sub>9</sub>	D*,F*	2 chiral diastereomers
q <sub>23</sub>	D*,F*	2 chiral diastereomers
q <sub>30</sub>	D*,F	2 diastereomers - 1 chiral, 1 achiral
q <sub>20</sub>	A*,N*	2 chiral astereomers
q <sub>21</sub>	A*,X*	2 chiral nonequimers
q <sub>42</sub>	D,F,N*	2 achiral diastereomers and a common chiral astereomer
q <sub>43</sub>	D,F,X*	2 achiral diastereomers and a common chiral nonequimer
q <sub>24</sub>	D*,F*,G*	3 chiral diastereomers

<b>q31</b>	D*,F*,N*	2 chiral diastereomers and a common chiral astereomer
<b>q32</b>	D*,F*,X*	2 chiral diastereomers and a common chiral nonequimer
<b>q27</b>	D*,F*,G*,J*	4 chiral diastereomers
<b>q37</b>	D*,F*,M*,N*	2 astereomeric chiral diastereomeric pairs
<b>q38</b>	D*,F*,X*,Y*	2 nonequimERIC chiral diastereomeric pairs
<b>q39</b>	D*,F*,M,N	2 astereomERIC diastereomeric pairs (1 pair chiral, 1 pair achiral)
<b>q40</b>	D*,F*,X,Y	2 nonequimERIC chiral diastereomeric pairs (1 pair chiral, 1 pair achiral)
<b>q41</b>	D*,F*,M*,N	2 astereomERIC diastereomeric pairs ( 1 pair chiral, 1 pair mixed achiral/chiral).

**Stereotopolysis, Stereopomutation, and Stereotopogenesis in  
Relation to Quartet Modes, Product Compositions and Composition Description**

(E\*/\*E, D\*/\*D, N\*/\*N and Z\*/\*Σ are racemates)

## Stereotopolysis

Quartet Mode <sup>15</sup>	Product Composition	Composition Description
<b>Class 1 A - Nonrotative Achirostereotopolysis</b>		
q1	H	1 achiral substance
q4	E*/*E	2 enantiomers
q5	E*/*E	2 enantiomers
q15	E*/*E,N	2 enantiomers and an achiral common astereomer
q16	E*/*E,X	2 enantiomers and a common achiral nonequimer
q18	E*/*E,N*/*N	2 astereomeric enantiomeric pairs
q19	E*/*E,Z*/*Σ	2 nonequimERIC enantiomeric pairs
<b>Class 1B - Rotative Achirostereotopolysis</b>		
q2	H*	1 chiral substance
q8	D*,F*	2 chiral diastereomers
q23	D*,F*	2 chiral diastereomers
q31	D*,F*,N*	2 chiral diastereomers and a common chiral astereomer
q32	D*,F*,X*	2 chiral diastereomers and a common chiral nonequimer
q37	D*,F*,M*,N*	2 astereomeric chiral diastereomeric pairs
q38	D*,F*,X*,Y*	2 nonequimERIC chiral diastereomeric pairs
q39	D*,F*,M,N	2 astereomeric diastereomeric pairs (1 pair chiral, 1 pair achiral)
q40	D*,F*,X,Y	2 nonequimERIC chiral diastereomeric pairs (1 pair chiral, 1 pair achiral)
q41	D*,F*,M*,N	2 astereomeric diastereomeric pairs (1 pair chiral, 1 pair achiral/chiral)

**Class 2A - Nonrotative Chirostereotopolysis**

q1	H	1 achiral substance
q7	D,F	2 achiral diastereomers
q22	D,F	2 achiral diastereomers
q12	E*/ <sup>*</sup> E,D	2 enantiomers and an achiral diastereomer
q28	D,F,G	3 achiral diastereomers
q10	E*/ <sup>*</sup> E,D*/ <sup>*</sup> D	2 diastereomeric enantiomeric pairs
q25	E*/ <sup>*</sup> E,D*/ <sup>*</sup> D	2 diastereomeric enantiomeric pairs
q35	D,F,M,N	2 astereomeric achiral diastereomeric pairs
q36	D,F,X,Y	2 nonequimERIC achiral diastereomeric pairs

**Class 2B - Rotative Chirostereotopolysis**

q2	H*	1 chiral substance
q8	D*,F*	2 chiral diastereomers
q9	D*,F*	2 chiral diastereomers
q23	D*,F*	2 chiral diastereomers
q17	E*/ <sup>*</sup> E,N*	2 enantiomers and a chiral common astereomer
q24	D*,F*,G*	3 chiral diastereomers
q29	D*,F,G	3 diastereomers -1 chiral and 2 achiral
q31	D*,F*,N*	2 chiral diastereomers and a common chiral astereomer
q32	D*,F*,X*	2 chiral diastereomers and a common chiral nonequimer
q27	D*,F*,G*,J*	4 chiral diastereomers
q37	D*,F*,M*,N*	2 astereomeric chiral diastereomeric pairs
q38	D*,F*,X*,Y*	2 nonequimERIC chiral diastereomeric pairs

**Stereotopomutation****Class 3A - Nonrotative Achirostereotopomutation**

q1	H	1 achiral substance
q6	D,F	2 achiral diastereomers
q22	D,F	2 achiral diastereomers
q35	D,F,M,N	2 astereomeric achiral diastereomeric pairs
q36	D,F,X,Y	2 nonequimERIC achiral diastereomeric pairs

**Class 3B - Rotative Achirostereotopomutation**

none

**Class 4A - Nonrotative Nonstereotopomutation**

<b>q1</b>	H	1 achiral substance
<b>q4</b>	E*/E	2 enantiomers
<b>q5</b>	E*/E	2 enantiomers
<b>q6</b>	D,F	2 achiral diastereomers
<b>q22</b>	D,F	2 achiral diastereomers
<b>q13</b>	A,N	2 achiral astereomers
<b>q14</b>	A,X	2 achiral nonequimers
<b>q15</b>	E*/E, N	2 enantiomers and an achiral common astereomer
<b>q16</b>	E*/E,X	2 enantiomers and a common achiral nonequimer
<b>q28</b>	D,F,G	3 achiral diastereomers
<b>q10</b>	E*,D*,D*	2 diastereomeric enantiomeric pairs
<b>q18</b>	E*,N*,N*	2 astereomeric enantiomeric pairs
<b>q19</b>	E*,Z*,Z*	2 nonequimERIC enantiomERIC pairs
<b>q25</b>	E*,E,D*,D*	2 diastereomERIC enantiomERIC pairs

**Class 4B - Rotative Nonstereotopomutation**

<b>q2</b>	H*	1 chiral substance
<b>q8</b>	D*,F*	2 chiral diastereomers
<b>q20</b>	A*,N*	2 chiral astereomers
<b>q21</b>	A*,X*	2 chiral nonequimers
<b>q23</b>	D*,F*	2 chiral diastereomers
<b>q24</b>	D*,F*,G*	3 chiral diastereomers
<b>q32</b>	D*,F*,X*	2 chiral diastereomers and a common chiral nonequimer (1 pair chiral, 1 pair achiral/chiral)
<b>q27</b>	D*,F*,G*,J*	4 chiral diastereomers
<b>q37</b>	D*,F*,M*,N*	2 astereomERIC chiral diastereomERIC pairs
<b>q38</b>	D*,F*,X*,Y*	2 nonequimERIC chiral diastereomERIC pairs
<b>q41</b>	D*,F*,M*,N	2 astereomERIC diastereomERIC pairs (1 pair chiral, 1 pair achiral/chiral)

**Class 5A - Nonrotative Chirostereotopomutation**

<b>q1</b>	H	1 achiral substance
<b>q3</b>	E*/E	2 enantiomers
<b>q5</b>	E*/E	2 enantiomers
<b>q6</b>	D,F	2 achiral diastereomers
<b>q7</b>	D,F	2 achiral diastereomers
<b>q22</b>	D,F	2 achiral diastereomers

q12	E*/*E,D	2 enantiomers and an achiral diastereomer
q28	D,F,G	3 achiral diastereomers
q44	D,F,M	2 achiral diastereomers and 1 achiral astereomer
q45	D,F,X	2 achiral diastereomers and 1 achiral nonequimer
q10	E*/*E, D*/*D	2 diastereomeric enantiomeric pairs
q11	E*/*E, D*/*D	2 diastereomeric enantiomeric pairs
q25	E*/*E, D*/*D	2 diastereomeric enantiomeric pairs
q26	D,F,G,J	4 achiral diastereomers

### Class 5B - Rotative Chirostereotopomutation

q2	H*	1 chiral substance
q8	D*,F*	2 chiral diastereomers
q9	D*,F*	2 chiral diastereomers
q20	A*,N*	2 chiral astereomers
q21	A*,X*	2 chiral nonequimers
q23	D*,F*	2 chiral diastereomers
q24	D*,F*,G*	3 chiral diastereomers
q31	D*,F*,N*	2 chiral diastereomers and a common chiral astereomer
q32	D*,F*,X*	2 chiral diastereomers and a common chiral nonequimer
q42	D,F,N*	2 achiral diastereomers and a common chiral astereomer
q43	D,F,X*	2 achiral diastereomers and a common chiral nonequimer
q27	D*,F*,G*,J*	4 chiral diastereomers
q37	D*,F*,M*,N*	2 astereomeric chiral diastereomeric pairs
q38	D*,F*,X*,Y*	2 nonequimERIC chiral diastereomeric pairs
q39	D*,F*,M,N	2 astereomERIC diastereomeric pairs (1 pair chiral, 1 pair achiral)
q40	D*,F*,X,Y	2 nonequimERIC chiral diastereomeric pairs (1 pair chiral, 1 pair achiral)

### Stereotopogenesis

#### Class 6A - Nonrotative Achirostereotopogenesis

q6	D,F	2 achiral diastereomers
q7	D,F	2 achiral diastereomers
q22	D,F	2 achiral diastereomers
q28	D,F,G	3 achiral diastereomers
q26	D,F,G,J	4 achiral diastereomers
q35	D,F,M,N	2 astereomERIC achiral diastereomeric pairs
q36	D,F,X,Y	2 nonequimERIC achiral diastereomeric pairs

**Class 6B - Rotative Achirostereotopogenesis**

none

**Class 7A - Nonrotative Chirostereotopogenesis**

q3	E*/*E	2 enantiomers
q4	E*/*E	2 enantiomers
q5	E*/*E	2 enantiomers
q6	D,F	2 achiral diastereomers
q7	D,F	2 achiral diastereomers
q12	E*/*E,D	2 enantiomers and an achiral diastereomer
q15	E*/*E,N	2 enantiomers and a common achiral astereomer
q16	E*/*E,X	2 enantiomers and a common achiral nonequimer
q10	E*/*E,D*/D*	2 diastereomeric enantiomeric pairs
q11	E*/*E,D*/D*	2 diastereomeric enantiomeric pairs
q18	E*/*E,N*,N*	2 astereomeric enantiomeric pairs
q19	E*/*E,Z*/Z*	2 nonequimERIC enantiomERIC pairs of products
q25	E*/*E,D*/D*	2 diastereomeric enantiomeric pairs
q26	D,F,G,J	4 achiral diastereomers

**Class 7B - Rotative Chirostereotopogenesis**

q8	D*,F*	2 chiral diastereomers
q9	D*,F*	2 chiral diastereomers
q20	A*,N*	2 chiral astereomers
q21	A*,X*	2 chiral nonequimers
q23	D*,F*	2 chiral diastereomers
q24	D*,F*,G*	3 chiral diastereomers
q31	D*,F*,N*	2 chiral diastereomers and a common chiral astereomer
q32	D*,F*,X*	2 chiral diastereomers and a common chiral nonequimer
q27	D*,F*,G*,J*	4 chiral diastereomers
q37	D*,F*,M*,N*	2 astereomeric chiral diastereomeric pairs
q38	D*,F*,X*,Y*	2 nonequimERIC chiral diastereomERIC pairs
q39	D*,F*,M,N	2 astereomERIC diastereomERIC pairs (1 pair chiral, 1 pair achiral)
q40	D*,F*,X,Y	2 nonequimERIC chiral diastereomERIC pairs (1 pair chiral, 1 pair achiral).

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"Reverence for the past is important,  
but so is regard for the future."

**Brad Herzog**, in *Trips: A Travel Journal*.

# 18

## Stereochemical Classification of Organic Transformations. 2. Chirotopoprocesses

As noted in Chapter 17, a multitude of terms in the literature have been advanced in order to describe and delineate specific characteristics or selective aspects of the *outcome* of chemical transformations. Despite the availability of these terms, there has been no systematic universal stereochemical classification of chemical transformations. In the preceding chapter, we presented a first approach at such a classification – that of stereotopoprocesses. These processes were categorized on the basis of (a) overall loss, (b) no gain/loss, and (c) gain of *stereogenic* atoms, respectively; the three categories were dubbed stereopolyysis, stereopomutation (stereomutation) and stereopogenesis, respectively. In this chapter, we provide an alternative universal classification of chemical transformations – that of chirotopoprocesses. The novel classification here is based on (a) overall loss, (b) no loss/gain, and (c) gain of *chirotopic* atoms, respectively; the corresponding three categories are termed chiropolyysis, chirotopomutation (chiromutation) and chirotopogenesis, respectively. Both universal classifications find their roots in the definitions of stereogenization, chirogenization, and chirostereogenization (and their corresponding reverse processes – destereogenization, dechirogenization, and dechirodestereogenization) (Chapter 16). In turn, these definitions are based on the change in the degree of stereogenicity ( $\Delta s$ ) and the degree of chirotopicity ( $\Delta c$ ) of individual atoms in the reacting molecule(s). In this chapter, we provide further subclassification of this alternative universal scheme, using the dual criteria of rotativity (expected optical activity) and stereoselectivity (preferential formation of one stereoisomer over another/others). Finally, we compare stereotopoprocesses with chirotopoprocesses, and, define the dual concepts of chirospecifity and chiroselectivity.

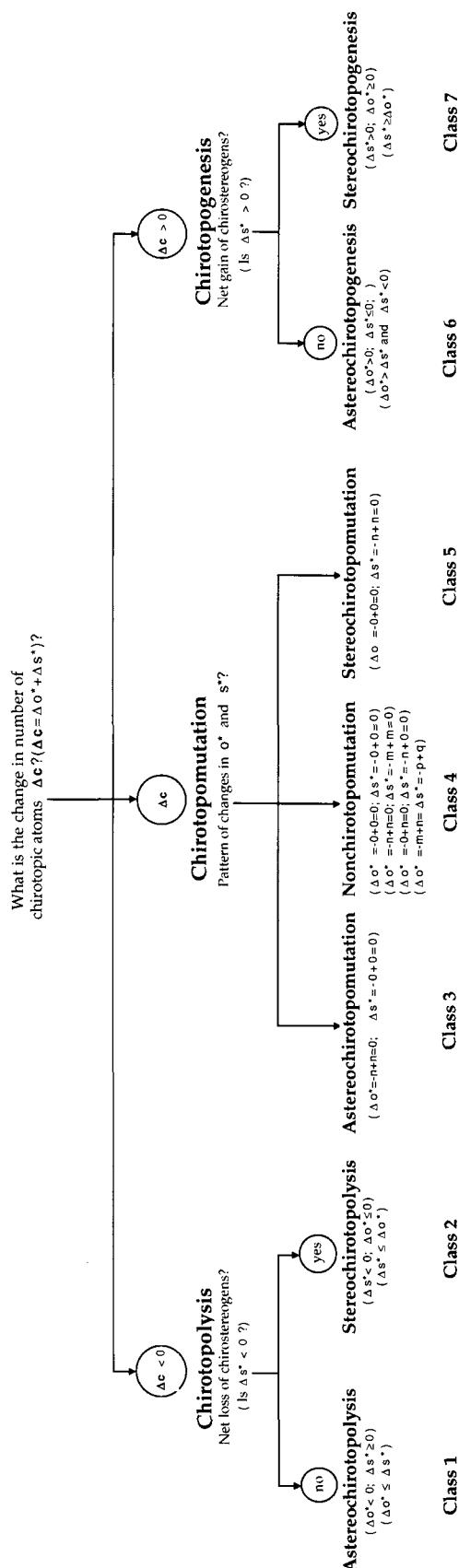


Figure 18.1. Stereochemical Classification of Chirotopoprocesses

## I. Chirotopology, Chirotopomutation, Chirotopogenesis

Every atom in a molecule is either chirotopic (types o\* and s\*) or achirotopic (types o and s). The degree of chirotopicity of a given molecule,  $c_m$ , is equal to the sum of the degrees of chirotopicity of all chirotopic atoms of types o\* and s\*:

$$c_m = n_{o^*} \cdot c_a + n_{s^*} \cdot c_a = n_{o^*} \cdot (+1) + n_{s^*} \cdot (+1) = n_{o^*} + n_{s^*}. \quad (18.1)$$

Here,  $n_{o^*}$  and  $n_{s^*}$  are the numbers of chiroastereogenic and chirostereogenic atoms, respectively;  $c_a$  is the degree of chirotopicity of a given chirotopic atom, be it of type o\* or s\*;  $c_a=+1$  (p. 16).

For a given *transformation*, the change in the degree of chirotopicity,  $\Delta c$ , is defined as follows:

$$\Delta c = \sum_{\text{products}} c_m - \sum_{\text{reactants}} c_m = \sum_{\text{products}} (n_{o^*} + n_{s^*})_{m_p} - \sum_{\text{reactants}} (n_{o^*} + n_{s^*})_{m_r} \quad (18.2)$$

$$= \sum (n_{o^*}(\text{reactants}) - n_{o^*}(\text{products})) + \sum (n_{s^*}(\text{reactants}) - n_{s^*}(\text{products})) \quad (18.3)$$

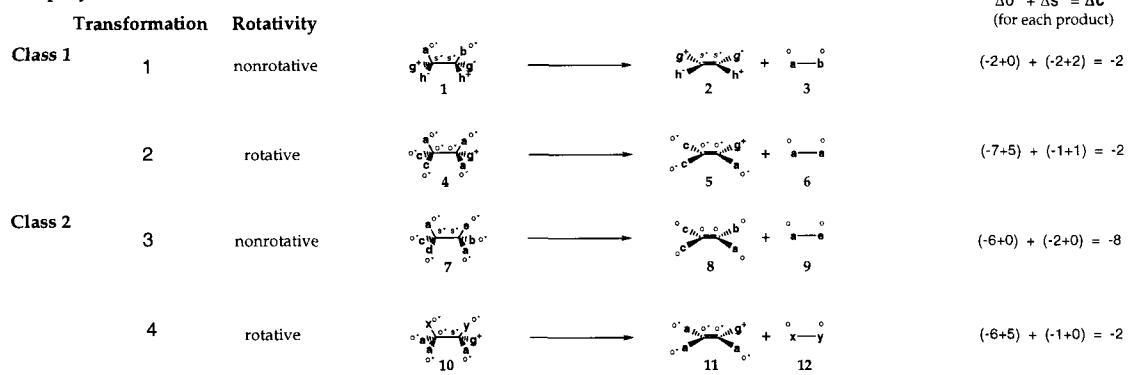
$$= \Delta o^* + \Delta s^* \quad (18.4)$$

where  $m_p$  and  $m_r$  are the numbers of stereogenic atoms in each product and reactant, respectively. In effect,  $\Delta c$ , for a given transformation, is the change in the number of chirotopic atoms of type o\* ( $\Delta o^*$ ) plus the change in the number of chirotopic atoms of type s\* ( $\Delta s^*$ ); this takes into account changes in connectivity and hybridization. A chemical transformation in which there is a net decrease in chirotopic atoms,  $\Delta c < 0$ , is termed a *chirotopolysis*. One, in which there is a net gain of chirotopic atoms,  $\Delta c > 0$ , is called a *chirotopogenesis*. Finally, a transformation in which there is no net gain or loss of chirotopic atoms is referred to as a *chirotopomutation* ( $\Delta c = 0$ , *vide infra*). These transformations are examined from ground state(s) of reactants to the corresponding transition states (assumed to have the highest degree of complexity), and to the ensuing products (assumed to be of comparable or lower degree of complexity than that of the corresponding transition states).

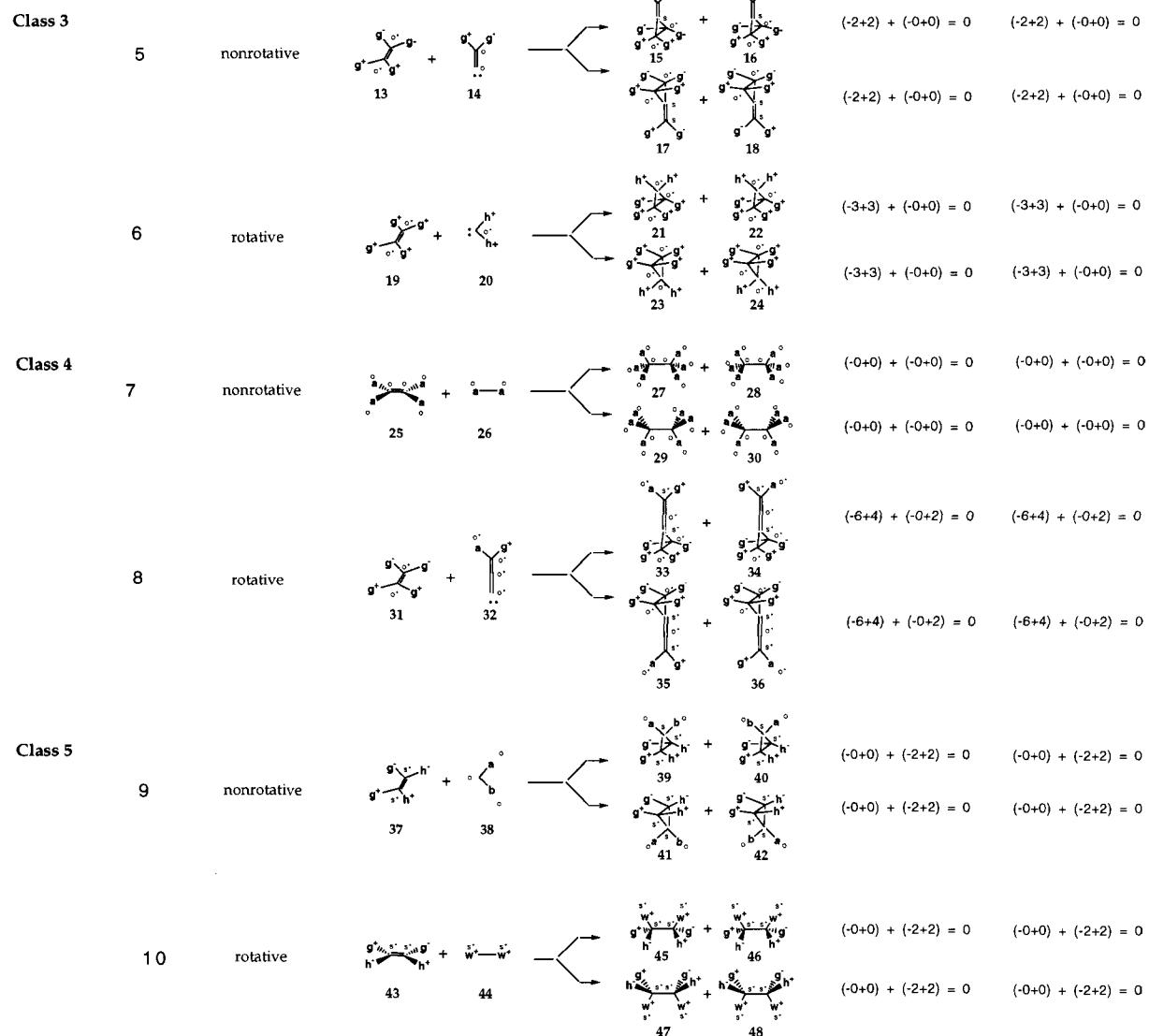
A chirotopolysis ( $\Delta c < 0$ ), in which there is a net loss of chirostereogenic atoms s\* (i.e.  $\Delta s^* < 0$ ;  $\Delta o^* \leq 0$ ), is a *stereochnirotopolysis* (Class 2). That, in which there is a net loss of chirotopic atoms (i.e.  $\Delta o^* < 0$ ), but no net loss of s\* ( $\Delta s^* \geq 0$ ), is termed an *astereochnirotopolysis* (Class 1). In *chirotopomutations* ( $\Delta c = 0$ ), one finds three subclasses - *astereochnirotopomutation* (Class 3), (if there is mutation of atoms of type o\* but no mutation of atoms of type s\*), *nonchirotopomutation* (Class 4) (if there are no mutations of either o\* or s\*, or, if the mutations of o\* offset those of s\*), and *stereochnirotopomutation* (Class 5) (if, indeed, there is mutation of chirotopic atoms of type s\* but no mutation of s\* atoms) (Figure 18.1). A chirotopogenesis ( $\Delta c > 0$ ), in which there is a net gain of chirostereogenic atoms s\* ( $\Delta s^* > 0$ ;  $\Delta o^* \geq 0$ ), is a *stereochnirotopogenesis* (Class 7); if  $\Delta s^* \leq 0$  ( $\Delta o^* > 0$ ), the process is termed an *astereochnirotopogenesis* (Class 6). All of these classes are presented in Figure 18.1.

Examples of each of the six classes of chirotopoprocesses are portrayed in Figures 18.2 and 18.3. In the former figure we include examples of chirotopolysis (Classes 1,2) and chirotopomutation (Classes 3-5), whereas the latter figure depicts examples of stereotopogenesis (Classes 6,7). In these figures, each transformation is shown to lead to two or four possible products bearing one of five types of morphic relationships - homomorphic, enantiomeric, diastereomeric, astereomeric or nonequimorphic. In each quartet, the two top structures result from the vectorial reversal (vectoselectivity) of the reagent relative to substrate, at the *top* face of the substrate. The lower two structures, in a quartet of structures, are the corresponding products resulting from the reaction of the reactant at the *bottom* face (facioselectivity) of the substrate.

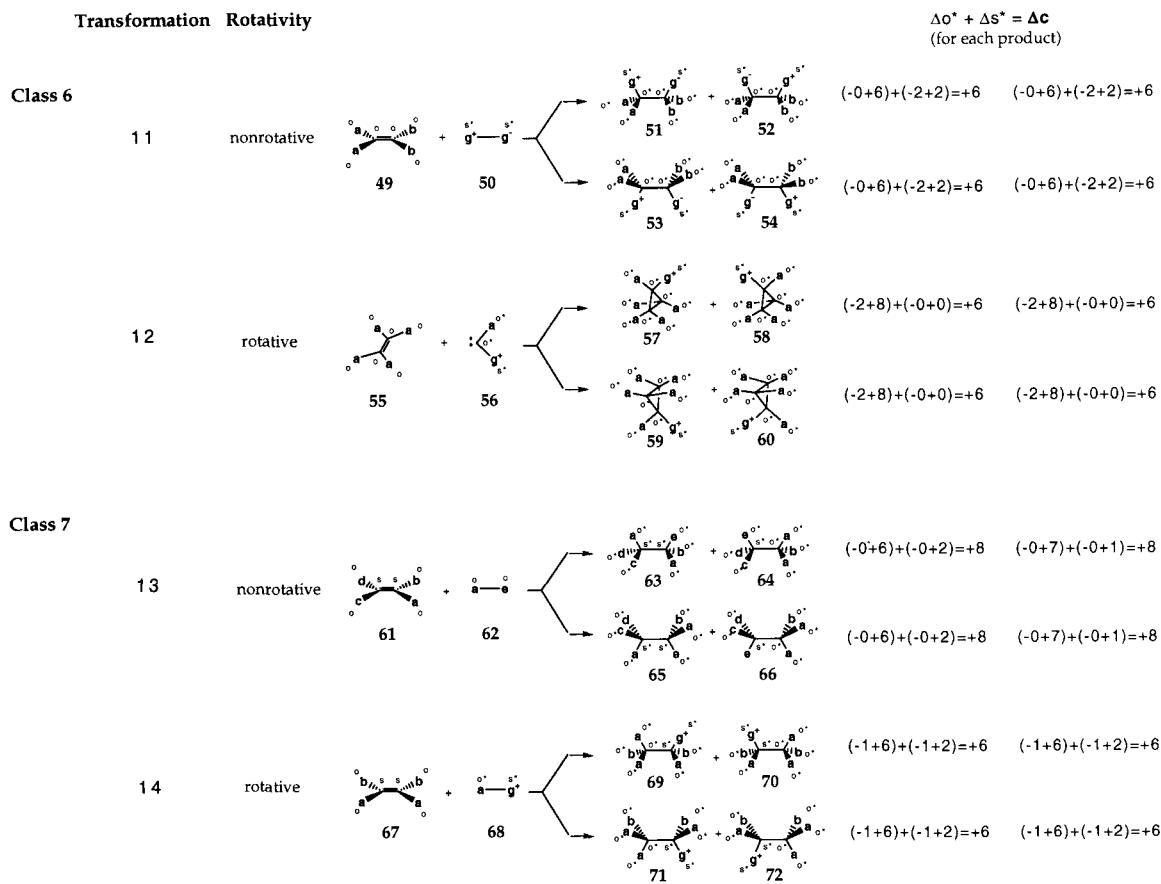
## Chirotopolysis



## Chirotopomutation



**Figure 18.2.** Examples of Nonrotative and Rotative Chirotopolysis and Chirotopomutation



**Figure 18.3.** Examples of (Nonrotative and Rotative) Chirotopogenesis

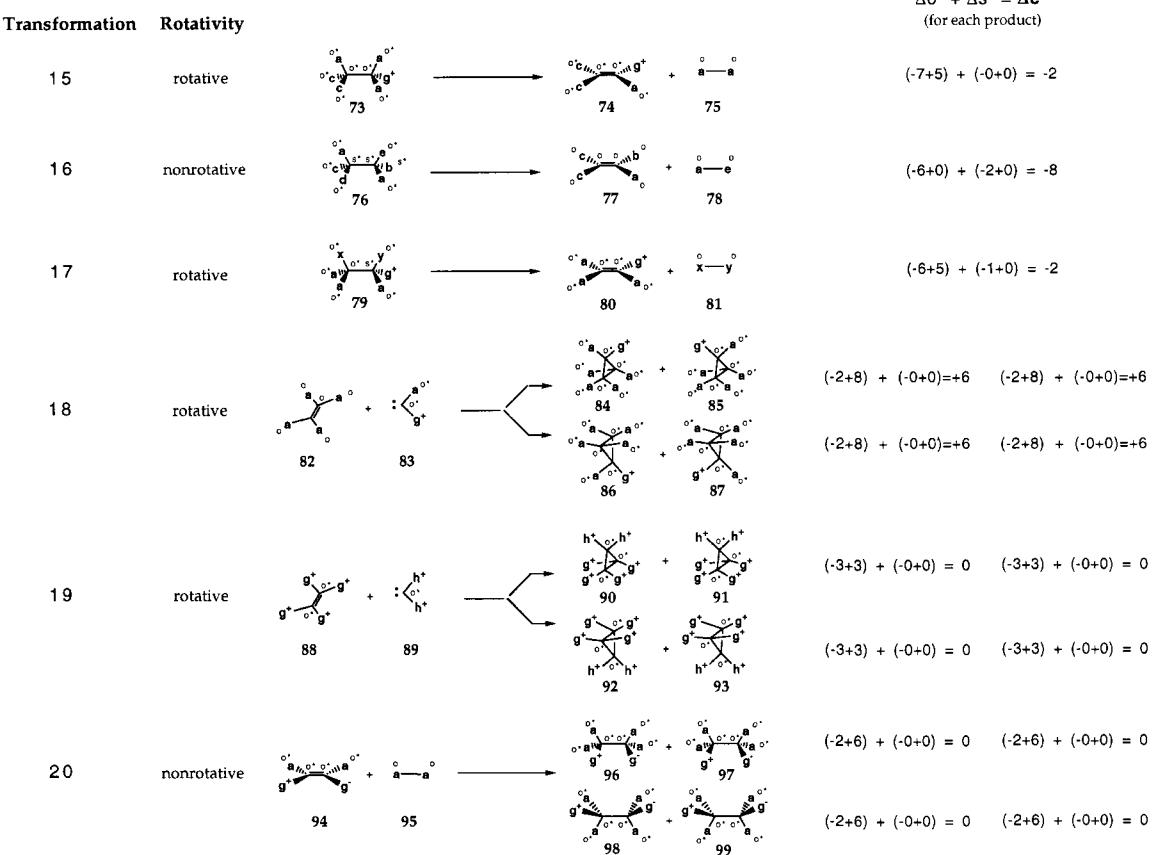
For each product, we indicate the values of  $\Delta\alpha^*$ ,  $\Delta\sigma^*$  and  $\Delta c$ . In the examples shown here, the individual values of these variables may or may not be identical for each member of the quartet (*vide infra*).

In Figures 18.2 and 18.3 we also indicate the nonrotative and rotative nature of the product/product mixture in each of the transformations. This is clarified in the following section.

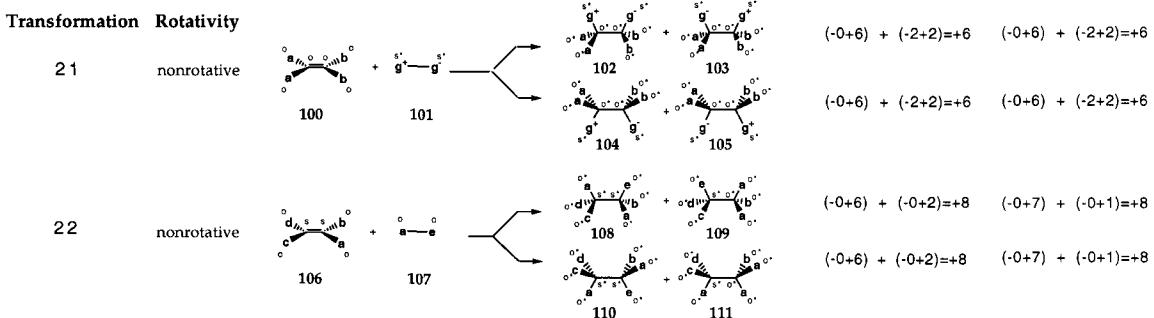
## II. Nonrotativity and Rotativity

A single substance, or a mixture of substances, is said to be *nonrotative* if it is *expected* to be optically inactive (at any wavelength). A single substance, or a mixture of substances, is said to be *rotative*, if it is *expected* to be optically active (at any wavelength).<sup>8</sup>

## Stereoaselectivity



## Nonstereoselectivity



**Figure 18.4.** Examples of Nonrotative/Rotative Stereoaselective and Nonstereoselective Transformations

Typically, products/product mixtures having one of the following compositions are nonrotative:

H	1 achiral substance (may be accompanied by achiral side-product)
E*/*E	2 enantiomers (equimolar amounts; racemate)
D,F	2 achiral diastereomers
E*/*E, N	2 enantiomers (equimolar amounts) and an achiral common stereomer
D,F,G	3 achiral diastereomers
D,F,G,J	4 achiral diastereomers
E*/*E, D*/*D	2 diastereomeric racemates
E*/*E, N*/*N	2 diastereomeric racemates

In the examples cited above, transformations 1,3,5,7,9,11 and 13 lead to nonrotative products/product mixtures (Figures 18.2 and 18.3). In the case of transformation 7 viz.  $25+26 \rightarrow 27 (=28=29=30)$  (Class 4), one expects a single achiral product, while transformations 1 ( $1 \rightarrow 2+3$ ) (Class 1) and 3 ( $7 \rightarrow 8+9$ ) (Class 2) generate two nonequimERIC achiral products (principal product 2 (8) and a by-product 3 (9)). Transformation 11 ( $49+50 \rightarrow 51 (=53)+52 (=54)$ ) (Class 6) is expected to give a racemate E/I; transformation 5 ( $13+14 \rightarrow 15 (=17)+16 (=18)$ ) (Class 3) produces two achiral diastereomeric products. In transformation 9 ( $37+38 \rightarrow 39+40+41+42$ ) (Class 5), one obtains four achiral diastereomers, and in transformation 13, two astereomeric racemic pairs ( $61+62 \rightarrow 63+65$  and  $64+66$ ) (Class 7).

In contrast to the list given above, the following compositions represent rotative systems:

H*	1 chiral substance
D*,F*	2 chiral diastereomers
D*,F*,G*	3 chiral diastereomers
D*,F*,G*,J*	4 chiral diastereomers

In the examples cited above, transformations 2,4,6,8,10,12 and 14 lead to rotative products/product mixtures. In the case of transformations 6 ( $19+20 \rightarrow 21 (=22=23=24)$ ) (Class 3), 8 ( $31+32 \rightarrow 33 (=34=35=36)$ ) (Class 4), 10 ( $43+44 \rightarrow 45 (=46=47=48)$ ) (Class 5), and 12 ( $55+56 \rightarrow 57 (=58=59=60)$ ) (Class 6), a single chiral substance H\* is expected, whereas each of transformations 2 ( $4 \rightarrow 5+6$ ) (Class 1) and 4 ( $10 \rightarrow 11+12$ ) (Class 2) yields two nonequimERIC products - one chiral, the other achiral. Transformation 14 ( $67+68 \rightarrow 69 (=72) + 70 (=71)$ ) (Class 7) should lead to two chiral diastereomers.

Appendix 17.A (pp. 89-90) provides an exhaustive list of nonrotative and rotative 1-, 2-, 3-, 4-component systems.

### III. Stereooselectivity, Nonstereoselectivity and Stereoselectivity

A *stereoselective* reaction is one in which at least one transition state/product can form in two (or more) stereomeric forms, and one of these stereomeric forms predominates over the other(s) (one enantiomeric form over the other, and/or one diastereomeric form over another).

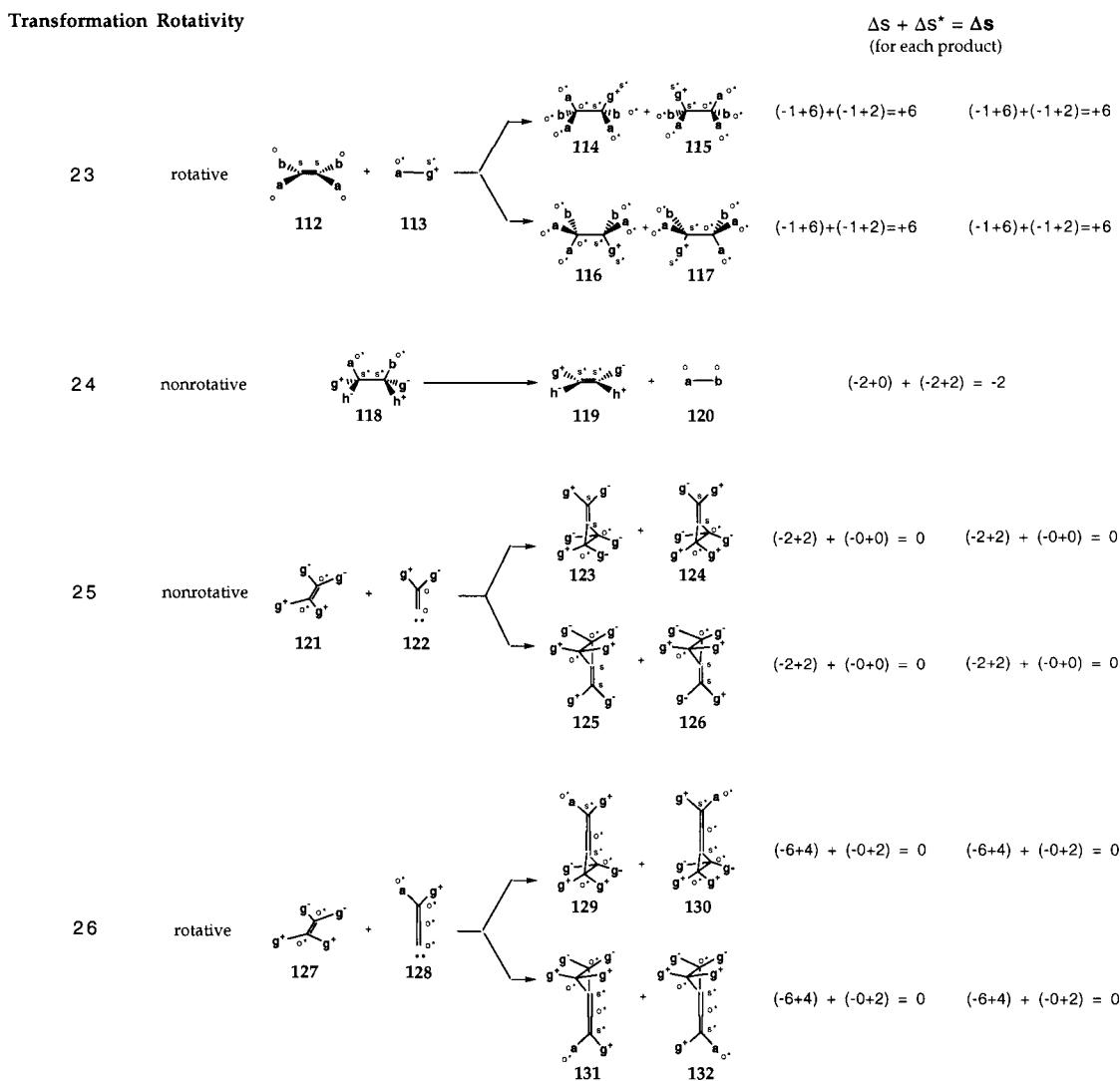
A *nonstereoselective* reaction is one in which at least one transition state/product can form in two (or more) stereomeric forms, and all stereomeric forms are formed in equal amounts (enantiomers are formed as 50:50 mixtures, and/or diastereomers as equimolar mixtures).

A *stereoaselective* reaction is one in which none of the transition states/products can form in stereomeric (enantiomeric or diastereomeric) forms, owing to the lack of relevant stereogenic

elements. If more than one transition state/product forms, the transition states/products would be nonstereomeric (anisomeric or nonequimERIC) with respect to each other.

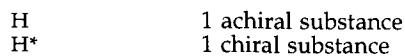
In Figures 18.4 and 18.5 we provide examples of stereoaselective, nonstereoselective and stereoselective transformations.

### Stereoselectivity



**Figure 18.5.** Examples of Nonrotative/Rotative) Stereoselective Transformations

Typically, stereoaselective substances consist of a single achiral or chiral component:



Nonstereoselective mixtures may consist of racemic mixtures, or, racemic mixtures along with an achiral common astereomer:

E*/E	2 enantiomers (racemate)
E*/E,N	2 enantiomers (racemate) and an achiral common astereomer

Stereoselective mixtures are exemplified by one of the following mixtures:

E*, E	2 enantiomers (nonequimolar amounts)
D,F	2 achiral diastereomers (in unequal amounts)
D*,F*	2 chiral diastereomers (in unequal amounts)
D,F,G	3 achiral diastereomers (in unequal amounts)
D*,F*,G*	3 chiral diastereomers (in unequal amounts)
E*/E, D*/D	2 diastereomeric racemates (in unequal amounts)
D*,F*,G*,J*	4 chiral diastereomers (in unequal amounts)

In Figure 18.4 (p. 106), transformations 15-20 constitute stereoaselective transformations, since there is convergence towards (one or more) products which are devoid of stereogenic elements. Transformations 21 and 22 are nonstereoselective; the former transformation leads to a racemate –  $102/103 = 104/105$ , while the latter one gives two nonequimolar racemates –  $108/110$  and  $109/111$ . In Figure 18.5 (p. 108), we depict transformations 23-26 which are stereoselective. In each of transformations 23 ( $112+113 \rightarrow 114 (=117)+115 (=116)$ ) and 26 ( $127+128 \rightarrow 129 (=132)+130 (=131)$ ), one obtains two chiral diastereomers; in the case of 25 ( $121+122 \rightarrow 123 (=125)+124 (=126)$ ), the product mixture consists of two achiral diastereomers. Stereoselectivity is also possible in transformation 24 ( $118 \rightarrow 119+120$ ), if *syn* elimination of a-b occurs concurrently with *anti* elimination. It should be noted that any one of these reactions would be considered *nonstereoselective*, if the component diastereomers were to form in accidentally equal amounts :

D,F	2 achiral diastereomers (in equal amounts)
D*,F*	2 chiral diastereomers (in equal amounts)
D,F,G	3 achiral diastereomers (in equal amounts)
D*,F*,G*	3 chiral diastereomers (in equal amounts)
E*/E, D*/D	2 diastereomeric racemates (in equal amounts)
D*,F*,G*,J*	4 chiral diastereomers (in equal amounts)

Appendix 17.B (pp. 91-94) shows compositions of substances (products or transition states) that result from stereoaselective, nonstereoselective and stereoselective transformations.

#### IV. Rotativity and Stereoselectivity

As in the case of stereotopoprocesses in Chapter 17, one can establish a link, between stereoselectivity and rotativity, for chirotopoprocesses as well.

In Figure 18.4 (p. 106), stereoaselective transformations 16 ( $76 \rightarrow 77+78$ ) and 20 ( $94+95 \rightarrow 96 (=97=98=99)$ ) yield product mixtures that are nonrotative; transformation 16 yields two achiral products, whereas transformation 20 converges into a single achiral product. Stereoaselective transformations 15 ( $73 \rightarrow 74+75$ ), 17 ( $79 \rightarrow 80+81$ ), 18 ( $82+83 \rightarrow 84 (=85=86=87)$ ) and 19 ( $88+89 \rightarrow 90 (=91=92=93)$ ) lead to mixtures that are rotative. Here, each product mixture from transformations 15, 17 contains an enantiopure chiral product, in admixture with an achiral product. In the case of 18 and 19, the transformations converge into single chiral products -  $84 (=85=86=87)$  and  $90 (=91=92=93)$ , respectively.

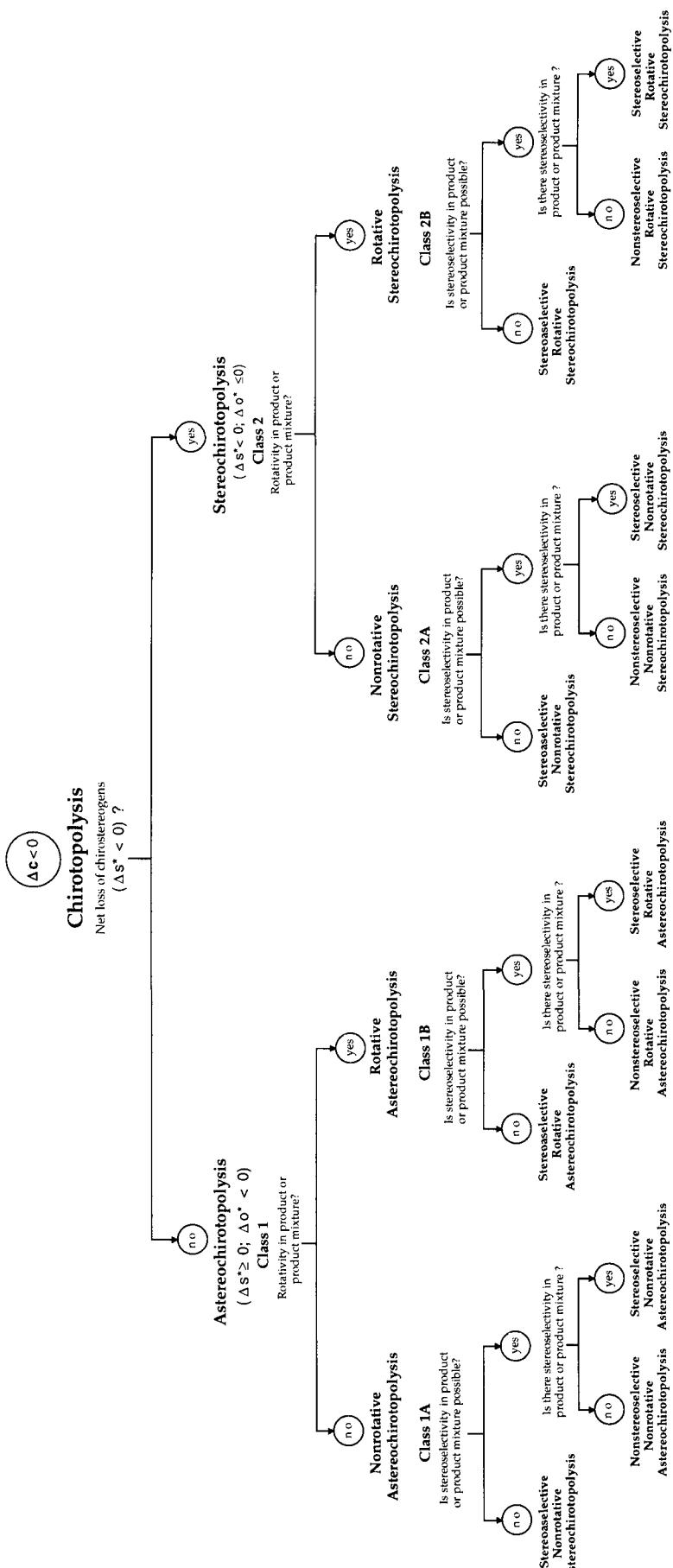


Figure 18.6. Classification of Chirotopolyis

Nonstereoselective transformations 21 and 22 yield nonrotative mixtures; transformation 21 ( $100+101 \rightarrow 102 (=104) + 103 (=105)$ ) yields a racemate, whereas transformation 22 ( $106+107 \rightarrow 108+110$  and  $109+111$ ), generates two astereomeric racemates. Nonstereoselective transformations may also yield mixtures that are *rotative* (*vide infra*).

Of the stereoselective transformations portrayed in Figure 18.5, transformations 24 ( $118 \rightarrow 119+120$ ) and 25 ( $121+122 \rightarrow 123 (=125) + 124 (=126)$ ) give rise to nonrotative mixtures, whereas transformations 23 ( $112+113 \rightarrow 114 (=117) + 115 (=116)$ ) and 26 ( $127+128 \rightarrow 129 (=132) + 130 (=131)$ ) yield rotative mixtures. Transformation 24 leads to two nonequimERIC achiral products; in the case of 25, two achiral diastereomers are generated. In the rotative cases, in each of transformations 23 and 26 one obtains two chiral diastereomers (in unequal amounts). It is to be noted that if, in each of the latter two transformations, the (chiral) diastereomers are accidentally formed in equal amounts, the transformations would be considered nonstereoselective (*vide supra*).

It is clear that when the two attributes - stereoselectivity and rotativity - of chemical transformations are taken into account, one finds that stereoaselective, nonstereoselective and stereoselective transformations all can lead to mixtures that are either nonrotative or rotative. Thus, nonrotative mixtures can result from stereoaselective, nonstereoselective, or stereoselective transformations; similarly, rotative mixtures also can form in the course of transformations that are stereoaselective, nonstereoselective, or stereoselective.

## V. Chirotopolysis, Rotativity and Stereoselectivity

We have already seen that chirotopolysis is subclassified into astereochirotopolysis (Class 1), if there is no net loss of chirostereogens, and stereochoirotopolysis (Class 2), if indeed there is a net loss of chirostereogens (Figure 18.1, p. 102). We now turn into the further classifications of Classes 1 and 2 (Figure 18.6).

Astereochirotopolysis (Class 1) may be subclassified into *nonrotative astereochirotopolysis* (Class 1A) and *rotative astereochirotopolysis* (Class 1B), depending on whether the resulting mixture is nonrotative or rotative, respectively. Nonrotative astereochirotopolysis (Class 1A) can be stereoaselective, nonstereoselective, or stereoselective. Where no stereoselectivity is possible, the transformation is deemed stereoaselective (*vide supra*). In contrast, if stereoselectivity is possible, then the transformation is said to be stereoselective, only if unequal amounts of stereomers are formed; in the special instance where stereomers are formed fortuitously in equal amounts, the process is said to be nonstereoselective. Rotative achirostereotopolysis (Class 1B) is similarly subclassified into stereoaselective, nonstereoselective and stereoselective categories.

Stereochoirotopolysis (Class 2), in turn, is subdivided into *nonrotative stereochoirotopolysis* (Class 2A) and *rotative stereochoirotopolysis* (Class 2B), depending on the nonrotativity or rotativity of the corresponding product mixtures. Class 2A can be broken down further into stereoaselective, stereoselective and nonstereoselective subclasses. If desired, one may distinguish further between  $sp^2$  and  $sp^3$  subcategories. Class 2B also may be subdivided into stereoaselective, nonstereoselective and stereoselective subclasses. In stereochoirotopolysis the particular chirostereogenic atoms lost may be of either  $sp^2$  or  $sp^3$  hybridization, and, if desired, this specification may be added to the terms given already.

Figures 18.7 and 18.8 depict examples of all the subclasses of Classes 1 and 2 defined in Figure 18.6. In Figure 18.7, transformations 27-31 are examples of nonrotative astereochirotopolysis

## Class 1A - Nonrotative Astereochirotopolyis

	Transformation	Selectivity		$\Delta O^*$	$\Delta S^*$	$\Delta C$
27	stereoaselective					-4+0 -0+0 -4
28	stereoselective or nonstereoselective					-4+0 -0+0 -4
29	stereoselective or nonstereoselective					-4+2 -2+2 -2
30	stereoselective or nonstereoselective					-5+2 -1+2 -2
31	stereoselective or nonstereoselective					-2+0 -2+2 -2

## Class 1B - Rotative Astereochirotopolyis

	Transformation	Selectivity		$\Delta O^*$	$\Delta S^*$	$\Delta C$
32	stereoaselective					-5+2 -0+0 -3
33	stereoaselective					-8+5 -0+0 -3
34	stereoselective or nonstereoselective					-6+2 -0+2 -2
35	stereoselective or nonstereoselective					-5+2 -1+2 -2

Figure 18.7. Examples of Nonrotative and Rotative Astereochirotopolyis

## Class 2A - Nonrotative Stereochirotopolyis

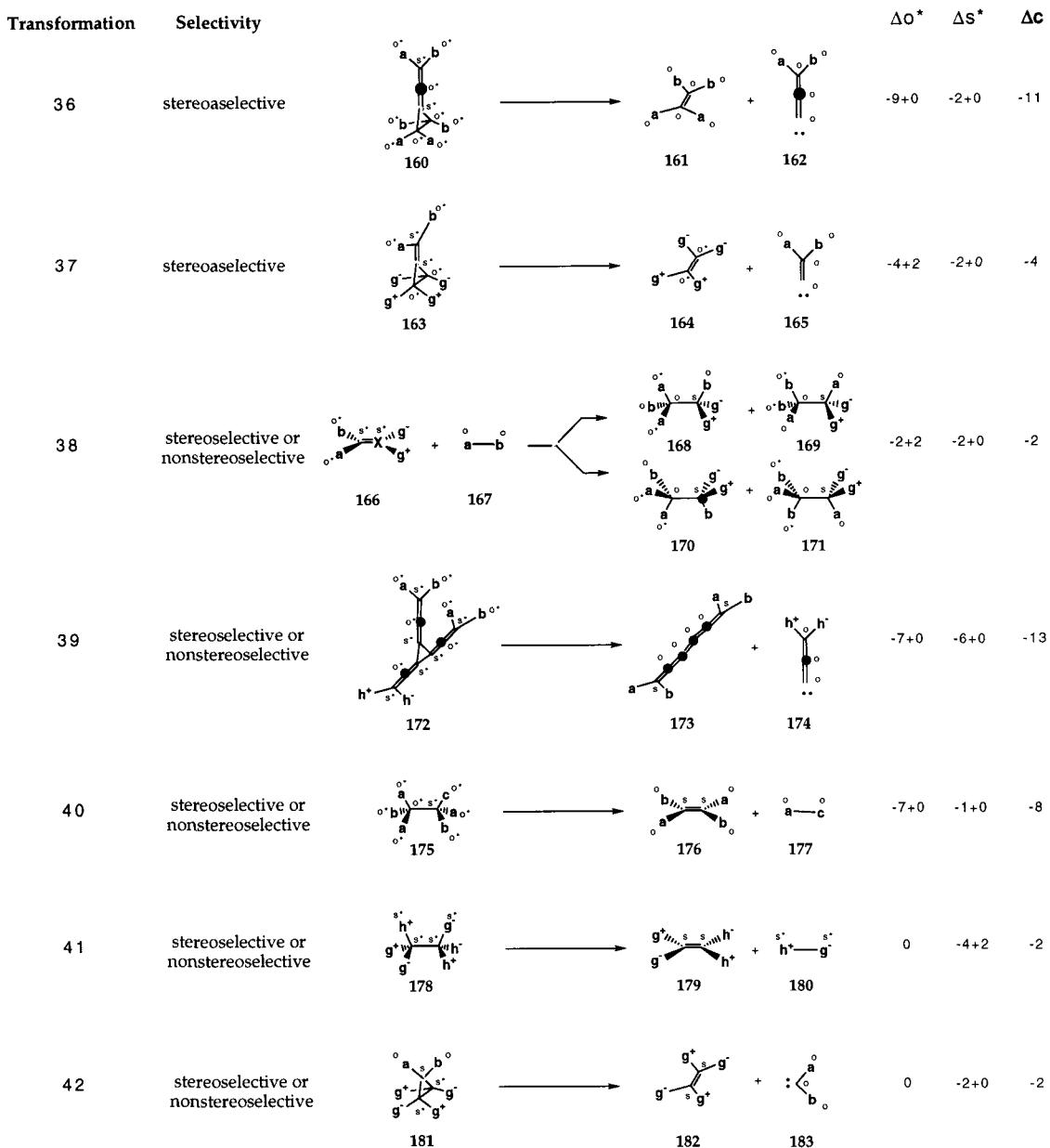


Figure 18.8. Examples of Nonrotative Stereochirotopolyis

(Class 1A), whereas transformations 32-35 are representative rotative astereocheirotopolyses (Class 1B). In Classes 1A and 1B, transformations 27, 32-33 are stereoaselective; the remaining transformations - 28-31, 34, and 35 - can be stereoselective or, accidentally, nonstereoselective.

Figure 18.8 portrays transformations 36-39, which exemplify cases  $sp^2$  nonrotative stereocheirotopolyses (Class 2A); transformations 40-42 represent instances of the  $sp^3$  variety. The  $\Delta\alpha^*$ ,  $\Delta\delta^*$ ,  $\Delta\epsilon$  numbers, given for these transformations, refer to the overall transformations; in the case of transformation 38, the values apply to each one of the four isomeric products. Finally, in Figure 18.9 (p. 114), we present transformations 41-45 as examples of  $sp^2$  rotative stereocheirotopolyis (Class 2B), and 46-49, as representative rotative  $sp^3$  stereocheirotopolyses (Class 2B).

## Class 2B - Rotative Stereocheirotopolyisis

	Transformation	Selectivity	$\Delta O^*$	$\Delta S^*$	$\Delta C$
41	stereoaselective		-7+4	-2+0	-5
42	stereoaselective		-8+4	-1+0	-5
43	stereoselective or nonstereoselective		-7+6	-6+2	-4
44	stereoselective or nonstereoselective		-6+6	-4+2	-2
45	stereoselective or nonstereoselective		-6+6	-6+2	-4
46	stereoaselective		-6+5	-1+0	-2
47	stereoaselective		-6+5	-1+0	-2
48	stereoselective or nonstereoselective		-5+1	-2+0	-6
49	stereoselective or nonstereoselective		-4+2	-4+2	-4

Figure 18.9. Examples of Rotative Stereocheirotopolyisis

## VI. Chirotopomutation, Rotativity and Stereoselectivity

As seen earlier (Figure 18.1, p. 102), chirotopomutation belongs to one three categories - *astereochirotopomutation* (Class 3), *nonchirotopomutation* (Class 4) and *stereochoirotopomutation* (Class 5). We now discuss the subclassification of these classes (Figure 18.10, p. 116).

Astereochirotopomutation (Class 3) is subdivided into *nonrotative astereochirotopomutation* (Class 3A) and *rotative astereochirotopomutation* (Class 3B), depending on whether the resulting product mixture is nonrotative or rotative, respectively. Astereochirotopomutations of both subclasses - nonrotative and rotative - can be stereoaselective, nonstereoselective or stereoselective.

Nonchirotopomutation (Class 4) is subdivided into *nonrotative nonchirotopomutation* (Class 4A) and *rotative nonchirotopomutation* (Class 4B). Each of these subclasses can be also stereoaselective, nonstereoselective or stereoselective.

Lastly, stereochoirotopomutation is subgrouped into *nonrotative stereochoirotopomutation* (Class 5A) and *rotative stereochoirotopomutation* (Class 5B). Each of these subclasses can be stereoaselective, nonstereoselective or stereoselective, as well.

In Figures 18.11-18.14 (pp. 118-121), we provide examples of all the above classes and their subclasses.

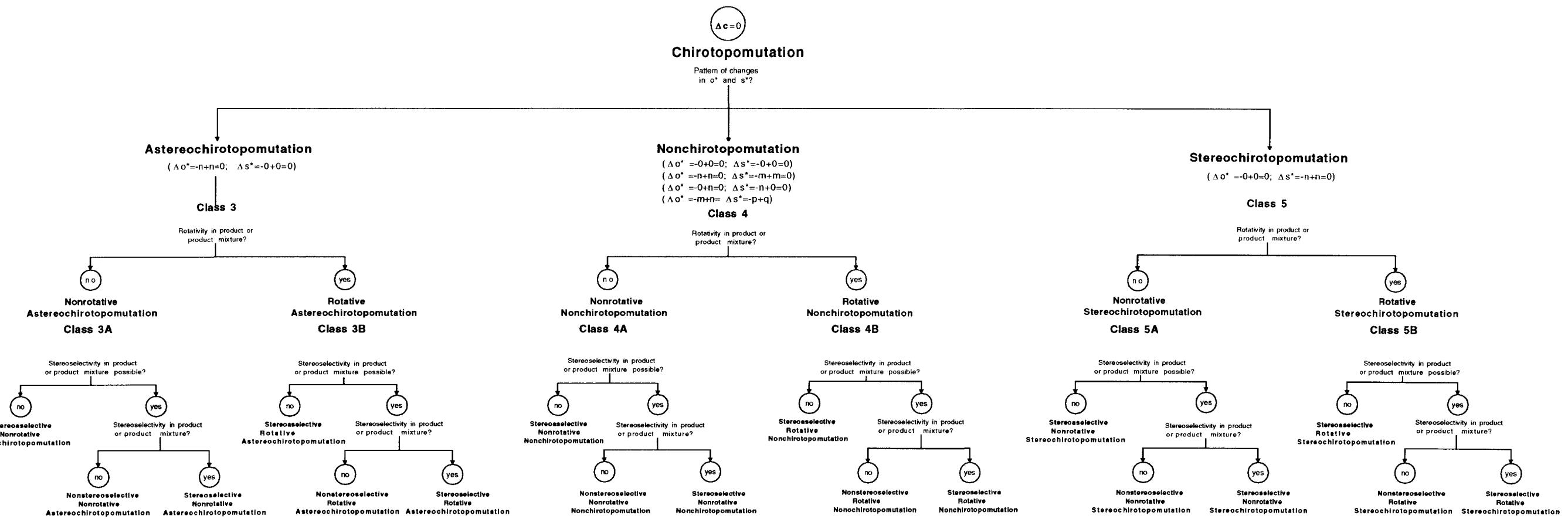
Transformations 50-52 (Figure 18.11) are examples of nonrotative astereochirotopomutation, (Class 3A), whereas transformations 53-55 represent the corresponding rotative mode (Class 3B). In all six cases of Figure 18.11, the topomutations are only in atoms of type  $o^*$ ; equal numbers of atoms type  $o^*$  are lost and generated, and there are no alterations in atoms of type  $s^*$ . It should be emphasized that for atoms of type  $s^*$ , one considers only the ones that undergo bond cleavages or changes in hybridization.

In Class 3A, transformations 50 and 52 are stereoselective (or accidentally nonstereoselective). Transformation 51 can be (a) doubly stereoselective (four diastereomers are formed), (b) stereoselective-and-nonstereoselective (of the four diastereomers, two are formed in equal amounts, along with unequal amounts of the other two (which, in turn, are also formed in equal amounts)), or, (c) doubly nonstereoselective (if equal amounts of all four diastereomers are formed). In Class 3B, transformations 53-55 are all stereoaselective.

Transformations 56-64 exemplify nonrotative nonchirotopomutations (Class 4A; Figure 18.12); transformations 65-72 represent rotative nonchirotopomutations (Class 4B; Figure 18.13). In all of these examples, we encounter either offsetting alterations in  $o^*$  and  $s^*$  (transformations 59, 61, 63, 64), or, no alterations in either  $o^*$ - or  $s^*$ -type atoms (transformations 56-58). Transformation 62 is a composite case, in which 285 and 287 constitute products of nonchirotopomutation, while the co-products - 286 and 288 - are formed by stereochoirotopomutation (*vide infra*).

In Class 4A, transformation 56 is stereoaselective. Transformations 57, 59, 63 and 64 can be either stereoselective, or, accidentally nonstereoselective. In contradistinction, transformation 58 is stereoselective (two diastereomers are formed in unequal amounts) and simultaneously nonstereoselective (each diastereomer consists of a racemate). Transformations 60, 61 and 62 can be doubly stereoselective, stereoselective-and-nonstereoselective, or doubly nonstereoselective, as in the case of 51 above.

Transformation 65, in Class 4B, turns out to be stereoaselective, whereas transformation 66 is nonstereoselective (a racemate is formed). In contrast, transformations 67, 69 and 71 are



**Figure 18.10.** Stereochemical Classification of Chirotopomutation

stereoselective (or accidentally nonstereoselective). In the case of transformations 68, 70 and 72, one may observe double stereoselectivity, (mono)stereoselectivity-and-nonstereoselectivity, or, double nonstereoselectivity (*vide supra*; transformation 51).

Next, we consider examples of stereochoirotopomutation – nonrotative (Class 5A) and rotative (Class 5B). In examples 73-78 (Figure 18.14, p. 121), we note that topomutations are only in atoms of type  $s^*$  - equal numbers of atoms type  $s^*$  are destroyed and generated, and there are no alterations in atoms of type  $o^*$ . It should be emphasized that in looking at atoms of type  $s^*$ , one considers only the ones that undergo bond cleavages and/or changes in hybridization (*vide supra*).

In Class 5A, transformations 73-75 can be doubly stereoselective, stereoselective-and-nonstereoselective, or doubly nonstereoselective (*vide supra*, transformation 51).

Finally, in Class 5B, transformations 77-79 are either stereoselective or accidentally nonstereoselective.

## VII. Chirotopogenesis, Rotativity and Stereoselectivity

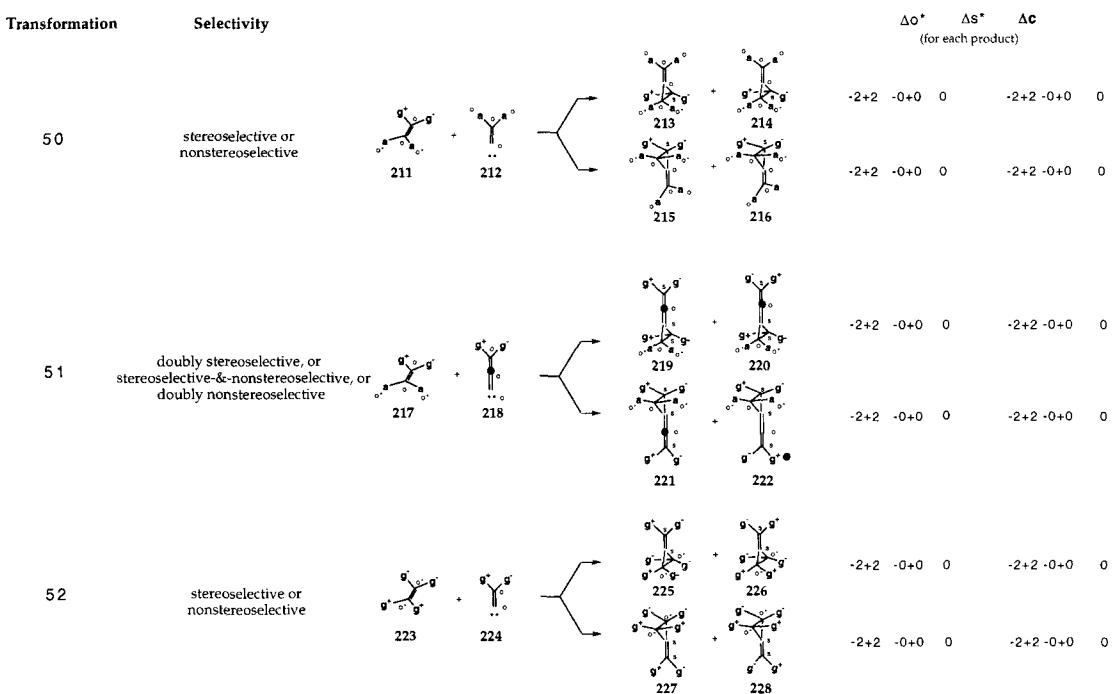
As seen earlier (Figure 18.1, p. 102), chirotopogenesis is subclassified into *astereochoirotopogenesis* (Class 6), if there is no net gain of chirostereogenic atoms  $s^*$ , and, *stereochoirotopogenesis* (Class 7), if there is, indeed, a gain of stereogenic atoms of type  $s^*$ . We now discuss the subclassification of Classes 6 and 7. The overall classification of chirotopogenesis is portrayed in Figure 18.15 (p. 122).

Astereochoirotopogenesis (Class 6) is subclassified into *nonrotative astereochoirotopogenesis* (Class 6A) and *rotative astereochoirotopogenesis* (Class 6B), depending on whether the resulting mixture is nonrotative or rotative, respectively. Each of the astereochoirotopogenesis subclasses can be stereoaselective, if no stereoselectivity is possible, nonstereoselective, if accidentally equal amounts of enantiomers and/or diastereomers are formed, or, stereoselective, if nonequal amounts of enantiomers and/or diastereomers are formed. Further, nonrotative astereochoirotopogenesis may be of the  $sp^2$  or  $sp^3$  type depending on whether the new astereochoirotopic atom is  $sp^2$  or  $sp^3$ -hybridized; similarly, rotative astereochoirotopogenesis may be of the  $sp^2$  or  $sp^3$  variety.

In turn, *stereochoirotopogenesis* is either *nonrotative* (Class 7A) or *rotative* (Class 7B). Each of the latter two subclasses can be stereoaselective, nonstereoselective or stereoselective (*vide supra*). Nonrotative and rotative stereochoirotopogeneses may be of the  $sp^2$  or  $sp^3$  variety. In Figures 18.16-18.19 (pp. 123,125-127), we provide examples of all the above subclasses.

Figure 18.16 exemplifies *nonrotative astereochoirotopogenesis* (Class 6A). In this figure, transformations 79 and 80 constitute examples of stereoselective (or accidentally nonstereoselective)  $sp^2$  nonrotative astereochoirotopogenesis; each of them leads to two diastereomeric products (381=384, diastereomeric with respect to 382=383; 387=389, diastereomeric with respect to 388=390). Transformations 81-87 are examples of  $sp^3$  nonrotative astereochoirotopogenesis; of these transformations, 81, 83-85 are stereoaselective (393=394=395=396, 405=406=407=408; 411=412=413=414, 417=418=419=420), 82 is nonstereoselective (399=402 enantiomeric with 400=401), while 81 and 86 are stereoselective (or accidentally nonstereoselective; 423=424 is diastereomeric with respect to 425=426). Transformation 87 is stereoselective-and-nonstereoselective (if the amount of racemate 429+430 is not equal to that of diastereomeric racemate 431+432), or, doubly nonstereoselective (if the two diastereomeric racemates are formed in equal amounts, i.e. [429+430] = [431+432]).

### Class 3A - Nonrotative Astereochirotopomutation



### Class 3B - Rotative Astereochirotopomutation

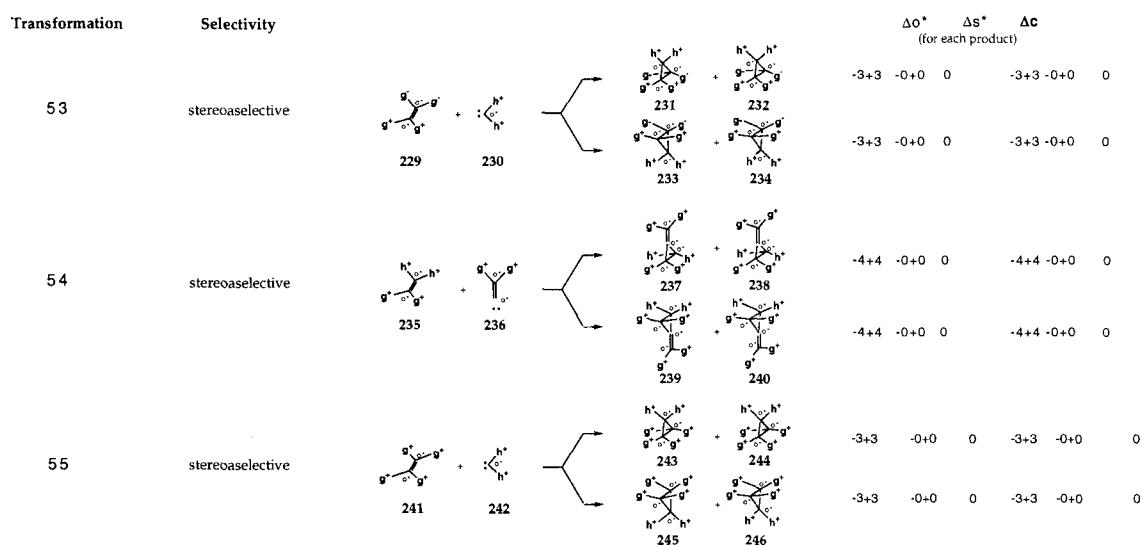


Figure 18.11. Examples of Nonrotative and Rotative Astereochirotopomutation

**Class 4A - Nonrotative Nonchirotopomutation**

Transformation	Selectivity		$\Delta O^*$	$\Delta S^*$	$\Delta C$
			(for each product)		
56	stereoselective		-0+0	-0+0	0
57	stereoselective or nonstereoselective		-0+0	-0+0	0
58	stereoselective & nonstereoselective		-0+0	-0+0	0
59	stereoselective or nonstereoselective		-2+2	-2+2	0
60	doubly stereoselective, or stereoselective-&-nonstereoselective, or doubly nonstereoselective		-2+2	-2+2	0
61	doubly stereoselective, or stereoselective-&-nonstereoselective, or doubly nonstereoselective		-2+4	-4+2	0
62	doubly stereoselective, or stereoselective-&-nonstereoselective, or doubly nonstereoselective		-0+2	-4+2	0
63	stereoselective or nonstereoselective		-4+2	-2+4	0
64	stereoselective or nonstereoselective		-2+0	-2+4	0
			$\Delta O^*$	$\Delta S^*$	$\Delta C$
			(for overall transformation)		

**Figure 18.12.** Examples of Nonrotative Nonchirotopomutation

## Class 4B - Rotative Nonchirotopomutation

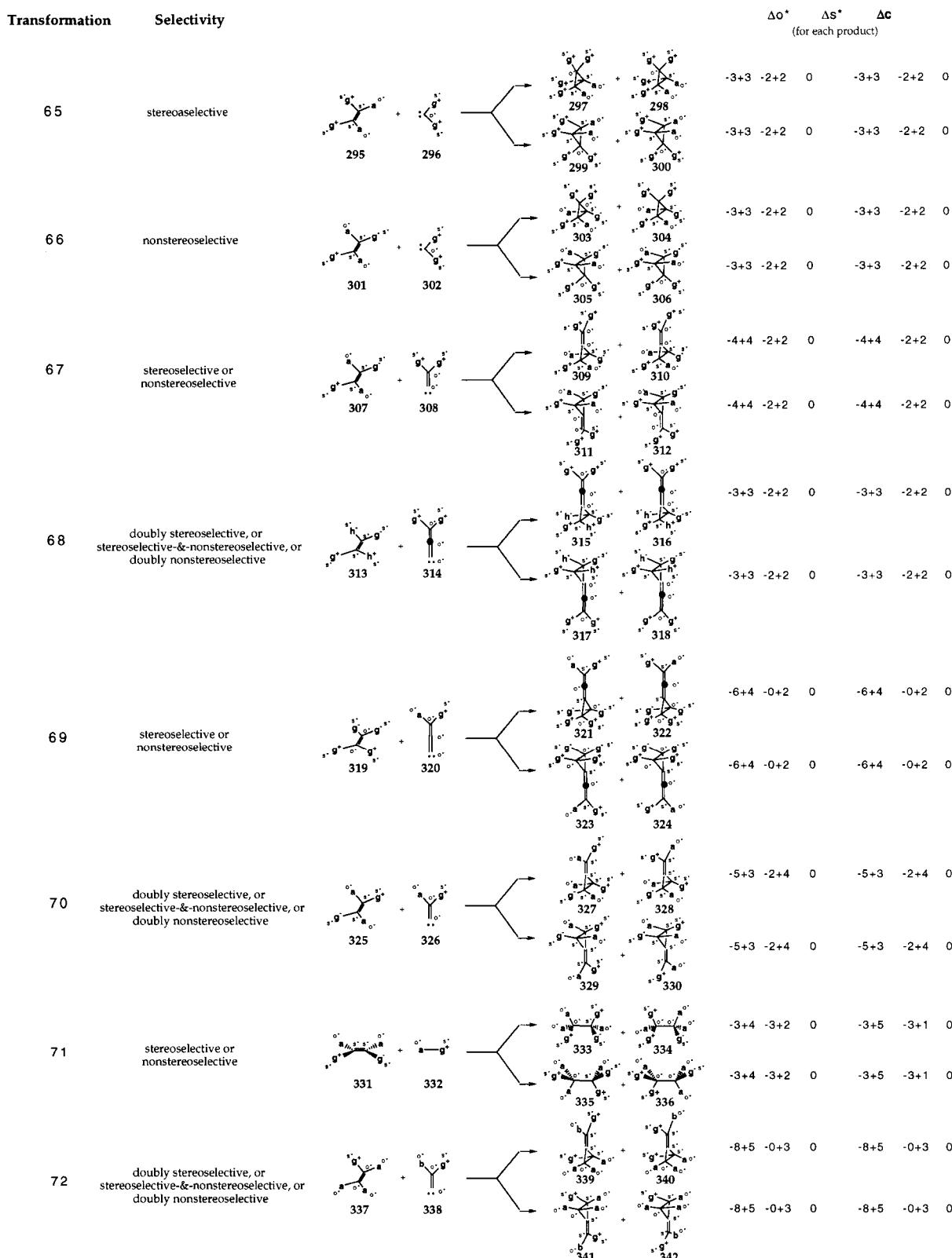


Figure 18.13. Examples of Rotative Nonchirotopomutation

### Class 5A - Nonrotative Stereochirotopomutation

Transformation	Selectivity		$\Delta O^*$	$\Delta S^*$	$\Delta C$
			(for each product)		
73	doubly stereoselective, or stereoselective-&-nonstereoselective, or doubly nonstereoselective		-0+0	-2+2	0 -0+0 -2+2 0
74	doubly stereoselective, or stereoselective-&-nonstereoselective, or doubly nonstereoselective		-0+0	-4+4 0	-0+0 -4+4 0
75	doubly stereoselective, or stereoselective-&-nonstereoselective, or doubly nonstereoselective		-0+0	-4+4 0	-0+0 -4+4 0

### Class 5B - Rotative Stereochirotopomutation

Transformation	Selectivity		$\Delta O^*$	$\Delta S^*$	$\Delta C$
			(for each product)		
76	stereoselective or nonstereoselective		-0+0	-4+4 0	-0+0 -4+4 0
77	stereoselective or nonstereoselective		-0+0	-4+4 0	-0+0 -4+2 0
78	stereoselective or nonstereoselective		-0+0	-4+4 0	-0+0 -4+4 0

Figure 18.14. Examples of Nonrotative and Rotative Stereochirotopomutation

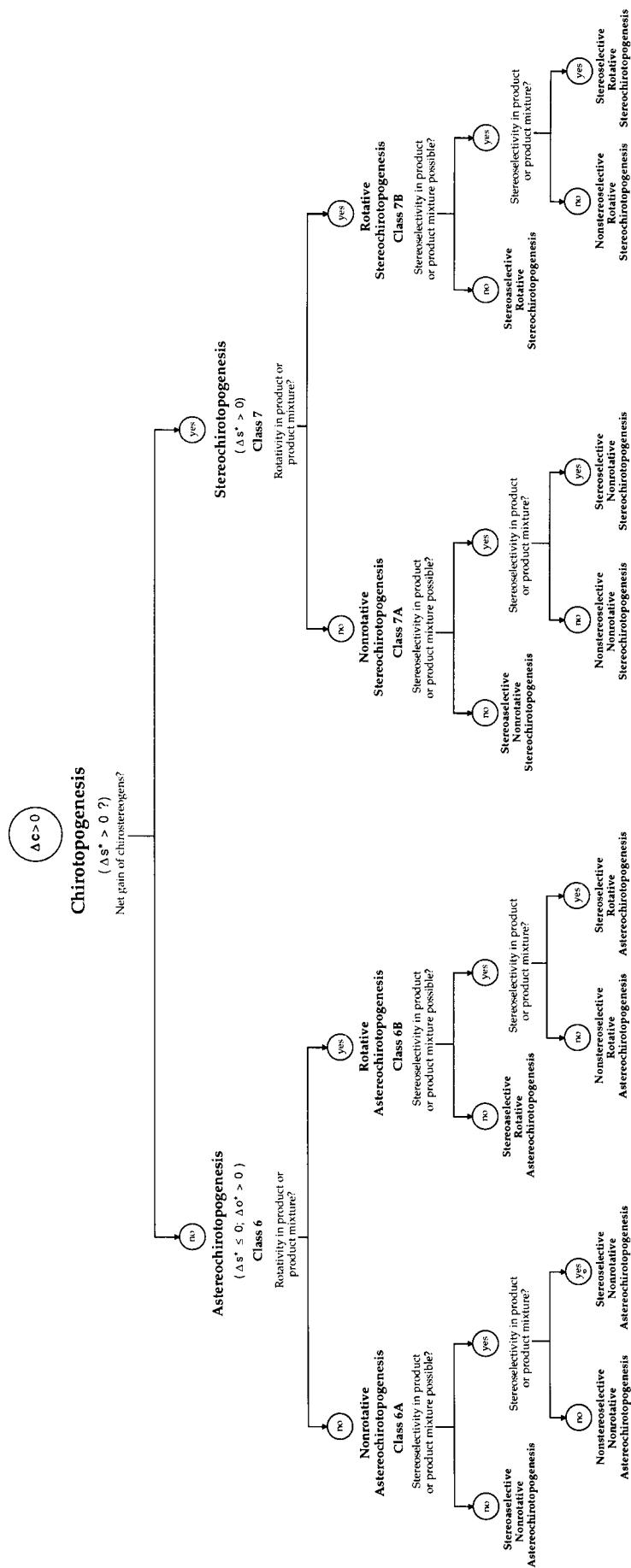


Figure 18.15 Classification of Chirotropogenesis

## Class 6A - Nonrotative Astereochirotopogenesis

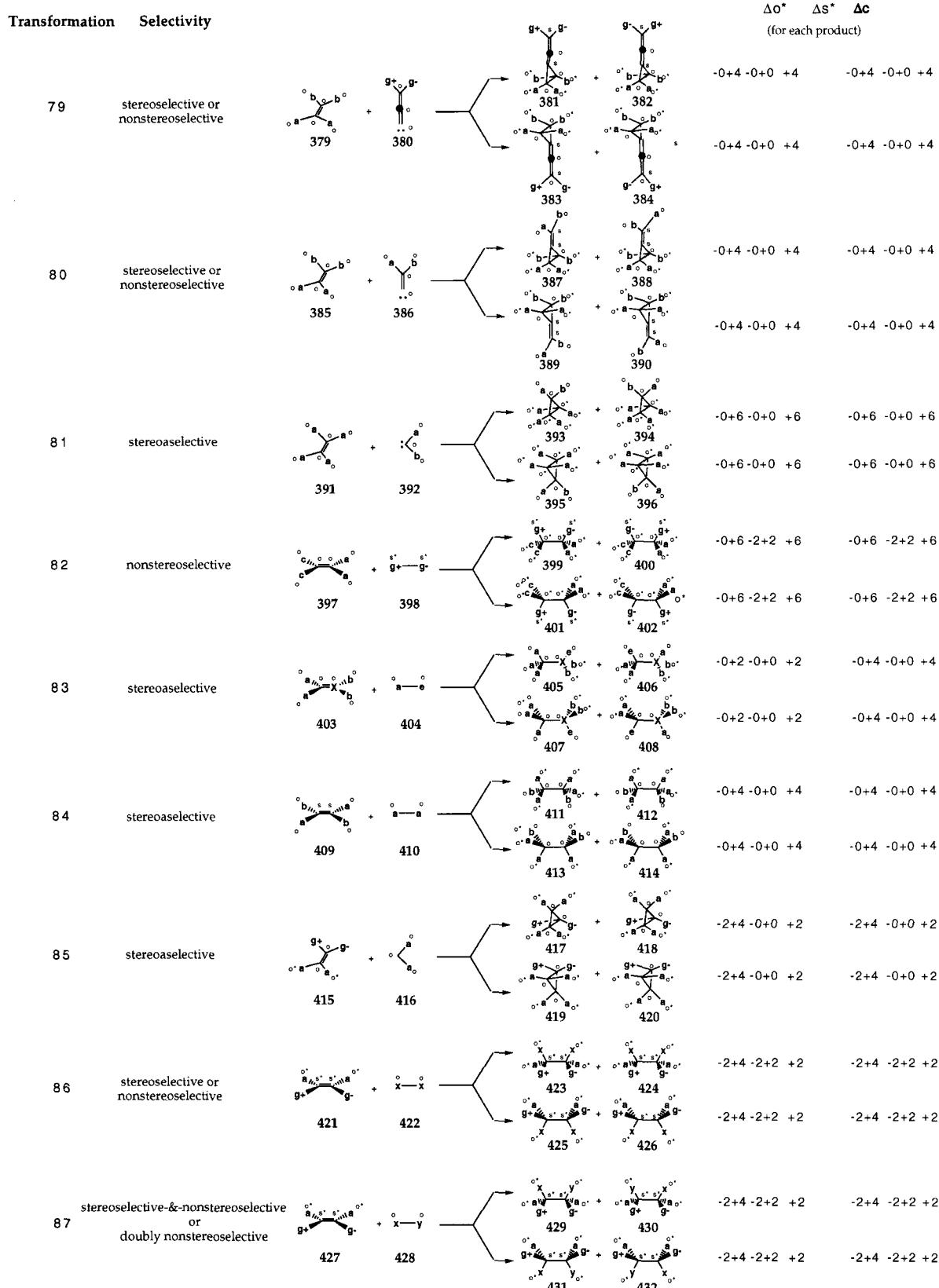


Figure 18.16. Examples of Nonrotative Astereochirotopogenesis

Figure 18.17 depicts cases of *rotative astereochirotopogenesis* (Class 6B). The  $sp^2$  rotative variety is represented by transformations 88 and 89, both of which are stereoaselective ( $435=436=437=438$ ;  $441=442=443=444$ ). Of the  $sp^3$  variants, 91, 92, 95 are stereoaselective ( $453=454=455=456$ ;  $459=460=461=462$ ;  $475=476=477=478$ ), 93 is nonstereoselective (one obtains racemate  $466/468$  along with astereomeric product  $465=467$ ), whereas transformations 90 and 94 are stereoselective (or accidentally nonstereoselective). Transformation 90 is stereoselective (if diastereomers  $448$  and  $450$  are formed in unequal amounts;  $448$  and  $450$  are astereomeric with respect to  $447=449$ ), or, nonstereoselective (if amount of  $448$  is accidentally equal to that of  $450$ ). On the other hand, transformation 94 can be two-fold stereoselective (if  $[471]\neq[473]$  and  $[472]\neq[474]$ ), one-fold stereoselective and one-fold nonstereoselective (if  $[471]\neq[473]$  and  $[472]=[474]$ , or *vice versa* -  $[471]=[473]$  and  $[472]\neq[474]$ ), or, two-fold nonstereoselective (if  $[471]=[473]$  and  $[472]=[474]$ );  $[471]+[473]$  may or may not be equal to  $[472]+[474]$ ); note that the  $471/473$  pair is astereomeric with respect to the  $472/474$  pair.

Figure 18.18 portrays examples of *nonrotative stereochirotopogenesis* (Class 7A). Transformations 96 and 97 represent two cases of the  $sp^2$  type. The first one of these transformations is nonstereoselective ( $483=486$  and  $484=485$  constitute a racemate), while the second one can be either nonstereoselective-and-stereoselective (if racemate  $489/490$  and diastereomeric racemate  $491/492$  are formed in unequal amounts), or, doubly nonstereoselective (if racemate  $489/490$  and diastereomeric racemate  $491/492$  are formed in equal amounts). The remaining five cases (transformations 98-102) are  $sp^3$  nonrotative stereochirotopogeneses. Among these examples, 98 is stereoaselective ( $495=496=497=498$ ), 99 is nonstereoselective ( $502/504$  is a racemate which is astereomeric with respect to  $501=503$ ), whereas 100 and 101 are stereoselective (if diastereomers  $507=508$  and  $509=510$  are formed in unequal amounts; if  $[507+508]=[509+510]$ , the transformation would be nonstereoselective). Transformation 102 is stereoselective-and-nonstereoselective (if diastereomeric racemates  $519/520$  and  $521/522$  are formed in unequal amounts), or doubly nonstereoselective (if diastereomeric racemates  $519/520$  and  $521/522$  are formed in accidentally equal amounts).

Finally, Figure 18.19 shows three cases of  $sp^2$  rotative stereochirotopogenesis (transformations 103-105), and six cases of  $sp^3$  rotative stereochirotopogenesis (transformations 106-111). Of the  $sp^2$  variety, 103 and 104 are stereoselective (or accidentally nonstereoselective). In transformation 103, stereoselectivity prevails if  $[525(=528)]\neq[526(=527)]$ ; it does not, if the diastereomers in question are formed in equal amounts. Transformation 104 is stereoselective, if diastereomers  $531(=534)$  and  $532(=533)$  are formed in unequal amounts, or nonstereoselective, if the diastereomers are formed in equal amounts. Transformation 105 can be doubly stereoselective (the product mixture consists of unequal amounts of the four diastereomeric products  $537,538,539,540$ ) or stereoselective-and-nonstereoselective (if two of the four diastereomers are formed in accidentally equal amounts), or, doubly nonstereoselective (if, fortuitously, all four diastereomers are formed in equal amounts).

Of the  $sp^3$  cases, 106 is nonstereoselective ( $543(=546)$  and  $544(=545)$  constitute a racemate). Transformations 107, 109, 110 can be either stereoselective, or accidentally nonstereoselective. Transformation 107 would be stereoselective, if diastereomers  $549(=550)$  and  $551(=552)$  are formed in unequal amounts, or, nonstereoselective, if the two diastereomers in question are formed in equal amounts. Transformation 109 gives two astereomeric diastereomers (diastereomeric mixture  $561+563$  is astereomeric with respect to diastereomeric mixture  $562+564$ ); the transformation can be two-fold stereoselective if, for each of the astereomeric pairs, the diastereomers are formed in unequal amounts ( $[561]\neq[563]$  and  $[562]\neq[564]$ ). If one pair of diastereomers is accidentally formed in equal amounts ( $[561]\neq[563]$  and  $[562]=[564]$ , or *vice versa*), the transformation may still be stereoselective with respect to the second diastereomeric pair. In principle, the transformation may be two-fold nonstereoselective, if both pairs of diastereomers are formed in pairwise equal amounts ( $[561]=[563]$  and  $[562]=[564]$ ). In the case

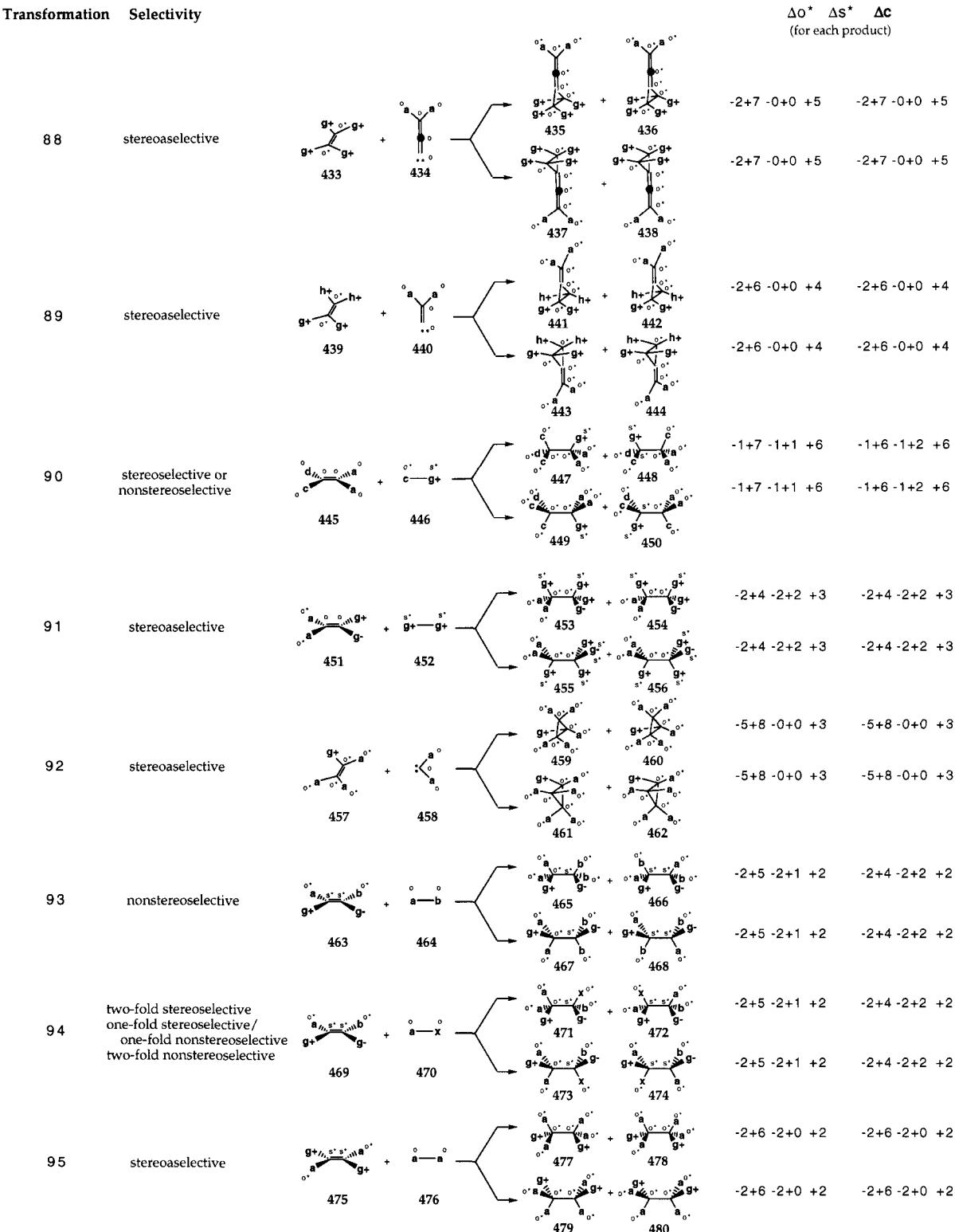


Figure 18.17. Examples of Rotative Astereochirotopogenesis

### Class 7A - Nonrotative Stereochirotopogenesis

#### Transformation Selectivity

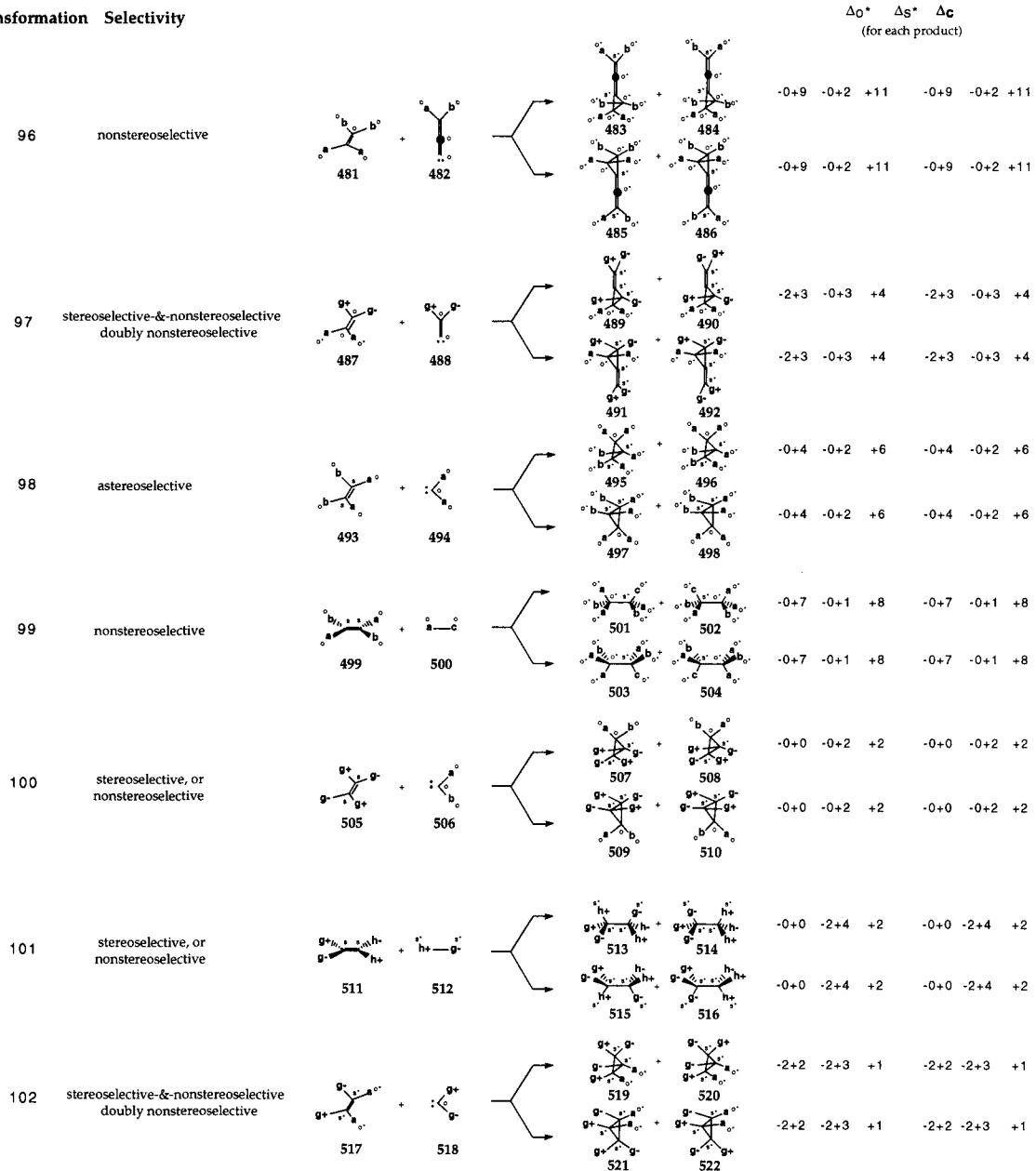


Figure 18.18. Examples of Nonrotative Stereochirotopogenesis

Class 7B - Rotative Stereocheiotopogenesis

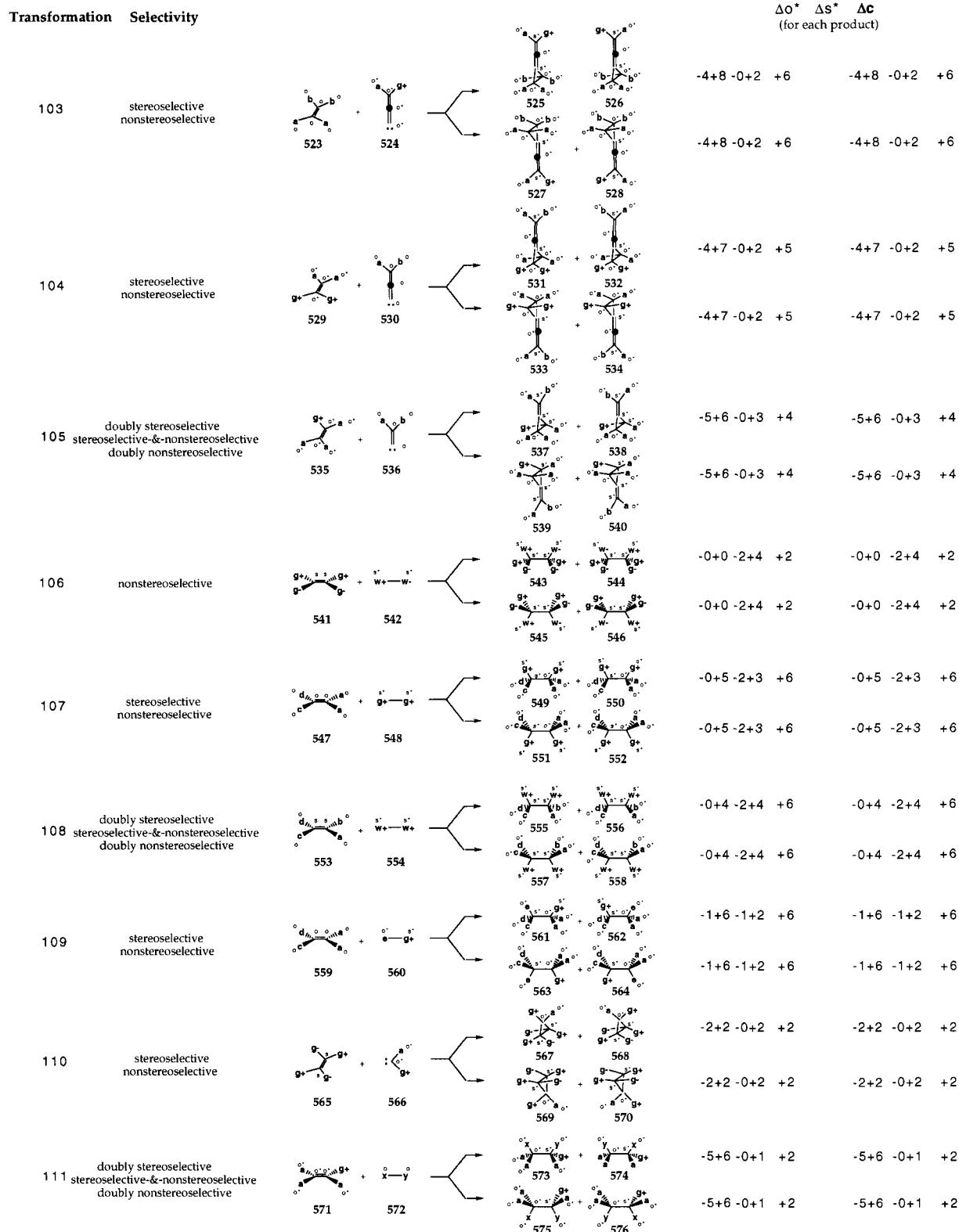


Figure 18.19. Examples of Rotative Stereocheiotopogenesis

of transformation 110, one expects two diastereomers - 567(=568) and 569(=570); this transformation is stereoselective, if the two diastereomers are formed in unequal amounts, or, nonstereoselective, if they are, indeed, formed in equal amounts. Finally, each of transformations 108 and 111 can be doubly stereoselective (the product mixture in each case consists of four unequal amounts of diastereomers – 555-558 and 573-576), stereoselective-and-nonstereoselective (if two in a set of four diastereomers are formed in equal amounts), or doubly nonstereoselective (if, accidentally, all four diastereomers are formed in equal amounts).

It should be noted that, that a given transformation may involve composites of the various subclasses i.e. in the product mixture, one component may be described as the result of one subclass, and another component, in the same mixture, may be the result of another subclass. Our analysis leads to composites of the following combination classes: 1A/4A, 1A/4B, 1B/4B, 2A/4A, 2A/4B, 2A/5A, 2A/6B, 4A/6A, 6A/6B, 6A/7A, 6B/7B. Clearly, a given composite may be either nonrotative (e.g. 1A/4A, 2A/4A, 2A/5A, 4A/6A, 6A/7A) or rotative (e.g. 6B/7B); nonrotative-rotative combinations 1A/4B, 2A/4B, 2A/6B, 6A/6B are necessarily rotative). Composite cases may be of the same general class e.g. 6A/6B (both are astereochirotopogeneses), or may cut across classes. For example, in the case of 1A/4A, 1A/4B, and 1B/4B, the cut is across astereochirotopolysis and nonchirotopomutation; for 2A/4A, 2A/4B – across stereochirotopolysis and nonchirotopomutation; for 2A/5A - across stereochirotopolysis and stereochirotopomutation; for 2A/6B - across stereochirotopolysis and astereochirotopogenesis; for 4A/6A - across nonchirotopomutation and astereochirotopogenesis, and, in the case of 6A/7A and 6B/7B - across astereochirotopogenesis and stereochirotopogenesis. Several examples are depicted in Figure 18.20.

## VIII. Chirotopoprocesses in Relation to the Stereotopic Faces

In the previous chapter, we established the relationships between stereotopoprocesses, on the one hand, and stereotopic molecular faces, on the other. We now proceed to show, similarly, the relationships between chirotopoprocesses and each of the stereotopic molecular faces. Tables 18.1-18.3 (pp. 130, 132-133) summarize our findings.

### A. Homotopic Faces

#### 1. Chirotopolysis

Homotopic faces h1-h4 do not undergo any chirotopolysis (Classes 1A-2B). In contrast, h5 faces are subject to nonrotative astereochirotopolysis (Class 1A) (chiral reagents), and h6 faces, to nonrotative stereochirotopolysis (Class 2A) (chiral reagents).

#### 2. Chirotopomutation

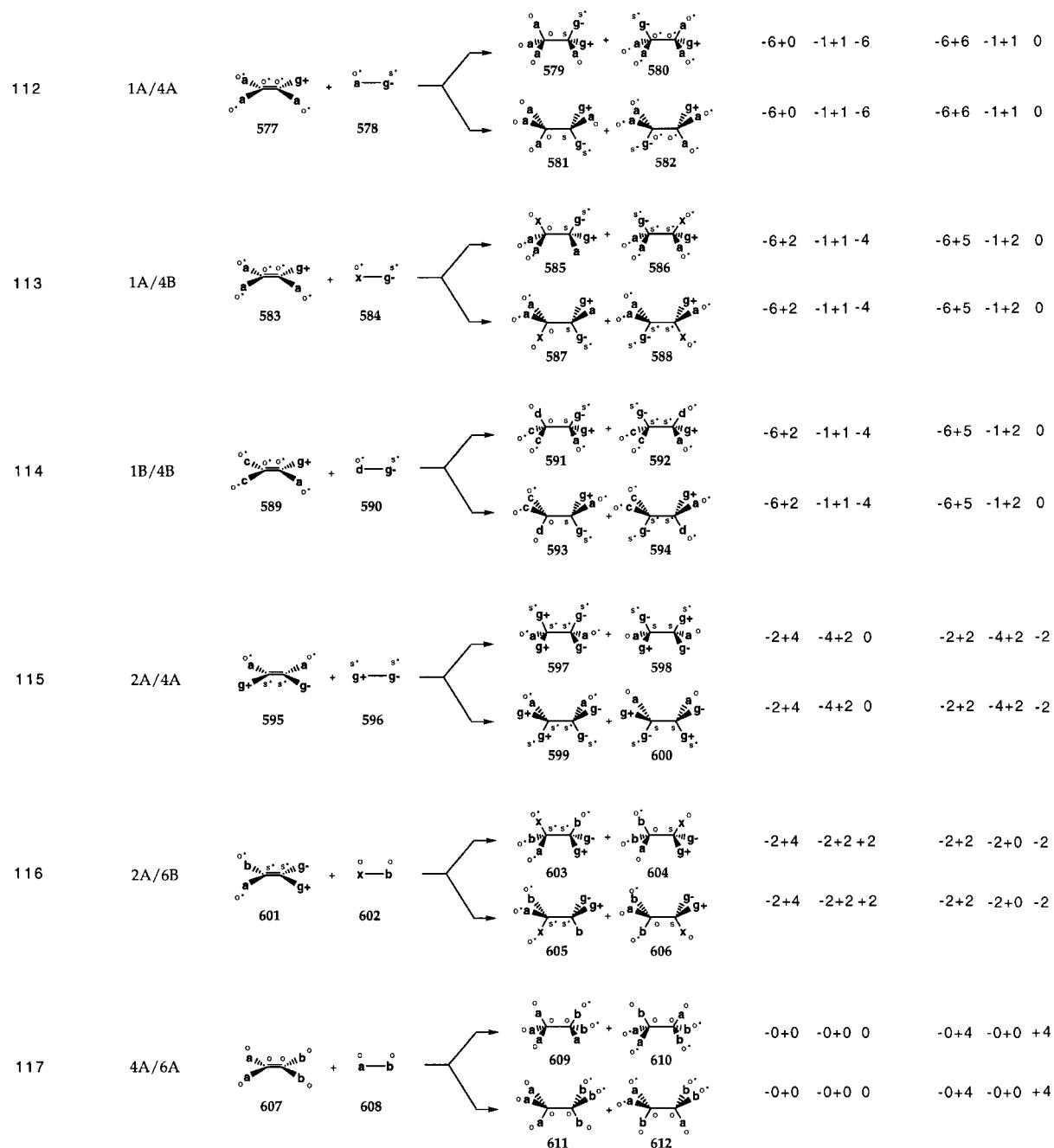
Nonrotative astereochirotopomutation (Class 3A) is indicated for h2 (achiral reagents), and the rotative mode (Class 3B), for h2, h4 (chiral reagents) and h5 (achiral or chiral reagents). Nonchirotopomutation is anticipated for all h1-h6 classes - h1 with achiral reagents, h2-h6 with achiral or chiral reagents. No nonrotative stereochirotopomutation (Class 5A) is expected for any of the h1-h6 classes; however, rotative stereochirotopomutation (Class 5B) is anticipated only for the h6 class (chiral reagents).

#### 3. Chirotopogenesis

Nonrotative astereochirotopogenesis (Class 6A) is observed for faces h1-h3 but not for faces h4-h6 (achiral reagents). Rotative astereochirotopogenesis (Class 6B) is noted for faces h1, h2, h6 (chiral reagents), h4, h5 (achiral reagents), but not for h3. Finally, nonrotative stereochirotopogenesis (Class 7A) is expected for h2, h3 (achiral reagents). The rotative mode (Class 7B) is noted for h2, h3 (chiral reagents), h5, h6 faces (achiral or chiral reagents), but not for h1 and h4 faces.

**Transformation Composite Classes**

$\Delta O^*$     $\Delta S^*$     $\Delta C$   
(for each product)



**Figure 18.20.** Examples of Composite Transformations

ac : achiral reagent  
c : chiral reagent

Classification	Nonrotative (nr) or Rotative (r)	Class	h1	h2	h3	h4	h5	h6
astereochirotopolyis	nr	1A						
	r	1B					Aa	
stereochirotopolyis	nr	2A						
	r	2B					Aa	
astereochirotopomutation	nr	3A			Aa Ns			
	r	3B			Aa		Aa	
nonchirotopomutation	nr	4A	Aa	Ns Nne Ns	Aa Ns			
	r	4B			Ns	Aa	Ns	Aa Ns
stereochirotopomutation	nr	5A						
	r	5B						Aa Ns
astereochirotopogenesis	nr	6A	Aa	Aa An Ns Nn Ns Nne	Aa			
	r	6B	Aa	Aa Ns Nne	Aa		Aa Ns Ns Ss	
stereochirotopogenesis	nr	7A		An Nn	Aa An Ns Nn			
	r	7B			Ns	Aa Ns	Ns	Ns

Table 18.1. Chirotopolyis/Chirotopomutation/Chirotopogenesis of Homotopic Faces h1-h6

## B. Enantiotopic Faces

### 1. Chirotopolysis

Only rotative astereochirotopolysis (Class 1B) and nonrotative stereochirotopolysis (Class 2A) are possible; the former occurs with chiral reagents, and the latter, with achiral reagents.

### 2. Chirotopomutation

Astereochirotopomutations (Classes 3A and 3B) are not indicated with either achiral or chiral reagents. Nonchirotopomutation (Classes 4A and 4B) and stereochirotopomutation (Classes 5A and 5B) are, however, observed – nonrotative modes, with achiral reagents, and rotative variants, with chiral reagents.

### 3. Chirotopogenesis

Nonrotative astereochirotopogenesis (Class 6A) and stereochirotopogenesis (Class 7A) are expected with achiral reagents; rotative modes (Classes 6B and 7B) are possible with chiral reagents.

## C. Diastereotopic Faces

### 1. Chirotopolysis

No chirotopolysis is expected for d1 faces. Nonrotative astereochirotopolysis (Class 1A) is expected for d2 faces (achiral reagents); the nonrotative and rotative modes (Classes 1A and 1B) are discerned only for d4 faces (chiral reagents). Nonrotative stereochirotopolysis (Class 2A) is indicated only for d3 (achiral reagents) and d4 faces (achiral or chiral reagents); the rotative mode is possible for d3 (achiral reagents) as well as d4 (chiral reagents) faces.

### 2. Chirotopomutation

Nonrotative astereochirotopomutation (Class 3A) is observed only for d2 (achiral reagents) faces, and the rotative mode (Class 3B), for d4 faces (achiral reagents). Nonrotative nonchirotopomutation (Class 4A) is noted for d1-d3 faces (achiral reagents); the chiral mode (Class 4B) is possible for d3 faces (chiral reagents) as well as d4 faces (achiral or chiral reagents). Nonrotative stereochirotopomutation (Class 5A) is noted only for d3 (achiral reagents), while the rotative mode (Class 5B) is expected for d2-d4 faces (chiral reagents).

### 3. Chirotopogenesis

Astereochirotopogenesis (Classes 6A and 6B) is possible for all four faces - d1-d4 are nonrotative (achiral reagents), d2-d3 are rotative (chiral reagents) and d4 is rotative (achiral and chiral reagents). Finally, nonrotative stereochirotopogenesis (Class 7A) is indicated for d1-d3 (achiral reagents); the rotative mode (Class 7B) is observed for all four types of diastereotopic faces - d1-d3 (chiral reagents) and d4 (achiral or chiral reagents).

## IX. New Terminology vs. Literature Terminology

As noted in Chapter 17, with increasing stereochemical complexity of novel synthetic transformations, older terms are being gradually supplanted by newer terms. We noted the drawbacks for the existing set of terms, and demonstrated that our novel theoretical framework, for the stereochemical classification of chemical transformations, overcomes all the noted disadvantages. The universal terms advanced in the previous chapter were based on changes in stereogenic atoms. We now extend our terminology to describe changes in chirotopic atoms.

We illustrate the new terminology through examples of four substrates - abC=X, ag<sup>+</sup>C=X, adC=Cbc, and ag<sup>+</sup>C=Cbc - reacting with a variety of achiral and chiral reagents, in the presence and absence of chiral influences (solvent, catalyst, etc.). Substrates abC=X and adC=Cbc represent

		CHIROTOPOLYSIS		CHIROTOPOMUTATION		CHIROTOPGENESIS		e
Classification		Nonrotative (nr)	or Rotative (r)	Class		ac	c	
astereochiropolymer		nr	r	1A				
stereochiropolymer		nr	r	1B			Ss	
astereochirotopomutation		nr	r	2A	Ns			
nonchirotopomutation		nr	r	2B				
stereochirotopomutation		nr	r	3A				
astereochirotopogenesis		nr	r	3B				
stereochirotopogenesis		nr	r	4A	Ns Ss			
astereochirotopogenesis		nr	r	4B		Sa	Ss	
stereochirotopogenesis		nr	r	5A	Ns			
stereochirotopogenesis		nr	r	5B		Ns	Sa Ss	
astereochirotopogenesis		nr	r	6A	Aa	Ns Nne		
stereochirotopogenesis		nr	r	6B		Nas	Nne	
				7A	Na	Ns Nne		
				7B		Nas Nne	Sa Ss Sns Sne	
								ac : achiral reagent c : chiral reagent

Table 18.2. Chirotopolymer, Chirotopomutation and Chirotopogenesis at Enantiotopic Faces e

ac : achiral reagent  
c : chiral reagent

			d1	d2	d3	d4
Classification	Nonrotative (nr) or Rotative (r)	Class	ac c	ac c	ac c	ac c
astereochirotopolyisis	nr	1A	Sa Sas Sme			Sas Sme
	r	1B				Sas Sme
stereochoirotopolyisis	nr	2A		Nas Nme	Sa Ss Sas Sme	Sa Ss Sas Sme
	r	2B		Nas Nme		Sa Ss Sas Sme
astereochirotopomutation	nr	3A	Sa Ss Sas Sme			
	r	3B				Sa Ss
nonchirotopomutation	nr	4A	Aa Sa Sas Sme			
	r	4B				
stereochoirotopomutation	nr	5A			Ns Sa	Aa Nas Nme Sa Ss Sas Sme
	r	5B		Sas Sme	Sa Ss	Sa Sas Sme
astereochirotopogenesis	nr	6A	Aa	An Sa Aa Sas Sme	Aa Sa Sme	Nas
	r	6B			Ss	Aa Sa Sas Sme
stereochoirotopogenesis	nr	7A	Sa	Sn		
	r	7B	Sa	Sa Ss Sas Sme	Ss	Sa Ss Sas Sme

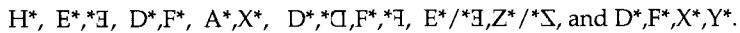
Table 18.3. Chirotopolyisis, Chirotopomutation, and Chirotopogenesis at Diastereotopic Faces d1-d4

molecules with enantiotopic faces;  $ag^+C=X$  and  $ag^+C=Cbc$  represent molecules with diastereotopic faces.

### A. $abC=X$

The stereotopoprocesses of this molecule were discussed in Figures 17.17-17.18 (pp. 53-54) of the previous chapter. We now discuss the same molecule, from the viewpoint of chirotopoprocesses, as depicted in Figures 18.21 and 18.22 (chiral influence).

In Figure 18.11, transformations 118-124 produce seven types of product(s):



The first one of these transformations (118) yields a single chiral product, and is described as a nonrotative nonchirotopomutation – one that is avectoselective and enantiofacioselective. Transformation 119, in contrast, yields a racemate; it is a case of nonrotative stereochirotopogenesis – nonvectoselective and enantiofaciononselective.

Transformation 120 generates two chiral diastereomers and is described as a rotative stereochirotopogenesis - nonvectoselective but enantiofacioselective. Transformation 121 produces two chiral nonequimers, and is a composite case - rotative chirotopogenesis (formation of **633=635**) and rotative stereochirotopogenesis (formation of **634=636**) - that happens to be characterized by nonequivectoselectivity and enantiofacioselectivity. Transformation 122 gives two racemic pairs of diastereomers and constitutes a nonrotative stereochirotopogenesis; it is diastereovectoselective and enantiofaciononselective. The next transformation (123) is also a nonrotative stereochirotopogenesis; it produces two racemic pairs of nonequimers in a nonequivectoselective and enantiofaciononselective conversion. Finally, transformation 124 leads to four chiral diastereostereomers in a nonequivectoselective and enantiofacioselective rotative stereochirotopogenesis.

Figure 18.22 portrays transformations 125-128 each of which is subject to a chiral influence. We point out the differences in the outcome of these transformations relative to those where the chiral influence is absent.

Transformation 125 is a nonrotative nonchirotopomutation (the counterpart of 118 where no chiral influence is exerted); the chiral influence is of no consequence, since all pathways converge onto a single chiral product  $H^*$ . Transformations 126-128 constitute rotative stereochirotopogeneses. In transformation 126 (the counterpart of transformation 119), the two enantiomers (**671=672** and **673=674**) are produced in unequal amounts owing to the involvement of diastereomeric transition states (**667** vs. **669**, and **668** vs. **670**). This is the classic case of an *asymmetric synthesis* - here also described as enantioselective synthesis. It satisfies the definition of "de novo synthesis of a chiral substance from an achiral precursor such that one enantiomer predominates over the other."<sup>9a</sup> Transformation 127 (the counterpart of transformation 122) yields two enantioenriched (=partially resolved) pairs of diastereomers **681,684** and **682,683** – the consequence of intervening diastereomeric/nonequimERIC sets of transition states **677-680**. This is an example of a *double asymmetric synthesis*, or, diastereoselective synthesis with concomitant enantioselective synthesis. Finally, transformation 128 (the counterpart of transformation 123) yields two enantioenriched (partially resolved) pairs of nonequimers **691,693** and **692,694** – here too, owing to the involvement of diastereomeric/nonequimERIC transition states, and to the interplay of nonequivectoselectivity and enantiofacioselectivity.

Transformation	Chirotopoprocess (Class)	Selectivity		Product(s)	$\Delta G^* + \Delta S^* = \Delta C$ (for each product)
118	nonrotative nonchirotopomutation (Class 4A)	avectoselective enantiofacioselective		H*	$(-0+0) + (-0+0) = 0$ $(-0+0) + (-0+0) = 0$ $(-0+0) + (-0+0) = 0$ $(-0+0) + (-0+0) = 0$
119	nonrotative stereochirotopogenesis (Class 7A)	nonvectoselective enantiofaciononselective (diastereoselective synthesis)		E*,*D	$(-0+5) + (-0+1) = 6$ $(-0+5) + (-0+1) = 6$ $(-0+5) + (-0+1) = 6$ $(-0+5) + (-0+1) = 6$
120	rotative stereochirotopogenesis (Class 7B)	nonvectoselective enantiofacioselective		D*,F*	$(-0+3) + (-2+3) = 4$ $(-0+3) + (-2+3) = 4$ $(-0+3) + (-2+3) = 4$ $(-0+3) + (-2+3) = 4$
121	rotative astereochirotopogenesis & rotative stereochirotopogenesis (Classes 6B & 7B)	nonequivvectoselective enantiofacioselective		A*,X*	$(-1+5) + (-1+1) = 4$ $(-1+5) + (-1+2) = 5$ $(-1+5) + (-1+1) = 4$ $(-1+5) + (-1+2) = 5$
122	rotative stereochirotopogenesis (Class 7A)	enantiofaciononselective diastereovectoselective (diastereoselective synthesis but not enantioselective synthesis)		D*,*Cl,F*,*I	$(-0+3) + (-2+3) = 4$ $(-0+3) + (-2+3) = 4$ $(-0+3) + (-2+3) = 4$ $(-0+3) + (-2+3) = 4$
123	nonrotative stereochirotopogenesis (Class 7A)	nonequivvectoselective enantiofaciononselective		E*,*D,Z*,*S	$(-0+5) + (-0+1) = 6$ $(-0+5) + (-0+1) = 6$ $(-0+5) + (-0+1) = 6$ $(-0+5) + (-0+1) = 6$
124	rotative stereochirotopogenesis (Class 7B)	nonequivvectoselective enantiofacioselective		D*,E*,X*,Y*	$(-1+4) + (-1+2) = 4$ $(-1+4) + (-1+2) = 4$ $(-1+4) + (-1+2) = 4$ $(-1+4) + (-1+2) = 4$

Figure 18.21. Examples of Transformations of abC=X

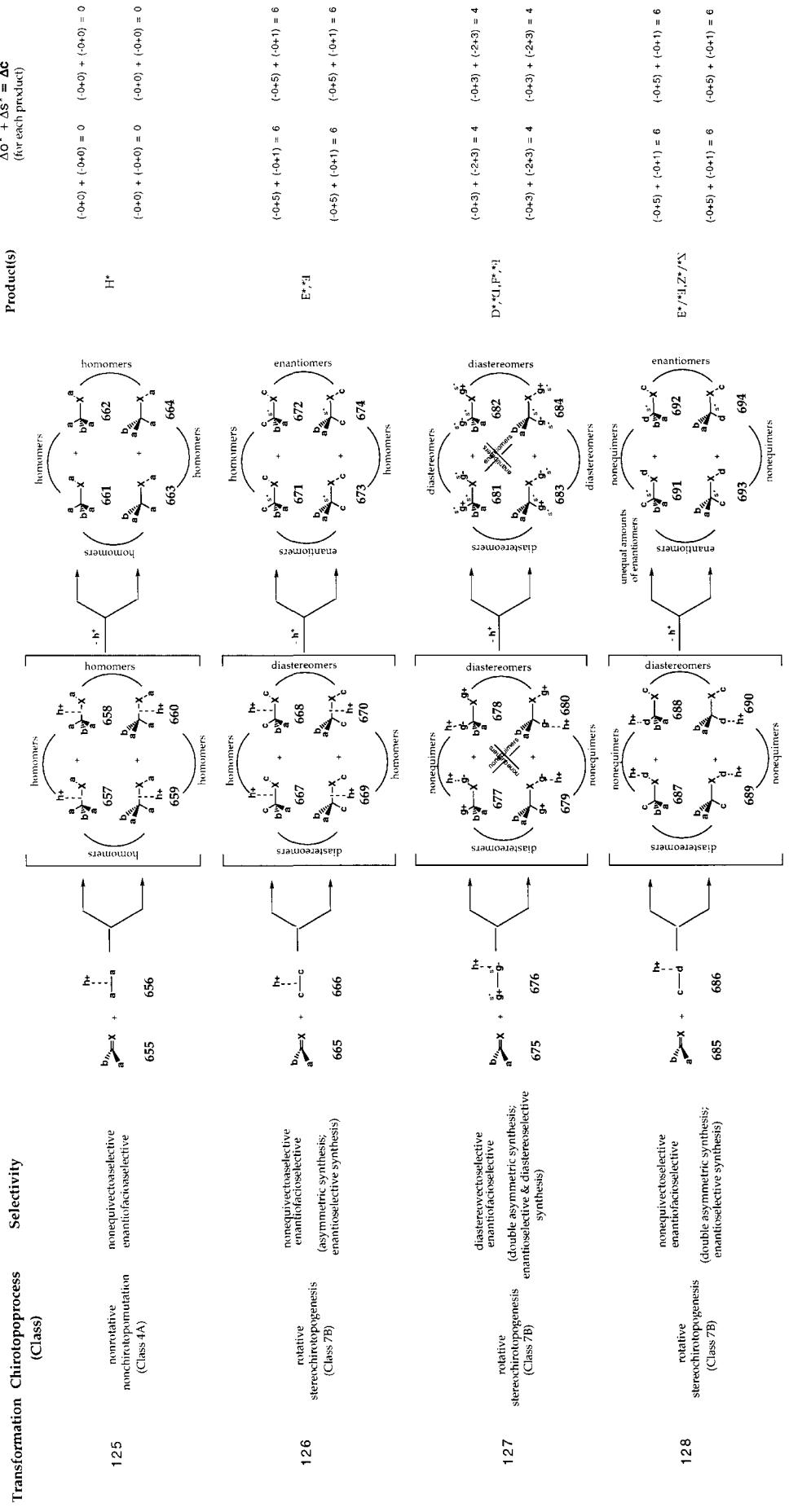


Figure 18.22. Examples of Transformations of abC=X (chiral influence)

### B. $\text{ag}^+\text{C=X}$

The stereotopoprocesses of this molecule were presented in Figures 17.19-17.21 (pp. 56-58) of the previous chapter. We now examine the corresponding chirotopoprocesses - as portrayed in Figures 18.23-18.25 (pp. 138-140). These transformations lead to the following product(s):

Transformations 129-133 :  $\text{H}^*, \text{A}^*, \text{X}^*, \text{and D}^*, \text{F}^*$

Transformations 134-139 :  $\text{D}, \text{F}, \text{X}^*, \text{D}^*, \text{F}^*, \text{G}^*, \text{D}^*, \text{F}^*, \text{X}^*, \text{D}^*, \text{F}^*, \text{X}, \text{Y}, \text{and D}^*, \text{F}^*, \text{X}^*, \text{Y}^*$

Transformations 140-143 :  $\text{H}^*, \text{D}^*, \text{F}^*, \text{D}^*, \text{F}^*, \text{G}^*, \text{and D}^*, \text{F}^*, \text{X}^*.$

Transformations 129 and 130 give the corresponding single chiral products  $\text{H}^* - 697 (=698=699=700)$  and  $703 (=704=705=706)$ , respectively. The former transformation is described as a rotative astereochirotopogenesis with attendant vectoaselectivity and diastereofacioaselectivity; the latter transformation is a rotative nonchirotopomutation that is vectoaselective and diastereofacioaselective. Transformation 131 gives two chiral nonequimers -  $709 (=711)$  and  $710 (=712)$ ; this is also a rotative nonchirotopomutation, albeit nonequivectoselective and diastereofacioaselective. Transformations 132 and 133 yield the corresponding pairs of chiral diastereomers -  $715 (=716), 717 (=718)$  and  $721 (=722), 723 (=724)$ , respectively, and are described as rotative stereochnirotopogeneses. The former one is a classic example of an *asymmetric induction*. Both of these transformations are vectoaselective and diastereofaciocoselective.

Transformation 134 (Figure 18.24) yields three diastereomers - two that are achiral (728 and 730) and one that is chiral (727 (=729)). The transformation is a composite case - rotative nonchirotopomutation and nonrotative astereochirotopolysis - and is characterized by nonequivectoselectivity and diastereofaciocoselectivity. The next transformation, 135, produces three chiral diastereomers -  $733 (=735), 734$  and  $736$  - and represents a case of dual rotative nonchirotopomutations - characterized by diastereovectoselectivity as well as diastereofaciocoselectivity. Each of transformations 136 and 137 yields two diastereomers and one nonequimer ( $740, 742, 739 (=741)$  and  $745, 747, 746 (=748)$ , respectively) - all three being chiral. The former transformation is a composite case of rotative astereochirotopogenesis and rotative stereochnirotopogenesis, while 137 is a composite case of rotative nonchirotopomutation and astereochirotopogenesis. They are both characterized by nonequivectoselectivity and diastereofaciocoselectivity. Transformation 138 yields two chiral diastereomers (751, 753) and two additional achiral diastereomers (752, 754) that are astereomeric with respect to the first two; the transformation represents a composite case of rotative nonchirotopomutation and nonrotative astereochirotopolysis, with attendant nonequivectoselectivity and diastereofaciocoselectivity. Finally, transformation 139 is a case of dual rotative nonchirotopomutations that result in two pairs of chiral astereomeric diastereomers, 757/759 and 758/760; these transformations are characterized by nonequivectoselectivity as well as diastereofaciocoselectivity.

Figure 18.25 (p. 140) depicts transformations 140-143 in which we examine the effect of the chiral influence on the reactions of  $\text{ag}+\text{C=X}$ . In these transformations, one notes the following changes relative to their counterparts where no chiral influence is exerted. In transformation 140 (the counterpart of 129), there is no overall effect, since all pathways converge onto a single product  $\text{H}^* - 767 (=768=769=770)$ . In transformation 141 (the counterpart of transformation 132), only two diastereomers (777=779 and 778=780) are expected to form, since the transformation is vectoaselective and diastereofaciocoselective. The next transformation, 142 (counterpart of transformation 135), yields three chiral diastereomers (787 (=789), 788, 790) in unequal amounts - the result of two diastereovectoselective and diastereofaciocoselective rotative nonchirotopomutations. Finally, transformation 143 (counterpart of transformation 136) leads to two chiral diastereomers - 798, 800 - and a chiral nonequimer 797 (=799). The process is a composite case of rotative astereochirotopogenesis and rotative stereochnirotopogenesis - overall nonequivectoselective and diastereofaciocoselective.

Transformation	Chirotopoprocess (Class)	Selectivity	Product(s)	$\Delta O^* + \Delta S^* = \Delta C$ (for each product)
129	rotative astereochirogenesis (Class 6f)	vectoselective diastereofaciaselective		$(-3+5) + (-0+0) = 2$ $(-3+5) + (-0+0) = 2$ $(-3+5) + (-0+0) = 2$ $(-3+5) + (-0+0) = 2$ $(-3+5) + (-0+0) = 2$ $(-3+5) + (-0+0) = 2$
130	rotative nonchiroisomerization (Class 4B)	vectoselective diastereofaciaselective		$(-3+5) + (-2+2) = 0$ $(-3+3) + (-2+2) = 0$ $(-3+3) + (-2+2) = 0$ $(-3+3) + (-2+2) = 0$ $(-3+3) + (-2+2) = 0$ $(-3+3) + (-2+2) = 0$
131	rotative nonchiroisomerization (Class 4B)	nonequivvectoselective diastereofaciaselective		$(-4+4) + (-1+1) = 0$ $(-4+4) + (-1+1) = 0$ $(-4+4) + (-1+1) = 0$ $(-4+4) + (-1+1) = 0$ $(-4+4) + (-1+1) = 0$ $(-4+4) + (-1+1) = 0$
132	rotative stereochirogenesis (Class 7B)	vectoselective diastereofaciaselective (asymmetric induction; diastereoselective synthesis)		$(-3+4) + (-0+1) = 1$ $(-3+4) + (-0+1) = 1$ $(-3+4) + (-0+1) = 1$ $(-3+4) + (-0+1) = 1$ $(-3+4) + (-0+1) = 1$ $(-3+4) + (-0+1) = 1$
133	rotative nonchiroisomerization (Class 4B)	vectoselective diastereofaciaselective (diastereoselective synthesis)		$(-3+2) + (-2+3) = 0$ $(-3+2) + (-2+3) = 0$ $(-3+2) + (-2+3) = 0$ $(-3+2) + (-2+3) = 0$ $(-3+2) + (-2+3) = 0$ $(-3+2) + (-2+3) = 0$

Figure 18.23. Examples of Transformations of  $\text{ag}^+\text{C}=\text{X}$

Transformation	Chirotoprocess (Class)	Selectivity		Products	$\Delta\sigma^* + \Delta S^* = \Delta C$ (for each product)
134	rotative nonchirotopomutation & nonrotative stereochirotopolyis (Classes 4B/1A)	nonequivtoselective diastereofacselective (diastereoselective synthesis & nonequimorphoselective synthesis)		D, F, X* D*, F*, G* D*, F*, X, Y*	(-4+0) + (-1+1) = 0 (-4+4) + (-1+1) = 0 (-4+4) + (-1+1) = 0 (-4+0) + (-1+1) = 0 (-4+0) + (-1+1) = -4
135	nonchirotopomutation (two-fold) (Class 4B)	diastereovtoselective diastereofacselective (double diastereoselective synthesis)		D, F, X* D*, F*, G* D*, F*, X, Y*	(-3+2) + (-2+3) = 0 (-3+3) + (-2+2) = 0 (-3+2) + (-2+3) = 0 (-3+4) + (-2+3) = 0 (-3+4) + (-2+3) = 0
136	rotative stereochirotopogenesis & rotative stereochirotopogenesis (Classes 6B/7B)	nonequivtoselective diastereofacselective (diastereoselective synthesis & nonequimorphoselective synthesis)		D, F, X* D*, F*, G* D*, F*, X, Y*	(-3+4) + (-0+1) = 1 (-3+4) + (-0+1) = 1 (-3+4) + (-0+1) = 1 (-3+4) + (-0+1) = 1 (-3+4) + (-0+1) = 2
137	rotative nonchirotopomutation & rotative stereochirotopogenesis (Classes 4B/6B)	nonequivtoselective diastereofacselective (diastereoselective synthesis & nonequimorphoselective synthesis)		D, F, X* D*, F*, G* D*, F*, X, Y*	(-3+4) + (-1+2) = 0 (-4+3) + (-1+2) = 0 (-4+3) + (-1+2) = 0 (-3+4) + (-1+2) = 0 (-3+4) + (-1+2) = 1
138	rotative nonchirotopomutation & nonrotative stereochirotopolyis (Class 4B)	nonequivtoselective diastereofacselective (double diastereoselective synthesis & nonequimorphoselective synthesis)		D, F, X*, D*, F*, G*, D*, F*, X, Y*	(-3+0) + (-1+1) = -3 (-3+2) + (-1+2) = 0 (-4+3) + (-1+2) = 0 (-4+3) + (-1+2) = 0 (-3+0) + (-1+1) = 0
139	rotative nonchirotopomutation (two-fold) (Class 4B)	(double diastereoselective synthesis & nonequimorphoselective synthesis)		D, F, X*, D*, F*, G*, D*, F*, X, Y*	(-3+2) + (-2+3) = 0 (-3+2) + (-2+3) = 0 (-3+2) + (-2+3) = 0 (-3+2) + (-2+3) = 0 (-3+2) + (-2+3) = 0

Figure 18.24. Examples of Composite Transformations of ag<sup>+</sup>C=X

Transformation	Chirotopoprocess (Class)	Selectivity	Product(s)
140	relative astereochirotopogenesis (Class 6B)	vecto-selective diastereofactoselective	$\Delta O^* + \Delta S^* = \Delta C$ (for each product)
141	relative stereochirotopogenesis (Class 7B)	vecto-selective diastereofactoselective (asymmetric induction; diastereoselective synthesis)	$\Delta O^* + \Delta S^* = \Delta C$ (for each product)
142	relative nonchirotopomutation (two-fold) (Class 4B)	disastero-selective (double diastereoselective synthesis)	$\Delta O^* + \Delta S^* = \Delta C$ (for each product)
143	relative astereochirotopogenesis & relative stereochirotopogenesis (Class 6B/7B)	nonequivalento-selective diastereoselective synthesis & nonequimorphoselective synthesis	$\Delta O^* + \Delta S^* = \Delta C$ (for each product)

Figure 18.25. Examples of Transformations of ag+C=X (chiral influence)

### C. adC=Cbc

Stereotopoprocesses of this molecule were portrayed in Figures 17.22-17.24 (pp. 60-62). We now discuss the analogous chirotopoprocesses (Figures 18.26-18.28, pp. 142-143). It turns out that transformations 144-152 generate nine types of product mixtures - E\*,\*E D\*,F\*, E\*,\*E,D, E\*,\*E,N, E\*,\*E,D\*,\*D, E\*,\*E,N\*,\*N, D\*,F\*,G\*,J\*, D\*,F\*,M\*,N\*, and D\*,F\*,M\*,N; transformations 153-158 lead to the following six product mixtures - E\*,\*E, E\*,\*E,D, E\*,\*E,N, E\*,\*E,D\*,\*D, E\*,\*E,N\*,\*N, and D\*,F\*,M\*,N.

In Figure 18.26, transformation 144 produces a racemic mixture - 803(=804)/805(=806). The process is a nonrotative stereochirotopogenesis - one that is avectoselective and enantiofaciononselective. Transformation 145, leading to two chiral diastereomers, 809(=810) and 811(=812), is an avectoselective and enantiofacioselective rotative stereochirotopogenesis. Transformation 146 gives a racemate, 816/818, along with an achiral diastereomer, 815(=817) - it is a diastereovectoselective nonrotative stereochirotopogenesis that is enantiofacioselective (815=817) and, simultaneously, enantiofaciononselective (enantiomers 816/818 are formed in equal amounts). The next transformation, 147, yields a racemate, 822/824, and an achiral astereomer, 821(=823) - the composite result of nonrotative astereochirotopogenesis and nonrotative stereochirotopogenesis - with attendant astereovectoselectivity and, again, a combined case of enantiofacioselectivity/enantiofaciononselectivity. Next, transformation 148, yielding two diastereomeric racemates, 827/830 and 828/829, is a nonrotative stereochirotopogenesis that is diastereovectoselective and enantiofacioselective with respect to both sets of products. Transformation 149 is similar to 148 - an astereovectoselective and enantiofaciononselective nonrotative stereochirotopogenesis yielding two astereomeric racemates - 833/835 and 834/836.

Turning to Figure 18.27, we note that transformation 150 is a rotative stereochirotopogenesis that is diastereovectoselective and enantiofacioselective - resulting in the formation of four chiral diastereomers, 839-842. This process would have been considered, in the older terminology, a case of double diastereoselective synthesis. Finally, each of transformations 151 and 152 yields two astereomeric sets of diastereomeric pairs, 845,846, 847,848 and 851,852, 853,854, respectively. Both transformations are rotative stereochirotopogeneses, with attendant astereovectoselectivity and enantiofacioselectivity.

Figure 18.28 portrays transformations 153-158 in which we consider the effect of the chiral influence. In transformation 153 (the counterpart of 144 where no chiral additional chiral influence is exerted), the effect is to generate an enantioenriched mixture of two enantiomers, 861(=862), 863(=864). The process is a rotative stereochirotopogenesis; there is a net loss of one stereogen, but concomitant generation of a rotative substance! In transformation 154 (the counterpart of transformation 146), one discerns a nonrotative stereochirotopogenesis - which process is enantiofacioselective (871 and 873 are homomers) and, simultaneously, enantiofacioselective (enantiomers 872 and 874 are formed in unequal amounts). It is interesting to note that 871 and 873, which are homomers, would be formed in unequal amounts, since they arise from diastereomeric transition states; naturally, this would be undetected experimentally. Transformation 155 (the counterpart of 147) yields an enantioenriched mixture of two enantiomers, 882,884, and an achiral astereomer, 881(=883). The overall conversion would be described as composite nonrotative astereochirotopogenesis/rotative stereochirotopogenesis, characterized by astereovectoselectivity, enantiofacioselectivity, as well as enantiofacioselectivity (the homomers again being formed in unequal amounts). The next transformation, 156 (the counterpart of 148), yields a mixture of two enantioenriched diastereomers, 891,894 and 892,893 - a case of double asymmetric synthesis or double diastereoselective synthesis - using the older terminology. This transformation, from the new viewpoint, constitutes a rotative stereochirotopogenesis that is diastereovectoselective and enantiofacioselective. Transformation 157 (the counterpart of 149) is astereovectoselective and enantiofacioselective; it yields two enantioenriched mixtures of astereomers, 901,903 and 902,904 - also a case of double asymmetric synthesis, or, a diastereoselective and astereomorphoselective synthesis. Finally, transformation 158 presents an interesting and

Transformation	Chirotopoprocess (Class)	Selectivity	Products
$\Delta O^* + \Delta S^* = \Delta C$ (for each product)			
144	nonrotative stereochirotopogenesis (Class 7A)	avectoselective enantiofacioselective	 enantiomers diastereomers homomers $(-0.7) + (0.1) = 8$ $(-0.7) + (0.1) = 8$ $(-0.7) + (0.1) = 8$ $(-0.7) + (0.1) = 8$
145	nonrotative stereochirotopogenesis (Class 7B)	avectoselective enantiofacioselective (diasteroselective synthesis)	 diastereomers homomers $(-1.5) + (-0.2) = 6$ $(-1.5) + (-0.2) = 6$ $(-1.5) + (-0.2) = 6$ $(-1.5) + (-0.2) = 6$
146	nonrotative stereochirotopogenesis (two-fold) (Class 7A)	diastereovectoselective enantiofacioselective & enantiofacioselective	 stereoisomers homomers diastereomers enantiomers $(-0.6) + (-0.3) = 9$ $(-0.6) + (-0.3) = 9$ $(-0.6) + (-0.3) = 9$ $(-0.6) + (-0.3) = 9$
147	nonrotative stereochirotopogenesis & nonrotative stereochirotopogenesis (Classes 6A / 7A)	astereovectoselective enantiofacialselective & enantiofacialselective	 stereoisomers homomers diastereomers astereomers $(-0.6) + (-0.2) = 8$ $(-0.6) + (-0.2) = 8$ $(-0.6) + (-0.2) = 8$ $(-0.6) + (-0.2) = 8$
148	nonrotative stereochirotopogenesis (Class 7A)	diastereovectoselective enantiofacialselective	 stereoisomers diastereomers astereomers $(-0.4) + (-0.3) = 7$ $(-0.4) + (-0.3) = 7$ $(-0.4) + (-0.3) = 7$ $(-0.4) + (-0.3) = 7$
149	nonrotative stereochirotopogenesis (two-fold) (Class 7A)	astereovectoselective enantiofacionselective	 stereoisomers diastereomers astereomers $(-0.6) + (-0.2) = 8$ $(-0.6) + (-0.2) = 8$ $(-0.6) + (-0.2) = 8$ $(-0.6) + (-0.2) = 8$

Figure 18.26. Examples of Transformations of adC=CbC

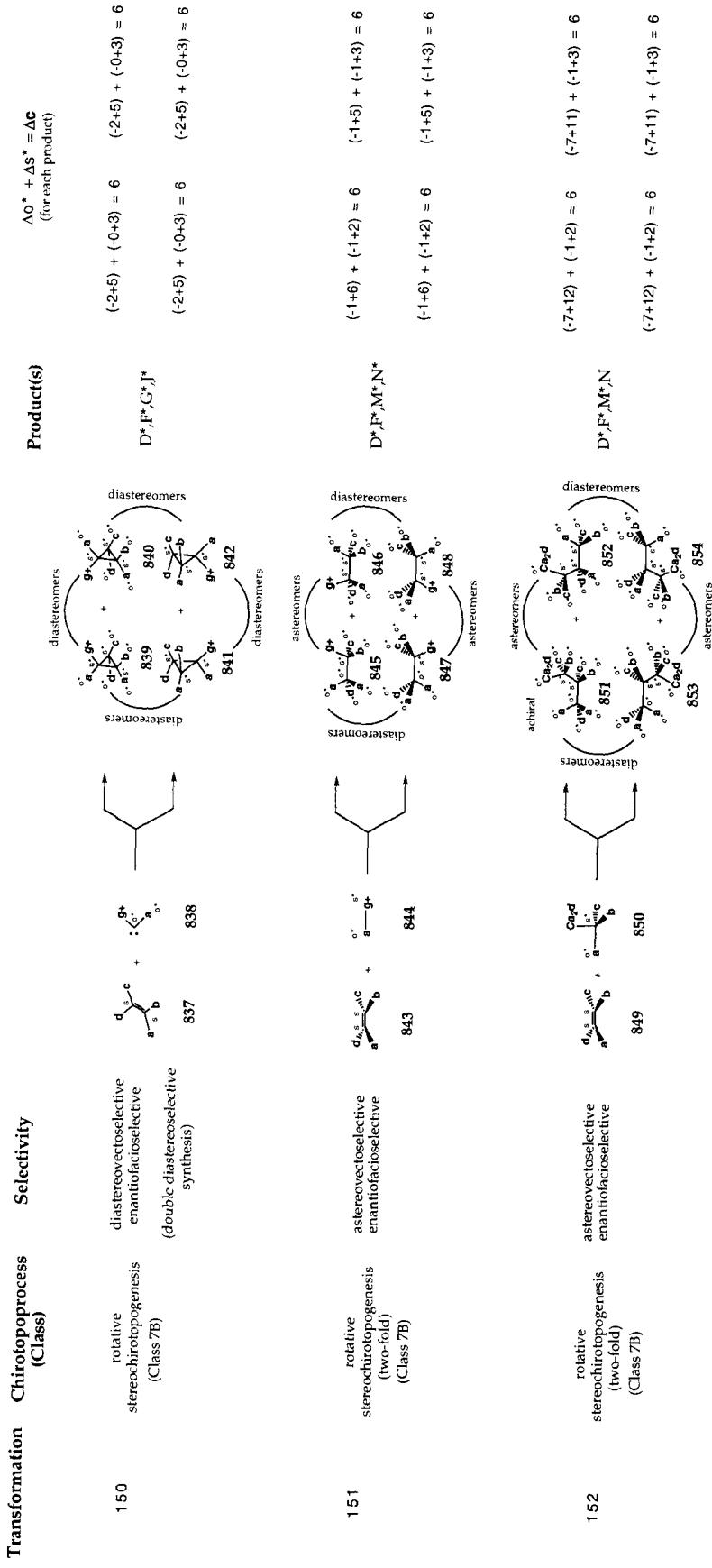


Figure 18.27. Examples of Transformations of adC=Cbc

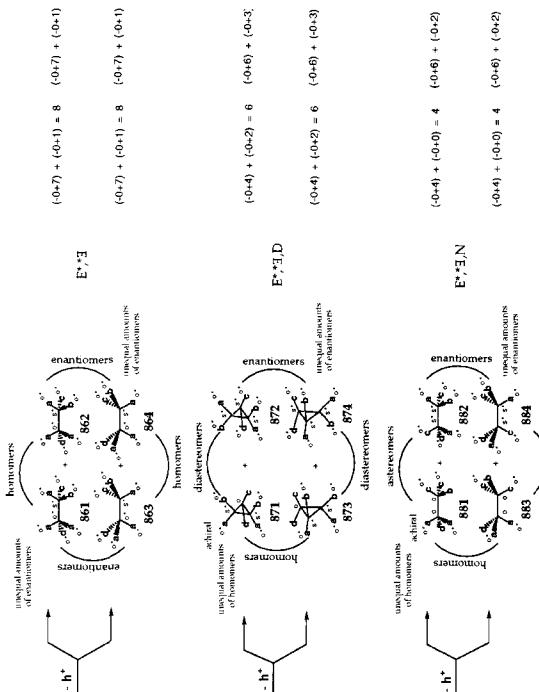
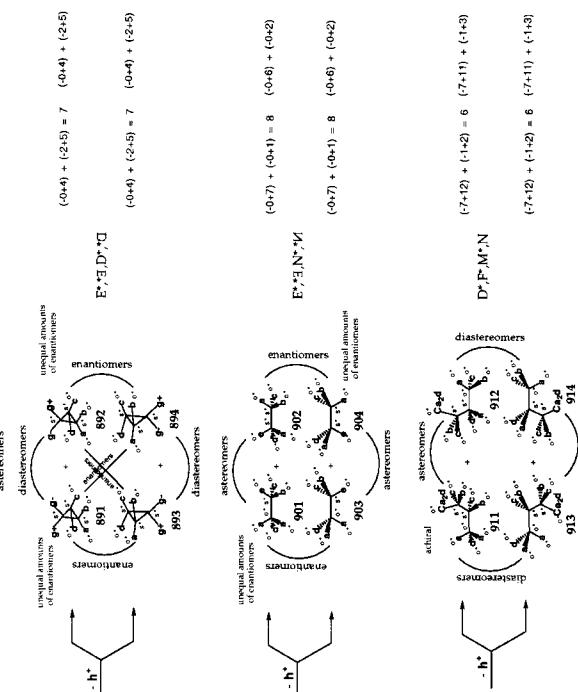
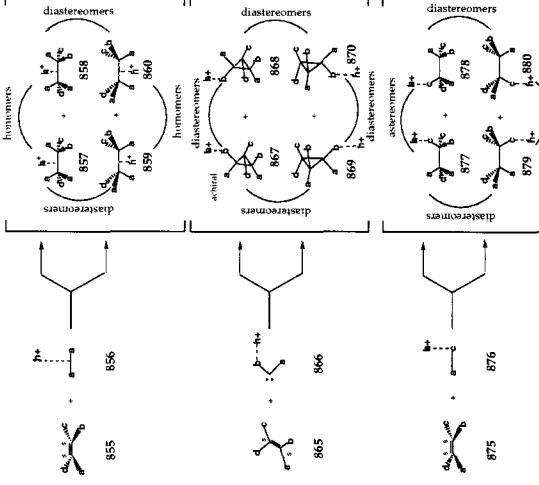
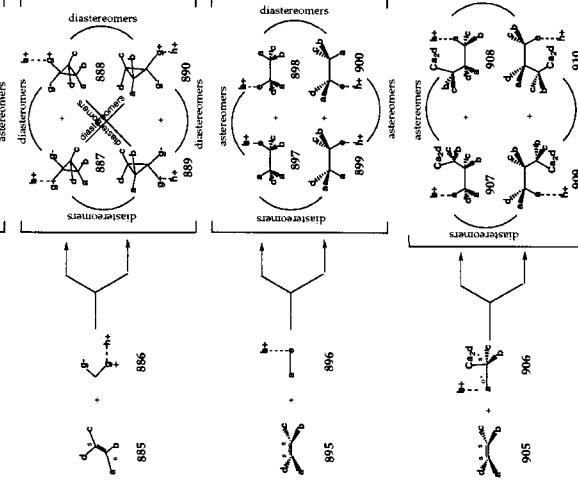
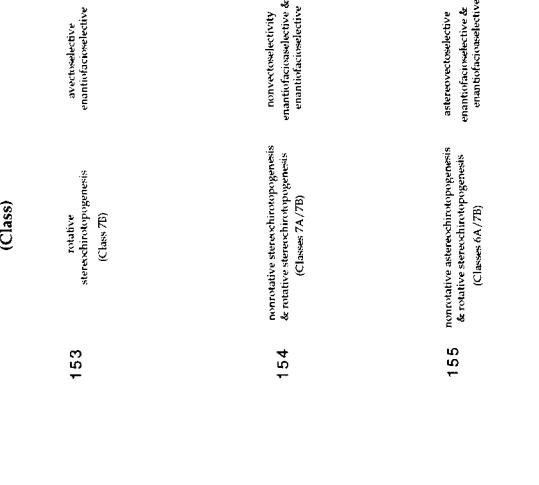
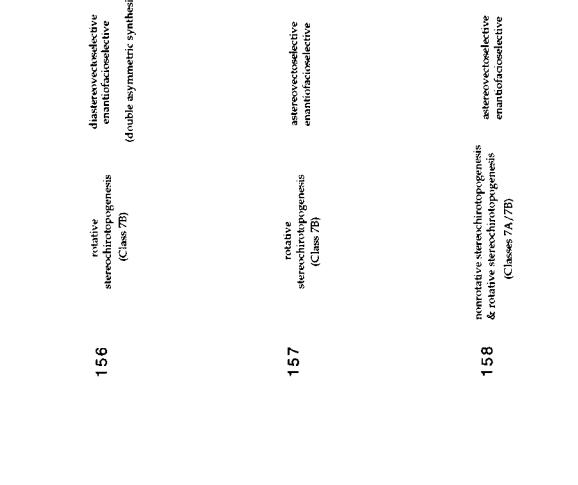
Transformation	Chirotoprocess (Class)	Selectivity	Products	$\Delta O^* + \Delta S^* = \Delta C$ (for each product)
153	rotative stereochirtopogenesis (Class 7B)	asymmetric-selective enantiomeric-selective		(-0.7) + (-0.1) = 8    (-0.7) + (-0.1)
154	nonrotative stereochirtopogenesis & rotative stereochirtopogenesis (Classes 7A/7B)	nonchirality-selective & enantiomeric-selective		(-0.4) + (-0.2) = 6    (-0.6) + (-0.3) (-0.7) + (-0.1) = 8    (-0.7) + (-0.1)
155	nonrotative stereochirtopogenesis & rotative stereochirtopogenesis (Classes 6A/7B)	asymmetric-selective & enantiomeric-selective		(-0.4) + (-0.2) = 6    (-0.6) + (-0.3) (-0.7) + (-0.1) = 8    (-0.7) + (-0.1)
156	rotative stereochirtopogenesis (Class 7B)	diastereovectoselective enantiomeric-selective (double symmetric synthesis)		(-0.4) + (-2.5) = 7    (-0.4) + (-2.5) (-0.4) + (-2.5) = 7    (-0.4) + (-2.5)
157	rotative stereochirtopogenesis (Class 7B)	asymmetric-selective enantiomeric-selective		(-0.7) + (-0.1) = 8    (-0.6) + (-0.2) (-0.7) + (-0.1) = 8    (-0.6) + (-0.2)
158	nonrotative stereochirtopogenesis & rotative stereochirtopogenesis (Classes 7A/7B)	asymmetric-selective enantiomeric-selective		(-7.12) + (-1.2) = 6    (-7.12) + (-1.2) = 6 (-7.12) + (-1.2) = 6    (-7.12) + (-1.2) = 6

Figure 18.28. Examples of Transformations of adC=Cbc (chiral influence)

unique instance where one obtains two chiral diastereomers - 912 and 914 - along with two astereomers (one chiral, 913, and the other one achiral, 911!). This transformation is a rotative stereochirotopogenesis that is astereovectoselective and enantiofacioselective.

#### D. ag<sup>+</sup>C=Cbc

Stereotopoprocesses of this molecule were presented in Figures 17.25-17.27 (pp. 64-66), and the chiral influence was explored through the transformations in Figures 17.28-17.30 (pp. 67-69). We now examine the corresponding chirotopoprocesses, as portrayed in Figures 18.29-18.33 (pp. 146-150). Transformations 160-184, depicted in these figures, lead to four types of product mixtures:



In Figure 18.29 (p. 146), each of transformations 159-161 leads to two chiral diastereomers  $D^*, F^*$  ( $917 (=918), 919 (=920); 923 (=924), 925 (=926); 929 (=930), 931 (=932)$ ) and constitutes a vectoaselective and diastereofacioselective rotative astereochirotopogenesis. By way of comparison, in Figure 17.25 (p. 64), the first two stereotopoprocesses were classified as rotative chirostereotopolyses and the third one, as rotative chirostereotopomutation; these transformations would be described, alternately, as diastereoselective syntheses. Curiously, transformations 105 and 106 are  $sp^3$  chirostereotopolyses but, simultaneously, astereochirotopogeneses as well!

Transformation 162 yields three chiral diastereomers - 935( $=937$ ), 936, and 938. This transformation is also a rotative astereochirotopogenesis; however, it is astereovectoselective, diastereofacioselective *and* diastereofacioselective - all at the same time. Transformations 163-167 yield four chiral diastereomers each - 941-944, 947-950, 953-956, 959-962. Under the current system, all five transformations would be described as double diastereoselective syntheses. In our new terminology, transformations 163 (Figure 18.29), 164, 165 and 167 (Figure 18.30) constitute rotative stereochirotopogeneses, while 166 (Figure 18.30) is a rotative nonchiropomutation; all five transformations are diastereovectoselective and concomitantly diastereofacioselective. Each one of the remaining six transformations, 168 (Figure 18.30) and 169-173 (Figure 18.31), yields two pairs of astereomeric diastereomers - 971-974, 977-980, 983-986, 989-992, 995-998 and 1001-1004; these transformations are astereovectoselective and diastereofacioselective. Here too, we notice subtle differentiations among them. Transformations 168, 170, 171, and 173 are rotative astereochirotopogeneses, while 169 and 172 are rotative nonchiropomutations.

Transformations 174-184 (Figures 18.32 and 18.33) reveal the effect of the chiral influence. Transformations 174-176 (the counterparts of 159-161) would be described as diastereoselective syntheses as they yield two chiral diastereomers each - 1011(1012), 1013( $=1014$ ), 1021( $=1022$ ), 1023( $=1024$ ) and 1031( $=1032$ ), 1033(1034). With our new terminology, all three transformations are vectoaselective but diastereofacioselective rotative astereochirotopogeneses. Transformation 177 (the counterpart of 162) leads to two chiral diastereomers (1042, 1044) along with a chiral astereomer (1041( $=1043$ )). The process is a rotative astereochirotopogenesis - characterized by astereovectoselectivity, diastereofacioselectivity, *and* diastereofacioselectivity. Each one of the next three transformations (178 (Figure 18.32) and 179-180 (Figure 18.33) - the counterparts of 163-165), generates four chiral diastereomers (1051-1054, 1061-1064, 1071-1074) - all double diastereoselective processes. The first one, in fact, is a rotative nonchiropomutation, while the last two are rotative stereochirotopogeneses. The remaining transformations (181-184 - the counterparts of 168, 170, 171, 173) are rotative astereochirotopogeneses that are astereovectoselective and diastereofacioselective, because each one of them leads to two astereomeric sets of diastereomers (1081, 1083, 1082, 1084; 1091, 1093, 1092, 1094; 1101, 1103, 1102, 1104; 1111, 1113, 1112, 1114) - all products being chiral.

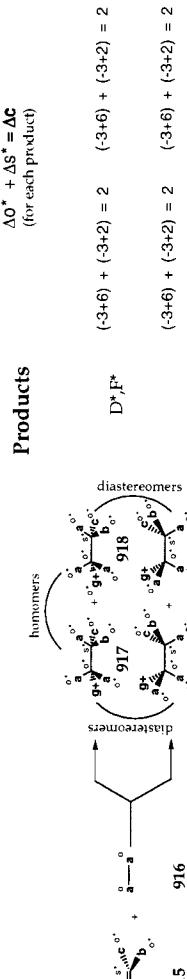
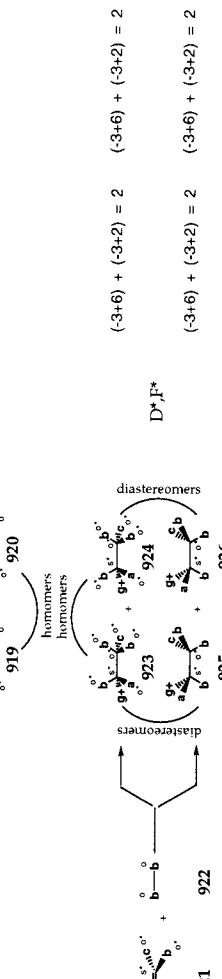
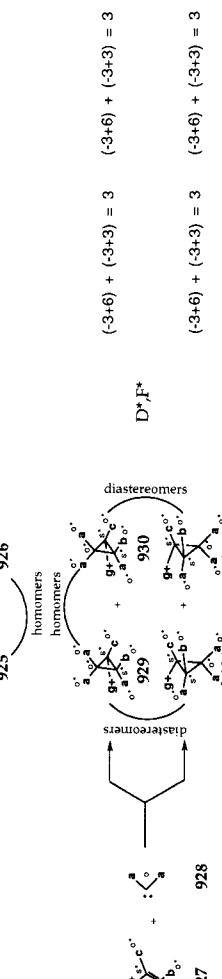
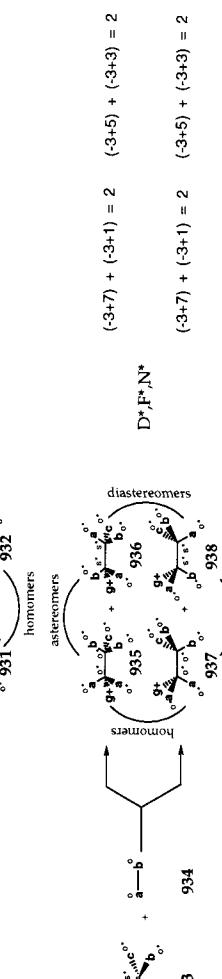
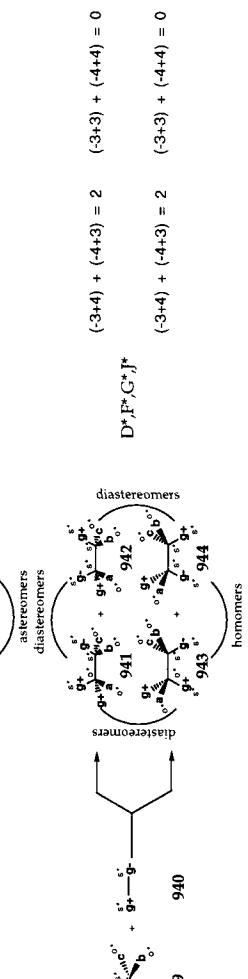
Transformation	Chirotopoprocess (Class)	Selectivity	Products
159	relative astereochirotopogenesis (Class 6B)	vecto-selective diastereofaciocoselective (diastereoselective synthesis)	
160	relative astereochirotopogenesis (Class 6B)	vecto-selective diastereofaciocoselective (diastereoselective synthesis)	
161	relative astereochirotopogenesis (Class 6B)	vecto-selective diastereofaciocoselective (diastereoselective synthesis)	
162	relative astereochirotopogenesis (Class 6B)	astereovecto-selective diastereofaciocoselective diastereofaciocoselective	
163	rotative stereochoirotopogenesis & rotative nonchirorotation (Class 7B/4B)	diastereovecto-selective diastereovecto-selective (two-fold)	

Figure 18.29. Examples of Transformations of  $\text{ag}^+ \text{C}=\text{Cbc}$

Transformation	Chirotoprocess (Class)	Selectivity	Products
164	rotative stereochirotopogenesis (two fold) (Class 7B)	diastereovectoselective diastereofacioidoselective	$\Delta\alpha^* + \Delta S^* = \Delta C$ (for each product)
945	946		$(-3+5) + (-2+3) = 3$ $D^*, F^*, G^*, J^*$
947	948		$(-3+5) + (-2+3) = 3$ $D^*, F^*, G^*, J^*$
949	950		$(-3+5) + (-2+3) = 3$ $(-3+5) + (-2+3) = 3$ $D^*, F^*, G^*, J^*$
165	rotative stereochirotopogenesis (Class 7B)	diastereovectoselective diastereofacioidoselective	$(-3+5) + (-2+3) = 3$ $D^*, F^*, G^*, J^*$
951	952		$(-3+5) + (-2+3) = 3$ $D^*, F^*, G^*, J^*$
953	954		$(-3+5) + (-2+3) = 3$ $D^*, F^*, G^*, J^*$
955	956		$(-3+5) + (-2+3) = 3$ $D^*, F^*, G^*, J^*$
166	rotative nonchirotopomutation (Class 4B)	diastereovectoselective diastereofacioidoselective	$(-3+4) + (-2+3) = 0$ $(-5+4) + (-2+3) = 0$ $D^*, F^*, G^*, J^*$
957	958		$(-3+4) + (-2+3) = 0$ $(-5+4) + (-2+3) = 0$ $D^*, F^*, G^*, J^*$
959	960		$(-3+4) + (-2+3) = 0$ $(-5+4) + (-2+3) = 0$ $D^*, F^*, G^*, J^*$
961	962		$(-3+4) + (-2+3) = 0$ $(-5+4) + (-2+3) = 0$ $D^*, F^*, G^*, J^*$
167	rotative stereochirotopogenesis (Class 7B)	diastereovectoselective diastereofacioidoselective	$(-3+3) + (-2+3) = 1$ $D^*, F^*, G^*, J^*$
963	964		$(-3+3) + (-2+3) = 1$ $D^*, F^*, G^*, J^*$
965	966		$(-3+3) + (-2+3) = 1$ $D^*, F^*, G^*, J^*$
967	968		$(-3+3) + (-2+3) = 1$ $D^*, F^*, G^*, J^*$
168	rotative astereochirotopogenesis (Class 6B)	astereovectoselective astereofacioidoselective	$(-3+6) + (-2+1) = 2$ $D^*, F^*, M^*, N^*$
969	970		$(-3+6) + (-2+1) = 2$ $(-3+6) + (-2+1) = 2$ $D^*, F^*, M^*, N^*$
971	972		$(-3+6) + (-2+1) = 2$ $(-3+6) + (-2+1) = 2$ $D^*, F^*, M^*, N^*$
973	974		$(-3+6) + (-2+1) = 2$ $(-3+6) + (-2+1) = 2$ $D^*, F^*, M^*, N^*$

Figure 18.30. Examples of Transformations of  $\text{ag}^+\text{C}=\text{Cbc}$

Transformation	Chirotopoprocess (Class)	Selectivity	Products
169	rotative nonchirotopopomutation (Class 4B)	astereovectoselective diastereofacioselective	<p style="text-align: center;"><math>\Delta O^* + \Delta S^* = \Delta C</math> (for each product)</p> <p style="text-align: center;">(4+5) + (-3+2) = 0      (4+5) + (-3+2) = 0</p> <p style="text-align: center;">(-4+5) + (-3+2) = 0      (-4+5) + (-3+2) = 0</p>
170	rotative astereochirotopogenesis (Class 6B)	astereovectoselective diastereofacioselective	<p style="text-align: center;">(3+6) + (-2+1) = 3      (3+6) + (-2+1) = 3</p> <p style="text-align: center;">(-3+5) + (-2+2) = 2      (-3+6) + (-2+1) = 3</p> <p style="text-align: center;">(-3+5) + (-2+2) = 2      (-3+6) + (-2+1) = 3</p>
171	rotative astereochirotopogenesis (Class 6B)	astereovectoselective diastereofacioselective	<p style="text-align: center;">(3+6) + (-2+1) = 2      (3+5) + (-2+1) = 2</p> <p style="text-align: center;">(-3+5) + (-2+2) = 2      (-3+6) + (-2+1) = 2</p>
172	rotative nonchirotopomutation (Class 4B)	astereovectoselective diastereofacioselective	<p style="text-align: center;">(4+4) + (-3+3) = 0      (4+4) + (-3+3) = 0</p> <p style="text-align: center;">(-4+5) + (-3+2) = 0      (-4+5) + (-3+2) = 0</p>
173	rotative astereochirotopogenesis (Class 6B)	astereovectoselective diastereofacioselective	<p style="text-align: center;">(3+5) + (-2+2) = 2      (3+5) + (-2+2) = 2</p> <p style="text-align: center;">(-3+5) + (-2+2) = 2      (-3+5) + (-2+2) = 2</p>

Figure 18.31. Examples of Transformations of  $ag^+C=Cbc$

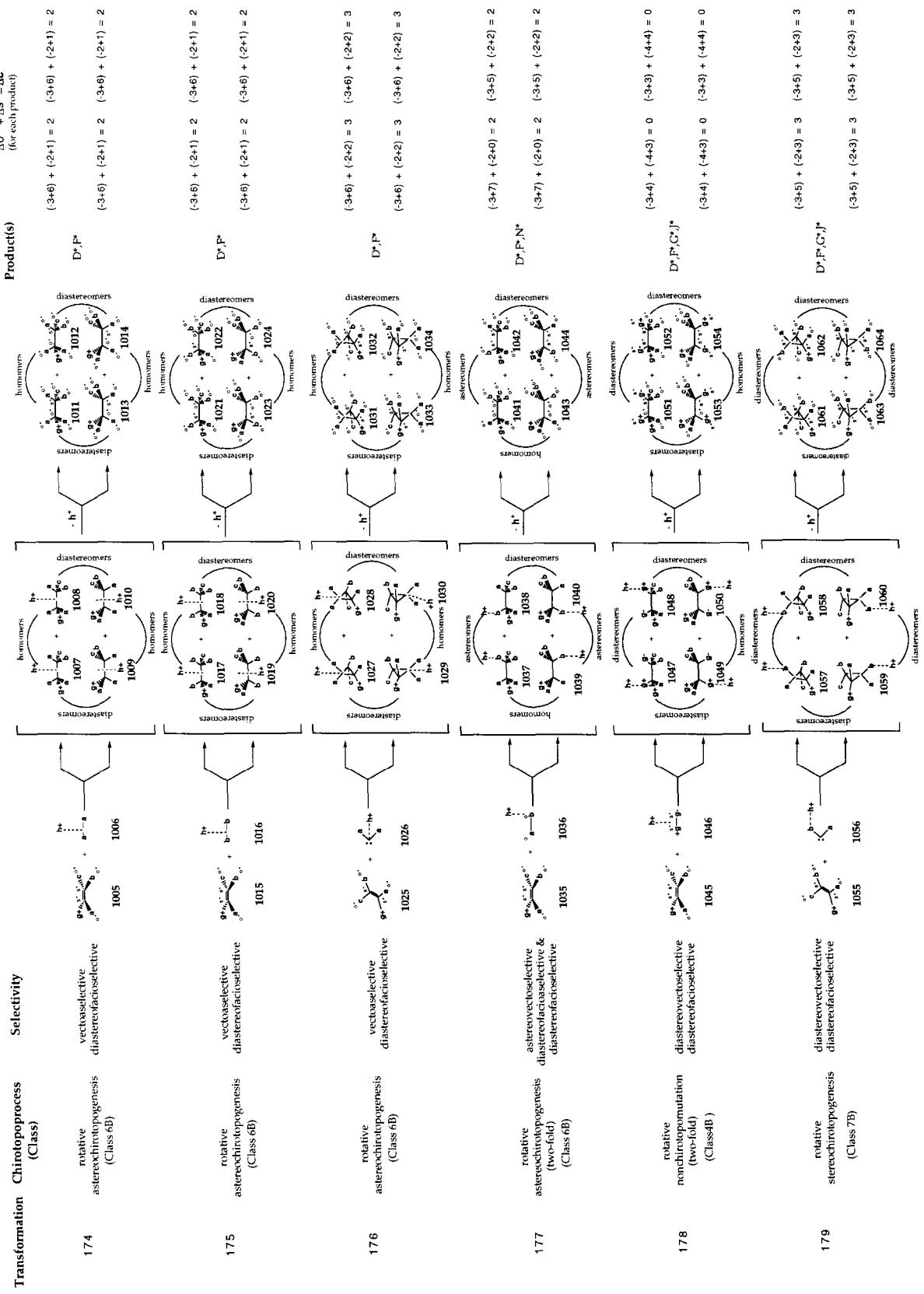


Figure 18.32. Examples of Transformations of ag<sup>+</sup>C=Cbc (chiral influence)

Transformation Chirotopoprocess (Class)	Selectivity	Products	$\Delta\sigma^* + \Delta S^* = \Delta C$ (for each product)
180 rotative stereochirotopogenesis (Class 7B)	diastereovectorselective diastereofacselective	 Diastereomers: 1071, 1072, 1073, 1074. Diastereoisomers: 1067, 1068, 1069, 1070.	$(-3+5) + (2+3) = 3$ $(-3+5) + (-2+3) = 3$ $(-3+5) + (2+3) = 3$ $(-3+5) + (-2+3) = 3$
181 rotative asterochirotopogenesis (Class 6B)	asterovertectorselective diastereofacselective	 Diastereomers: 1077, 1078, 1079, 1080. Diastereoisomers: 1075, 1076, 1081, 1082, 1083, 1084.	$(-3+6) + (2+1) = 2$ $(-3+5) + (2+2) = 2$ $(-3+6) + (2+1) = 2$ $(-3+5) + (2+2) = 2$
182 rotative asterochirotopogenesis (two-fold) (Class 6B)	asterovertectorselective diastereofacselective	 Diastereomers: 1085, 1086, 1093, 1094. Diastereoisomers: 1075, 1076, 1087, 1088, 1089, 1090, 1091, 1092, 1093, 1094.	$(-3+6) + (2+1) = 2$ $(-3+6) + (2+2) = 2$ $(-3+6) + (2+1) = 2$ $(-3+5) + (2+2) = 2$
183 rotative asterochirotopogenesis (two-fold) (Class 6B)	asterovertectorselective diastereofacselective	 Diastereomers: 1095, 1096, 1100, 1101. Diastereoisomers: 1085, 1086, 1097, 1098, 1099, 1100, 1101, 1102, 1103.	$(-3+6) + (2+1) = 2$ $(-3+6) + (2+2) = 2$ $(-3+6) + (2+1) = 2$ $(-3+5) + (2+2) = 2$
184 rotative asterochirotopogenesis (Class 6B)	asterovertectorselective diastereofacselective	 Diastereomers: 1105, 1106, 1109, 1110. Diastereoisomers: 1105, 1106, 1112, 1113, 1114.	$(-3+5) + (2+2) = 2$ $(-3+5) + (2+2) = 2$ $(-3+5) + (2+2) = 2$ $(-3+5) + (2+2) = 2$

Figure 18.33. Examples of Transformations of  $\text{ag}^+\text{C}=\text{Cbc}$  (chiral influence)

## X. Chiroselectivity, Nonchiroselectivity, Achiroselectivity

The concepts of chiroselectivity, nonchiroselectivity and achiroselectivity apply to transformations that lead to mixtures of chiral and/or achiral products.<sup>16</sup> A *chiroselective* reaction is one in which one or more chiral products are formed in excess of any achiral one(s).

An *achiroselctive* reaction is one in which one or more achiral products are formed in excess of any chiral one(s). A *nonchiroselective* reaction is one in which achiral and chiral products are formed in equal amounts.

Figure 18.34 illustrates chiroselective, nonchiroselective and achiroselctive transformations.

Transformation 185 is chiroselective because it produces two chiral products (1117 and 1118); no achiral product is expected. Transformation 186 is also chiroselective, if the chiral product (1121) is formed in excess of the two diastereomeric achiral products (1122,1123). In contrast, transformation 187 is nonchiroselective if the amount of chiral products (1126+1127) is *equal* to that of the achiral product 1128. Transformations 188,189a/b, in contradistinction, are achiroselctive since only achiral products (1131 and 1132, 1135 and 1136) are anticipated.

## XI. Quantitation of Chiroselectivity and Chirospecificity

Chiroselectivity and chirospecificity (*vide infra*), just like stereospecificity, stereoselectivity, regioselectivity, and facioselectivity, become non-transparent, and experimentally verifiable, with the proper substrates (see p. 74). The chiroselectivity or chirospecificity of an S<sub>N</sub>2 process cannot be established using CH<sub>3</sub>I or iodocyclohexane as substrates. The chirospecificity becomes nontransparent and is established experimentally when one uses 4-*t*-butyliodocyclohexane or enantiopure 2-octyl iodide. Surely, the inversions occur with CH<sub>3</sub>I or iodocyclohexane as well; however, with the latter two substrates, they are experimentally unverifiable.

Chiroselectivity is defined by the following equation:

$$\% \text{ chiroselectivity} = (\% \text{ chiral products} - \% \text{ achiral products}) \quad (18.4)$$

For partially chiroselective transformations, % chiroselectivity is a positive number, the upper limit being 100%.

Achiroselctivity is defined by Equation 18.5:

$$\% \text{ achiroselctivity} = (\% \text{ achiral products} - \% \text{ chiral products}) \quad (18.5)$$

For partially achiroselctive transformations, % achiroselctivity is also a positive number. At the upper limit, it can be 100%.

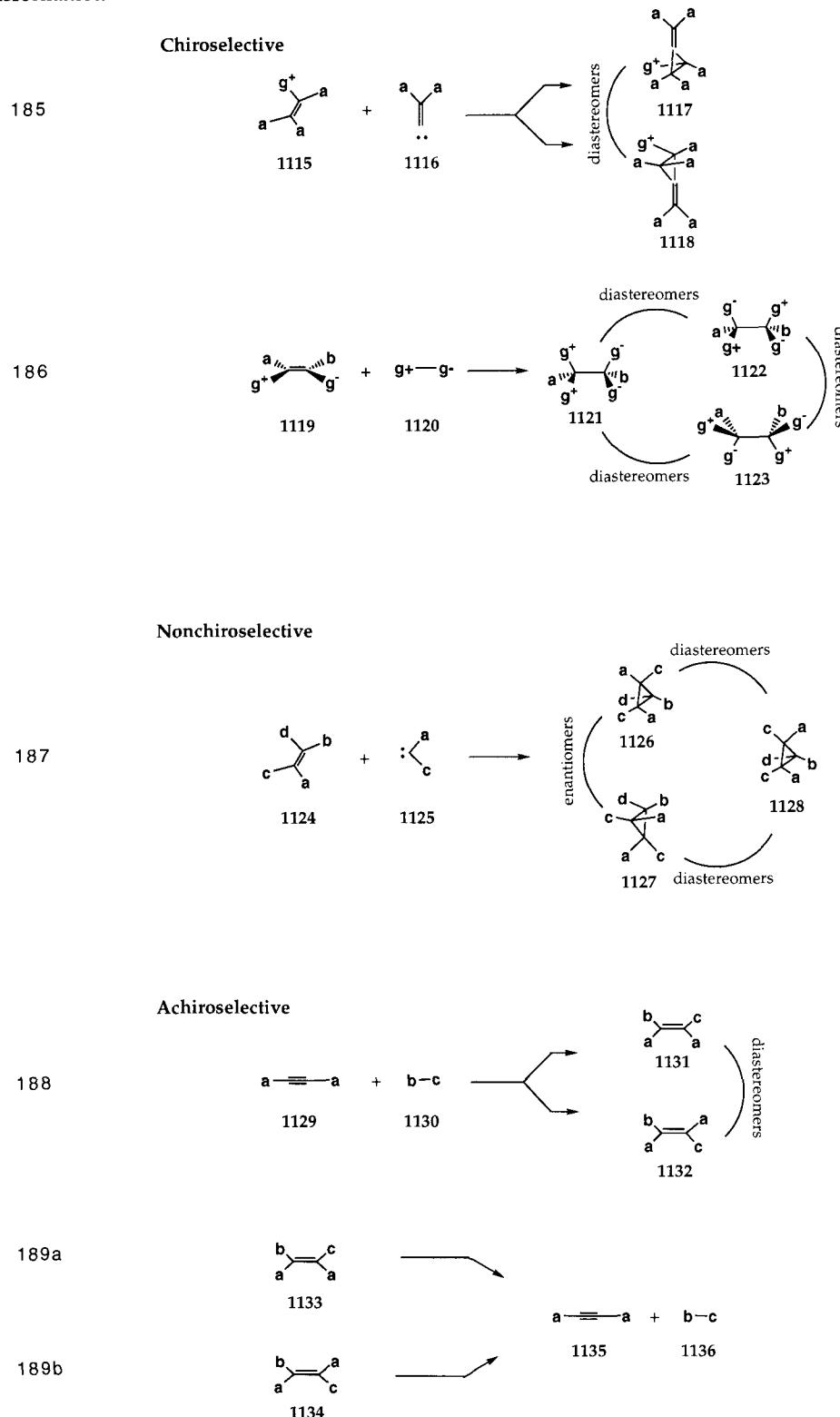
It follows that

$$\% \text{ chiroselectivity} = - \% \text{ achiroselctivity} \quad (18.6)$$

and, for nonchiroselective transformations, % chiroselectivity = % achiroselctivity = 0.

In Figures 18.35-18.37, we provide examples and define the chiroselectivity/achiroselctivity for each one.

## Transformation



**Figure 18.34.** Examples of Chiroselective, Nonchiroselective and Achiroselective Transformations

Chiroselectivity for transformations 190a/b-193a/b would range between 0 and 100%, if the chiral products 1139(=1145), 1141(=1147), 1151(=1153=1157=1159), 1163(=1164), 1169(=1172), 1176, 1177, 1178, 1182, 1183, 1184 predominate over the corresponding achiral ones (1140(=1142), 1146(=1148), 1152, 1154, 1158, 1160, 1165(=1166), 1170(=1171), 1175(=1181)). The chiral and achiral products refer to the principal organic products, and not to any organic/inorganic by-products.

Achiroselectivity for transformations 190a/b-193a/b would range between 0 and 100, if the amount(s) of achiral product(s) (1140(=1142), 1146(=1148), 1152, 1154, 1158, 1160, 1165(=1166), 1170(=1171), 1175(=1181)) exceed those of the corresponding chiral ones (1139(=1145), 1141=1147, 1151(=1153=1157=1159), 1163(=1164), 1169(=1172), 1176, 1177, 1178, 1182, 1183, 1184).

Chirospecificity is a measure of the difference in the amounts of chiral products (rotative and nonrotative) obtained from two stereomeric (enantiomeric or diastereomeric) substrates  $S_1$  and  $S_2$ . As in the case of stereospecificity, the discussion of chirospecificity is meaningful if one is considering transformations under kinetic control. Furthermore, the concept of chirospecificity is especially useful for reactions in which chiral and achiral products are both formed. In general, for two substrates  $S_1$  and  $S_2$ , chirospecificity can be expressed quantitatively as the difference between the amounts of chiral products, from the chirospecific route for substrate  $S_1$ , and those from the corresponding chirospecific route for substrate  $S_2$ .

$$\% \text{ chirospecificity} = |[\% \text{ chiral product(s)} \text{ from } S_1] - [\% \text{ chiral product(s)} \text{ from } S_2]| \quad (18.7)$$

Chirospecificity is greater than zero and less than or equal to 100. For a nonchirospecific reaction, % chirospecificity is equal to zero. There is no direct relationship between chiroselectivity and chirospecificity; we do not favor the trivial definition of chirospecificity to mean 100% chiroselectivity.

In Figures 18.35-18.36, we provide the quantitative expressions for chirospecificity, and contrast them with the corresponding definitions of chiroselectivity.

For each of 190a, 190b, 191a, 191b, 192a, 192b, 193a, 193b, chirospecificity is given by:

$$190a: \% \text{ chirospecificity} = |[(E^*+{}^*\Xi)_1 - \%D] - |[(E^*+{}^*\Xi)_2 - \%F|$$

$$190b: \% \text{ chirospecificity} = |[(E^*+{}^*\Xi)_2 - \%F] - |[(E^*+{}^*\Xi)_1 - \%D|$$

$$191a: \% \text{ chirospecificity} = |[(D^*_1 - (\%F + \%G)) - (D^*_2 - (\%K + \%L))|$$

$$191b: \% \text{ chirospecificity} = |[(D^*_2 - (\%K + \%L)) - (D^*_1 - (\%F + \%G))|$$

$$192a: \% \text{ chirospecificity} = |[(E^*_1 - \%D_1) - (E^*_2 - \%D_2)|$$

$$192b: \% \text{ chirospecificity} = |[(E^*_2 - \%D_2) - (E^*_1 - \%D_1)|$$

$$193a: \% \text{ chirospecificity} = |[(D^* + F^* + M_1^*) - \%N_1] - [(G^* + H^* + M_2^*) - \%N_2]|$$

$$193b: \% \text{ chirospecificity} = |[(G^* + H^* + M_2^*) - \%N_2] - [(D^* + F^* + M_1^*) - \%N_1]|.$$

Transformation	Products	Composition of Products		Chiroselectivity
		Chiroselectivity		
190a		$\left[ \begin{array}{l} (\%E^* + \%E^*)_1 - \%D \\ (\%E^* + \%E^*)_2 - \%F \end{array} \right]$	$\left  \begin{array}{l} (\%E^* + \%E^*)_1 - \%D \\ (\%E^* + \%E^*)_2 - \%F \end{array} \right $	
190b		$\left[ \begin{array}{l} (\%E^* + \%E^*)_1 - \%D \\ (\%E^* + \%E^*)_2 - \%F \end{array} \right]$	$\left  \begin{array}{l} (\%E^* + \%E^*)_1 - \%D \\ (\%E^* + \%E^*)_2 - \%F \end{array} \right $	
191a		$\left[ \begin{array}{l} (\%E^* + \%E^*)_1 - \%D \\ (\%E^* + \%E^*)_2 - \%F \end{array} \right]$	$\left  \begin{array}{l} (\%E^* + \%E^*)_1 - \%D \\ (\%E^* + \%E^*)_2 - \%F \end{array} \right $	
191b		$\left[ \begin{array}{l} (\%E^* + \%E^*)_1 - \%D \\ (\%E^* + \%E^*)_2 - \%F \end{array} \right]$	$\left  \begin{array}{l} (\%E^* + \%E^*)_1 - \%D \\ (\%E^* + \%E^*)_2 - \%F \end{array} \right $	
				$\left  \begin{array}{l} (\%E^* + \%E^*)_1 - \%D \\ (\%E^* + \%E^*)_2 - \%F \end{array} \right $
				$\left  \begin{array}{l} (\%D^* + \%D^*)_1 - \%F \\ (\%D^* + \%D^*)_2 - \%L \end{array} \right $
				$\left  \begin{array}{l} (\%D^* + \%D^*)_1 - \%F \\ (\%D^* + \%D^*)_2 - \%L \end{array} \right $
				$\left  \begin{array}{l} (\%D^* + \%D^*)_1 - \%F \\ (\%D^* + \%D^*)_2 - \%G \end{array} \right $
				$\left  \begin{array}{l} (\%D^* + \%D^*)_1 - \%F \\ (\%D^* + \%D^*)_2 - \%G \end{array} \right $

Figure 18.35. Comparison of Chiroselectivity and Chiroselectivity

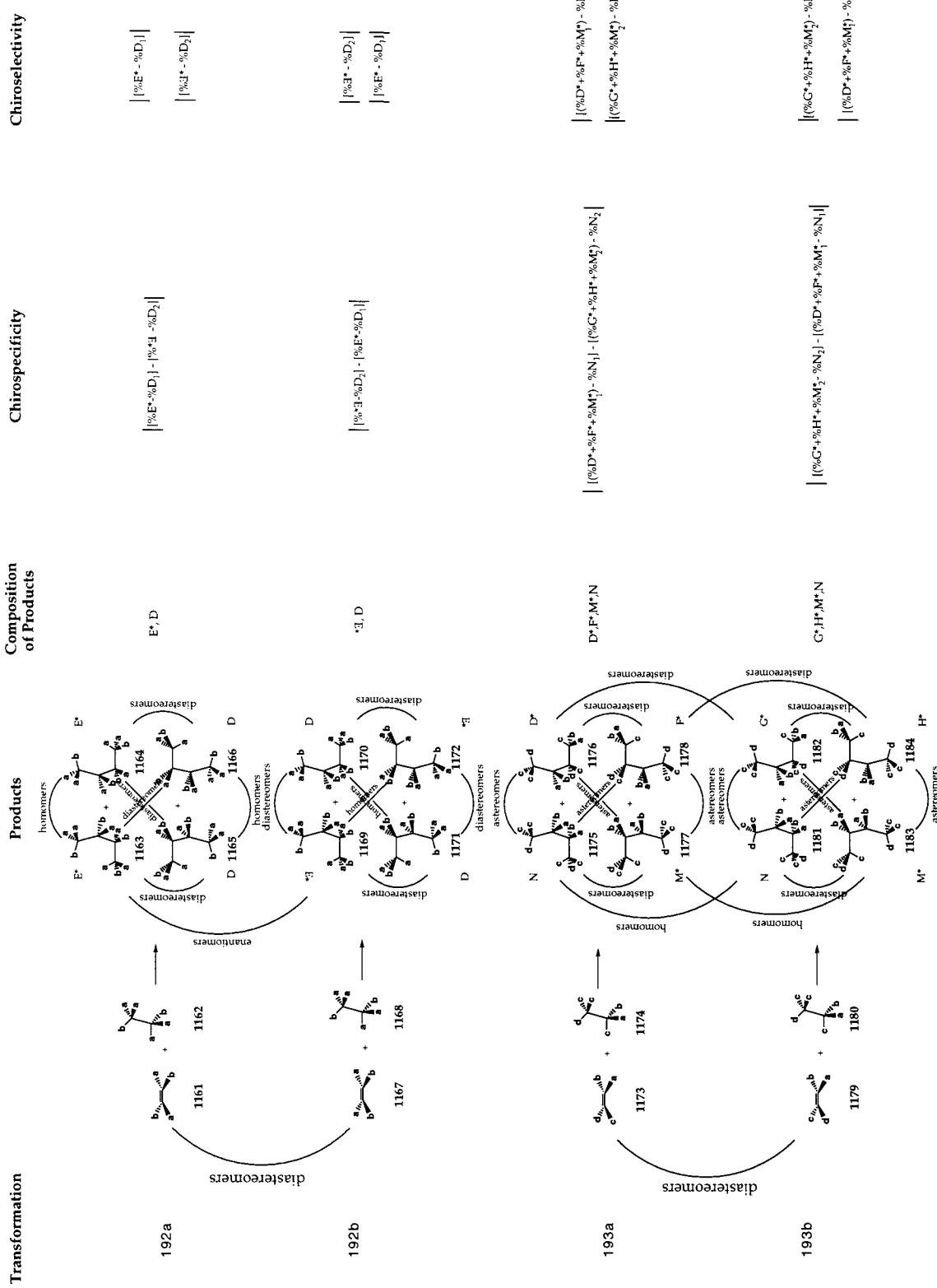


Figure 18.36. Comparison of Chiroselectivity and Chiroselectivity

## XII. Chiroselectivity vs. Stereoselectivity

Chiroselectivity and stereoselectivity are two distinct attributes of a given transformation.

Chiroselectivity is numerically identical with stereoselectivity for transformations 190a/b and 192a/b, because the divide between stereomers coincides with that between achiral and chiral products - a diastereomer (**1140=1142, 1146=1148; 1164=1166, 1170=1172** - consisting of achiral molecules) is pitted against a racemate (**1139/1141, 1145=1147; 1163=1165, 1169=1171** consisting of chiral molecules). For these examples, chiroselectivity correlates directly with stereoselectivity.

However, 191a/b yields three diastereomers) and, thus, provides two divides of stereoselectivity ( $\Delta 1$  and  $\Delta 2$ , see Volume 1, Addendum A, p. 143) but one-and-only divide of chirality - achiral vs. chiral. Thus the process may be chiroselective if the chiral diastereomer **D\*** (**1151=1153=1157=1159khatcher**)

) dominates over achiral F (**1168**) and G (**1170**) (or K (**1174**) and L (**1176**)). The process may also be nonchiroselective if  $\%D^*=\%F+\%G$  (or  $\%D^*=\%K+\%L$ ). For the latter two *nonchiroselective* instances, there can still be attendant stereoselectivity if D\*, F and G (or D\*,K,L) are formed in unequal amounts. However, if  $\%D^*=\%F=\%G$  (or  $\%D^*=\%K=\%L$ ), the process becomes nonstereoselective.

In the more complex case of 193a (or 193b), the transformation may be chiroselective if D\*,F\*,M\* (or G\*,H\*,M\*) dominate over achiral N (in both cases). However, the process is deemed nonchiroselective if  $\%(D^*+F^*+M^*)$  accidentally equals  $\%N$ . The latter composition may still display stereoselectivity favoring a given diastereomer for either one of the two pairs (e.g. D\* over F\*, or M\* over N; one of the three divides delineates astereomers, and the other two divides separate two diastereomeric pairs - D\*,F\* vs. M\*,N).

A chiroselective transformation may also be stereoaselective (transformation 197, Figure 18.37). Here a single chiral product is formed, and no stereomers are anticipated. In sum, a chiroselective process may be stereoaselective (transformation 197), stereoselective (transformations 190a/b, 191a/b, 192a/b, 193a/b), or nonstereoselective (191a/b).

A nonchiroselective transformation must yield a chiral product in amounts equal to those of an achiral product. Since a chiral product necessarily has an enantiomeric counterpart, one must consider any attendant stereoselectivity; thus, the concept of stereoaselectivity becomes irrelevant. That is to say, transformations cannot be nonchiroselective and simultaneously stereoaselective. Therefore, a nonchiroselective process is either stereoselective (191a/b, 193a/b, 198a/b, 199a/b) or nonstereoselective (190a/b, 192a/b, 198a/b, 199a/b).

Finally, an achiroselective process may be stereoaselective (194), stereoselective (195a/b, 196a/b), or nonstereoselective (195a/b, 196a/b).

	Achiroselective	Chiroselective	Nonchiroselective
Stereoaselective	194	197	---
Stereoselective	195a/b, 196a/b	190a/b 191a/b, 192a/b, 193a/b	191a/b, 193a/b 198a/b, 199a/b
Nonstereoselective*	195a/b, 196a/b	191a/b	190a/b, 192a/b 198a/b, 199a/b

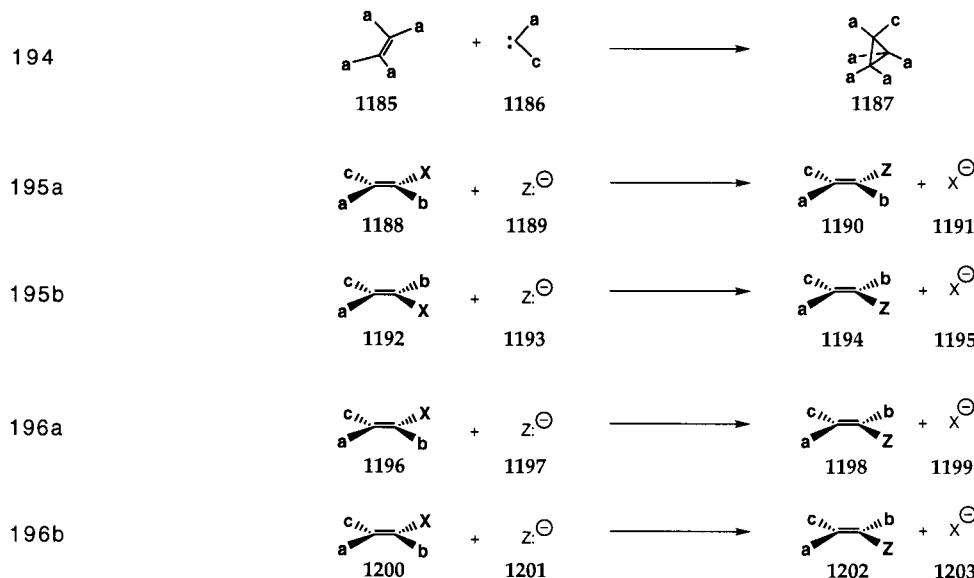
\* accidental 0% stereoselectivity

**Table 18.4** Correlation between Stereoselectivity and Chiroselectivity

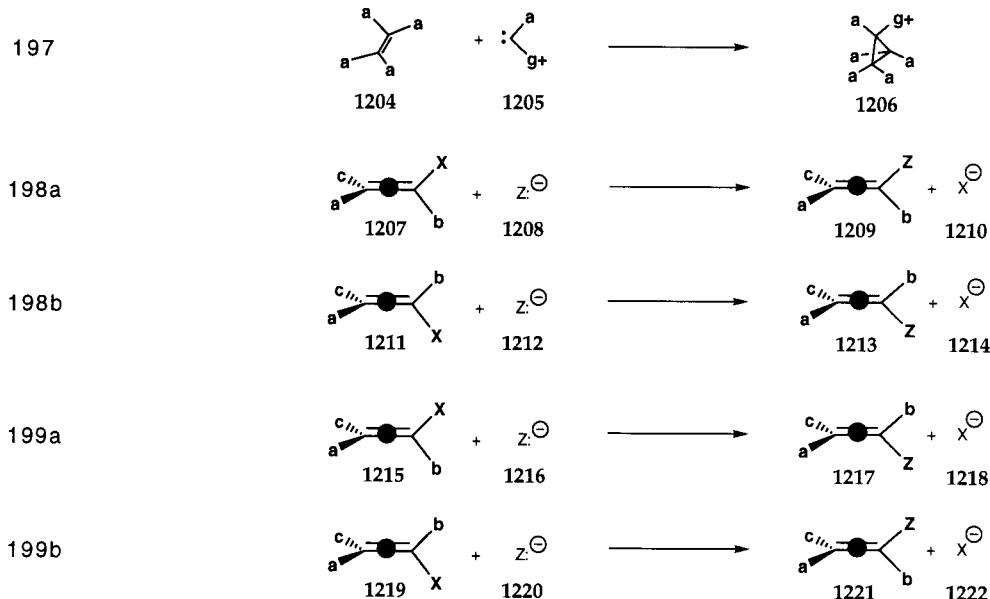
Conversely, a stereoselective process may be achiroselective (193a/b, 196a/b), chiroselective (190a/b, 191a/b, 192a/b, 193a/b), or nonchiroselective (191a/b, 193a/b, 198a/b, 199a/b). A nonstereoselective process may also be achiroselective (195a/b, 196a/b), chiroselective (191a/b), or nonchiroselective (190a/b, 192a/b, 198a/b, 199a/b). Finally, an stereoaselective process may be achiroselective (194) or chiroselective (197), but not nonchiroselective. Table 18.4 above summarizes these correlations along with the representative transformations.

### Transformation

#### Achiroselective



#### Chiroselective



**Figure 18.37.** Examples of Achiroselective and Chiroselective Transformations

### XIII. Chiospecificity vs. Chioselectivity

In Chapter 17 we defined the concept of stereospecificity and compared it with stereoselectivity. We now draw the analogous comparison between chiospecificity and chioselectivity.

Chioselectivity and chiospecificity are two distinct concepts, and no correlation is expected between them. Chiospecificity is a measure of the mechanistic chiral purity of a kinetically-controlled transformation. Chioselectivity characterizes the relative proportions of the chiral vs. achiral products in any given transformation, regardless of the mechanistic purity of the transformation (Figure 18.38).

Chioselectivity		
Chiospecificity	chiral product(s) (from reactant S <sub>1</sub> )	achiral product(s)
	chiral product(s) (from reactant S <sub>2</sub> )	achiral product(s) (from reactant S <sub>2</sub> )

**Figure 18.38.** Relationship Between Chioselectivity and Chiospecificity

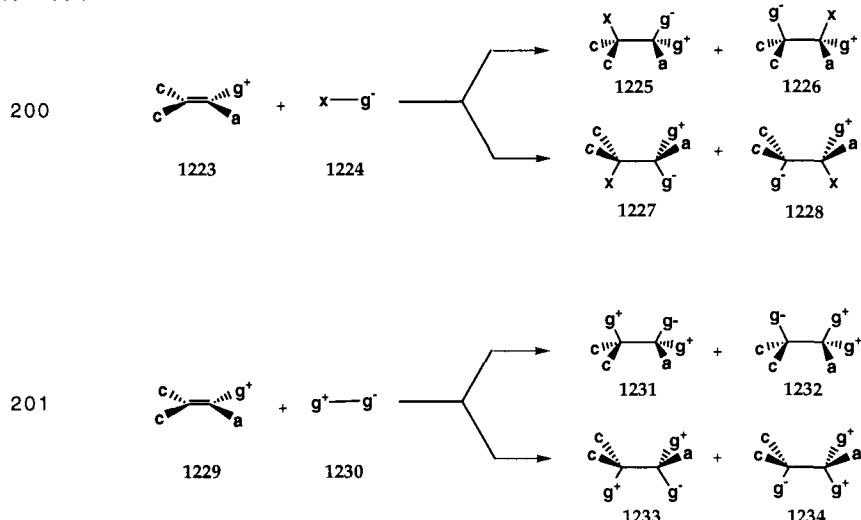
In principle, a reaction that is characterized by high chioselectivity may display high or low chiospecificity; one, that is characterized by low chioselectivity, may exhibit high or low chiospecificity. Generally, for practical applications, one would like to have transformations that have high chioselectivity/achiroselectivity, high chiospecificity or both. It must be noted that as achiroselectivity increases, with correspondingly increasing amounts of the achiral product(s), the issue of chiospecificity disappears.

Looking at examples in Figures 18.35-18.36, one notes that, for transformations 190a/b and 192a/b, chioselectivity can range between 0-100%, depending on whether E\*/\*E or D (or, E\*/\*E vs. F) dominates. Simultaneously, chiospecificity (operationally undeterminable, because of identity of E\*/\*E products) may vary over the 0-100% range. Transformations 191a/b and 193a/b are more complex, and chioselectivity and chiospecificity are, *a priori*, uncorrelatable.

Figure 18.39 portrays examples of achirospecific transformations 200 and 201 each of which may be achiroselective, nonchiroselective or chioselective.

In sum, an achiroselective, nonchiroselective, or chioselective process may be achirospecific, chiospecific, or nonchiospecific.

### Transformation



**Figure 18.39.** Examples of Achirospecific Transformations

Conversely, an achirospecific, chirospecific or nonchirospecific process may be achiroselective, nonchiroselective or chiroselective. Table 18.5 summarizes these correlations along with the referenced representative transformations.

	Achiroselective	Nonchiroselective	Chiroselective
<b>Achirospecific</b>	200a/b, 201a/b	200a/b, 201a/b	200a/b, 201a/b
<b>Chirospecific</b>	190a/b, 192a/b 191a/b, 193a/b	190a/b, 192a/b 191a/b, 193a/b	190a/b, 192a/b 191a/b, 193a/b
<b>Nonchirospecific*</b>	190a/b, 192a/b 191a/b, 193a/b	190a/b, 192a/b 191a/b, 193a/b	191a/b, 193a/b

\* accidental 0% chiroselectivity

**Table 18.5** Connection between Chiroselectivity and Chiroselectivity

### XIV. Stereotopoprocesses vs. Chirotopoprocesses in Relation to Stereotopic Molecular Faces

Having established the stereotopoprocesses 1A-7B (pp. 47-51; S1A-S7B) and chirotopoprocesses 1A-7B (pp. 128-133; C1A-C7B) for stereotopic molecular faces h1- h6, e, and d1- d4, we now examine the intercorrelation of the two sets of transformations, i.e. S1A-S7B vs. C1A-C7B, for the said molecular faces. These correlations are detailed in Tables 18.6-18.8.

It is not unreasonable to expect that there would be a good diagonal correlation between the two sets of transformations. That is to say, chirotopolysis (C1A-C2B) should correlate with stereotopolysis (S1A-S2B), chirotopomutation (C3A-C5B) with stereotopomutation (S3A-S5B), and chirotopogenesis (C6A-C7B) with stereotopogenesis (S7A-S7B). On the other hand, the fundamental differences between the two sets of processes should surface in off-diagonal correlations *viz.* chirotopolysis (C1A-C2B) vs. stereotopomutation (S3A-S5B) and stereotopogenesis (S6A-S7B), chirotopomutation (C3A-C5B) vs. stereotopolysis (S1A-S2B) and stereotopogenesis (S6A-S7B), and, finally, chirotopogenesis (C6A-C7B) vs. stereotopolysis (S1A-S2B) and stereotopomutation (S3A-S5B). The mere existence of off-diagonal correlations is intriguing and fascinating.

### A. Homotopic Faces

#### 1. Diagonal Correlations

In the first diagonal element (top left) of Table 18.6, stereochirotopolysis (C2A) correlates with chirostereotopolysis (S2A) for h<sub>6</sub> faces (chiral reagents).

In the second diagonal element, nonrotative astereochirotopomutation (C3A) correlates with nonrotative nonstereotopomutation (S4A) for h<sub>2</sub> faces (achiral reagents). The rotative version is seen in the correlation of astereochirotopomutation (C3B) with nonstereotopomutation (S4B) for h<sub>2</sub>, h<sub>4</sub>, h<sub>5</sub> faces (chiral reagents).

Further, in the second diagonal element of Table 18.6 (center), nonchiropopomutation (C4A) correlates with achirostereotopomutation (S3A; h<sub>3</sub> faces, achiral reagents), nonstereotopomutation (S4A; h<sub>1</sub> and h<sub>2</sub> faces, achiral reagents), and chirostereotopomutation (S5A; h<sub>2</sub> faces, achiral reagents). However, correlations between nonchiropopomutation (C4B) and chirostereotopomutation (S5B) are noted for faces h<sub>2</sub>, h<sub>4</sub>, h<sub>5</sub>, h<sub>6</sub> (chiral reagents), as well as for face h<sub>5</sub> faces (achiral reagents). Finally, in the second diagonal element, one sees a correlation between stereochirotopomutation (C5B) with chirostereotopomutation (S5B) for h<sub>6</sub> faces (chiral reagents).

In the third diagonal element of Table 18.6 (bottom right), astereochirotopogenesis (C6A) accompanies achirostereotopogenesis for faces h<sub>2</sub> (achiral reagents); stereochirotopogenesis (C7A) correlates with chirostereotopogenesis (S7A) for faces h<sub>2</sub>, h<sub>3</sub> (achiral reagents); stereochirotopogenesis (C7B) is associated with chirostereotopogenesis (S7B) for h<sub>2</sub>, h<sub>3</sub> faces (chiral reagents), and h<sub>5</sub>, h<sub>6</sub> faces (achiral reagents).

#### 2. Off-Diagonal Correlations

These correlations bring out the marked differences between the two classifications – the ones based on chirotopoprocesses (C1A-C7B) and those that are based on stereotopoprocesses (S1A-S7B).

Under nonrotative chirotopolysis, one sees a correlation between astereochirotopolysis (C1A) and nonstereotopomutation (S4A) for h<sub>5</sub> faces (chiral reagents). Strikingly, there is no correlation between chirotopolysis (C1A-C2B) and stereotopogenesis (S6A-S7B).

Among chirotopomutations, in the nonrotative mode, astereochirotopomutation (C3A) correlates with astereotopogenesis (S6A) (h<sub>2</sub> faces) (achiral reagents), and, nonchiropopomutation (C4A) with achirostereotopogenesis (S6A) (h<sub>3</sub> faces) (achiral reagents). In the rotative mode, nonchiropopomutation (C4B) correlates with achirostereotopolysis (S1B) (h<sub>3</sub> faces), with chirostereotopolysis (S2B) (h<sub>6</sub> faces) (both with chiral reagents), and with chirostereotopogenesis (S7B) for faces h<sub>2</sub>, h<sub>5</sub>, h<sub>6</sub> (all with chiral reagents).

		CHIROTOPOLYSIS				CHIROTOMUTATION				CHIROTOPOGENESIS					
		stereochirotopolysis		astereochirotopolysis		stereochirotopomutation		nonchirotopomutation		stereochirotopomutation		astereochirotopogenesis		stereochirotopogenesis	
Relative (r) or Nonrelative (nr)		nr	r	nr	r	nr	r	nr	r	nr	r	nr	r	nr	r
STEREOTOPOLYSIS	Class	C1A	C1B	C2A	C2B	C3A	C3B	C4A	C4B	C5A	C5B	C6A	C6B	C7A	C7B
achirostereotopolysis	nr	S1A													
chirostereotopolysis	r	S1B													
chirostereotopomutation	nr	S2A		<b>h6</b>											<b>h3</b>
achirostereotopomutation	r	S2B													
nonstereotopomutation	nr	S3A													
chirostereotopomutation	r	S3B													
STEREOTOPGENESIS		S4A	<b>h5</b>												
achirostereotopogenesis	r	S4B													
chirostereotopogenesis	nr	S5A													
chirostereotopogenesis	r	S5B													
STEREOTOPFACES		S6A													
chirostereotopogenesis	r	S6B													
chirostereotopogenesis	nr	S7A													
chirostereotopogenesis	r	S7B													

Table 18.6. Correlations of Chirotopoprocesses and Stereotopoprocesses for Homotopic Faces

ac: achiral reagent  
c: chiral reagent

nonstereotopomutation (S4A) (h1-h3 faces), and chirostereotopomutation (S5A) (h1, h2 faces) – all with achiral reagents. Rotative stereochoiropogenesis (C6B) correlates with achirostereotopolysis (S1B) (h3 faces, chiral reagents) and chirostereotopolysis (S2B) (h6 faces, achiral reagents); it also correlates with nonstereotopomutation (S4B) (h1, h2, h4, h5 faces) and chirostereotopomutation (S5B) (h1, h2, h6 faces) - h1, h2 faces with chiral reagents, h4-h6 with achiral reagents.

Finally, nonrotative stereochoiropogenesis (C7A) correlates with achirostereotopolysis (S1A) and chirostereotopogenesis (S4A) (h3 faces, achiral reagents). The rotative mode of stereochoiropogenesis (C7B) correlates with rotative achirostereotopolysis (S1B) and rotative nonstereotopomutation (S4B) (h3 faces, chiral reagents).

Thus, for homotopic faces, chirotopolysis correlates with stereotopolysis and stereotopomutation, but not with stereotopogenesis. In contradistinction, chirotopomutation and chirotopogenesis correlate with all three types of stereotopoprocesses.

Reciprocally, stereotopolysis and stereotopomutation correlate with all three types of chirotopoprocesses. However, stereotopogenesis correlates only with chirotopomutation and chirotopogenesis, and not with chirotopolysis. In every instance, a nonrotative mode correlates with a nonrotative mode, while a rotative mode correlates only with a rotative mode.

## B. Enantiotopic Faces

### 1. Diagonal Correlations

In the first diagonal element of Table 18.7 (top left), there is a correlation between stereochoiropolysis (C2A) and chirostereotopolysis (S2A) (achiral reagents).

In the second diagonal element (center), nonchirotopomutation (C4A) correlates with chirostereotopomutation (S5A) (achiral reagents) – both in the nonrotative mode. The rotative mode is noted in the correlation of nonchirotopomutation (C4B) with chirostereotopomutation (S5B) for (chiral reagents). Also in the nonrotative mode, stereochoiropomutation (C5A) correlates with chirostereotopomutation (S5A) (achiral reagents), whereas rotative stereochoiropomutation (C5B) correlates with rotative chirostereotopomutation (S5B) (chiral reagents).

In the third diagonal element (bottom right), nonrotative stereochoiropogenesis (C7A) correlates with chirostereotopogenesis (S7A) (achiral reagents). Also, the rotative mode of stereochoiropogenesis (C7B) correlates with the rotative mode of chirostereotopogenesis (S7B) (chiral reagents).

### 2. Off-Diagonal Correlations

With respect to chirotopolysis, there is no correlation between chirotopolysis (C1A-C2B) and stereotopomutation (S3A-S5B). However, one does find, in the rotative mode, a correlation between astereochoiropolysis (C1B) and chirostereotopogenesis (S7B) (chiral reagents).

Under chirotopomutation, one finds no link between astereochoiropomutation (C3A-C3B) and any stereotopoprocess (S1A-S7B). In terms of nonchirotopomutation, the nonrotative mode (C4A) correlates with that of chirostereotopolysis (S2A) (achiral reagents), while the rotative mode of nonchirotopomutation (C4B) correlates with those of chirostereotopolysis (S2B) and chirostereotopogenesis (S7B) (chiral reagents). Furthermore, nonrotative stereochoiropomutation (C5A) correlates with nonrotative chirostereotopolysis (S2A) (achiral reagents),

ac : achiral reagent  
c : chiral reagent

		CHIROTOPYLISIS				CHIROPOMUTATION				CHIROPOGENESIS						
		stereochirotopylisis		astereochirotopylisis		nonchiropomutation		astereochiropomutation		stereochiropomutation		astereochiropogenesis		stereochirogenesis		
Relative (r) or Nonrelative (nr)		nr	r	nr	r	nr	r	nr	r	nr	r	nr	r	nr	r	
Rotatable (r) or Nonrotatable (nr)		Class	C1A	C1B	C2A	C2B	C3A	C3B	C4A	C4B	C5A	C5B	C6A	C6B	C7A	C7B
achirostereotopylisis			SI A										e		e	
chirostereotopylisis			SI B													e
achirostereotopomutation			S2A		e				e		e		e		e	
nonstereotopomutation			S2B						e			e				
chirostereotopomutation			S3A													
achirostereotopogenesis			S3B													
chirostereotopogenesis			S4A										e		e	
achirostereotopogenesis			S4B													e
chirostereotopogenesis			S5A										e		e	
achirostereotopogenesis			S5B										e		e	
chirostereotopogenesis			S6A													
achirostereotopogenesis			S6B													
chirostereotopogenesis			S7A										e		e	
chirostereotopogenesis			S7B		e							e		e		e

Table 18.7. Correlations of Chirotopoprocesses and Stereotopoprocesses for Enantiopic Faces

while rotative stereochoirotopomutation (C5B) correlates with the rotative modes of chirostereotopolysis (S2B) and chirostereotopogenesis (S7B) (both with chiral reagents).

For chirotopogeneses, one finds that astereochoirotopogenesis (C6A) correlates with achirostereotopolysis (S1A), chirostereotopolysis (S2A), nonstereotopomutation (S4A) and chirostereotopomutation (S5A) (all with achiral reagents). The corresponding rotative mode (C6B) correlates with rotative chirostereotopomutation (S5B). Finally, nonrotative stereochoirotopogenesis (C7A) correlates with achirostereotopolysis (S1A), chirostereotopolysis (S2A) and nonstereotopomutation (S4A) (achiral reagents) – all in the nonrotative mode. In contrast, rotative stereochoirotopogenesis (C7B) correlates with rotative achirostereotopolysis (S1B) and nonstereotopomutation (S4B) (chiral reagents).

In sum, chirotopolyses correlate with only stereotopolysis and stereotopogenesis (and not with stereotopomutation). In contradistinction, chirotopomutation and chirotopogenesis correlate with all three types of stereotopoprocesses. Reciprocally, stereotopolysis and stereotopogenesis correlate with all three types of chirotopoprocesses; however, stereotopomutation correlates only with chirotopomutation and chirotopogenesis (and not with chirotopolysis). Again, in every instance, a nonrotative mode correlates with a nonrotative mode, and a rotative mode correlates only with a rotative mode.

### C. Diastereotopic Faces

#### 1. Diagonal Correlations

In the first diagonal element (top left) of Table 18.8, stereochoirotopolysis (C2A) correlates with chirostereotopolysis (S2A) for d<sub>3</sub> (achiral reagents) and d<sub>4</sub> faces (achiral and chiral reagents).

In the second diagonal element (center), nonchirotopomutation (C4A) correlates with achirostereotopomutation (S3A) (d<sub>1</sub>, d<sub>2</sub> faces) and with chirostereotopomutation (S5A) (d<sub>3</sub> and d<sub>4</sub> faces) - d<sub>1</sub>-d<sub>3</sub> faces with achiral reagents, d<sub>4</sub> with chiral reagents. Rotative nonchirotopomutation (C4B) correlates with nonstereotopomutation (S4B) (d<sub>4</sub> faces, chiral reagents), and with chirostereotopomutation (S5B) (d<sub>3</sub> faces, chiral reagents; d<sub>4</sub> faces, achiral and chiral reagents). Next, stereochoirotopomutation (C5A) correlates with chirostereotopomutation (S5A) (d<sub>3</sub> faces, achiral reagents), while rotative stereochoirotopomutation (C5B) correlates with chirostereotopomutation (S5B) (d<sub>3</sub> faces, chiral reagents; d<sub>4</sub> faces, achiral and chiral reagents).

In the third diagonal element (bottom right), in the nonrotative mode, stereochoirotopogenesis (C7A) correlates with chirostereotopogenesis (S7A) (d<sub>2</sub>, d<sub>3</sub> faces, achiral reagents), whereas rotative stereochoirotopogenesis (C7B) correlates with rotative chirostereotopogenesis (S7B) (d<sub>2</sub> faces - chiral reagents; d<sub>4</sub> faces - achiral and chiral reagents).

#### 2. Off-Diagonal Correlations

Under chirotopolysis, nonrotative astereochoirotopolysis (C1A) correlates with chirostereotopomutation (S5A) (d<sub>4</sub> faces, chiral reagents), and with achirostereotopogenesis (S6A) (d<sub>2</sub> faces, achiral reagents; d<sub>4</sub> faces, chiral reagents). Rotative astereochoirotopolysis (C1B) correlates with chirostereotopomutation (S5B) (d<sub>4</sub> faces, chiral reagents). Stereochoirotopolysis (C2A) correlates with nonstereotopomutation (S4A) (d<sub>3</sub> faces, achiral reagents; d<sub>4</sub> faces, achiral and chiral reagents).

With respect to chirotopomutation, one finds a link between astereochoirotopomutation (C3A) and achirostereotopogenesis (S6A) (d<sub>2</sub> faces, achiral reagents). Further, nonchirotopomutation (C4A) correlates with chirostereotopolysis (S2A) (d<sub>3</sub> faces, achiral reagents), achirostereotopogenesis

a: achiral reagent  
c: chiral reagent

		CHIROTOLYSIS				CHIROTOMUTATION				CHIROGENESIS			
		stereochirotolysis		stereochirotolysis		stereochirotomutation		stereochirotomutation		stereochirotomutation		stereochirotogenesis	
Relative (r) or Nonrelative (nr)	Class	nr	r	nr	r	nr	r	nr	r	nr	r	nr	r
<b>achirostereotolysis</b>	nr	S1A								d1		d2	
	r	S1B									d2		d1 d2
<b>chirostereotolysis</b>	nr	S2A								d3			
	r	S2B											
<b>achirostereotomutation</b>	nr	S3A											
	r	S3B											
<b>nonstereotomutation</b>	nr	S4A											
	r	S4B											
<b>chirostereotomutation</b>	nr	S5A	<b>d4</b>							d3		d2 d3 d4	
	r	S5B		<b>d4</b>									
<b>STEREOTOGENESIS</b>	nr	S6A	c2 <b>d4</b>			d2		c2 d3		d3			
	r	S6B											
<b>chirostereotogenesis</b>	nr	S7A						d2 d3		d3		d2 d3	
	r	S7B							<b>d3 d4</b>			<b>d2 d4</b>	

Table 18.8. Correlations of Chirotoprocesses and Stereotoprocesses at Diastereotopic Faces

(S6A) and chirostereotopogenesis (S7A) (d<sub>2</sub>, d<sub>3</sub> faces, achiral reagents). The rotative mode of nonchirotopomutation (C4B) correlates with chirostereotopolysis (S2B) and with chirostereotopogenesis (S7B) (d<sub>3</sub> faces - chiral reagents; d<sub>4</sub> faces - achiral and chiral reagents). Next, stereochirotopomutation (C5A) correlates with achirostereotopogenesis (S6A) and with chirostereotopogenesis (S7A) (d<sub>3</sub> faces, achiral reagents).

For chirotopogeneses, we note that astereochirotopogenesis (C6A) correlates with achirostereotopolysis (S1A) (d<sub>1</sub> faces), chirostereotopolysis (S2A) (d<sub>3</sub> faces), achirostereotopomutation (S3A) and nonstereotopomutation (S4A) (d<sub>2</sub> faces), and chirostereotopomutation (S5A) (d<sub>2</sub>, d<sub>3</sub>, d<sub>4</sub> faces) – all with achiral reagents. The rotative mode of astereochirotopogenesis (C6B) correlates with achirostereotopolysis (S1B) (d<sub>2</sub> faces, chiral reagents), chirostereotopolysis (S2B) (d<sub>4</sub> faces, achiral reagents), nonstereotopomutation (S4B) (d<sub>4</sub> faces, achiral and chiral reagents), and with chirostereotopomutation (S5B) (d<sub>2</sub>, d<sub>3</sub> - chiral reagents; d<sub>4</sub> - achiral and chiral reagents). Finally, stereochirotopogenesis (C7A) correlates with achirostereotopolysis (S1A) (d<sub>2</sub> faces – achiral reagents) and nonstereotopomutation (S4A) (d<sub>1</sub>, d<sub>2</sub> faces - achiral reagents). The rotative mode of stereochirotopogenesis (C7B) correlates with achirostereotopolysis (S1B) (d<sub>1</sub>, d<sub>2</sub> faces, chiral reagents) and nonstereotopomutation (S4B) (d<sub>1</sub>, d<sub>2</sub> faces) - all with chiral reagents.

In contrast with the situations for homotopic and enantiotopic faces, one finds that for diastereotopic faces, every chirotopoprocess correlates with the corresponding stereotopoprocess (Table 18.8). Nevertheless, in every instance, a nonrotative mode still correlates with a nonrotative mode, while a rotative mode correlates only with a rotative mode.

### Summary

We presented an alternative, universal stereochemical classification of chemical transformations based on (a) overall loss, (b) no loss/gain, and (c) overall gain of *chirotopic* atoms; we labelled these chirotopoprocesses *chirotopolysis*, *chirotopomutation* and *chirotopogenesis*, respectively. Further subclassification was carried out using the dual criteria of rotativity (expected optical activity) and stereoselectivity (preferential formation of one stereoisomer over another). We also introduced and defined the novel concepts of *chiroselectivity* and *chirospecificity*. Finally, the merits of the classification of chirotopoprocesses were discussed, and the stereotopoprocesses and chirotopoprocesses were correlated in relation to the stereotopic molecular faces.

**Chirotopolysis, Chirotopomutation, and Chirotopogenesis  
in Relation to the Quartet Modes, Product Compositions  
and Composition Description**

(E<sup>\*</sup>/<sup>†</sup>E, D<sup>\*</sup>/<sup>‡</sup>D, N<sup>\*</sup>/<sup>†</sup>N and Z<sup>\*</sup>/<sup>‡</sup>Z are racemates)

**Chirotopolysis**

**Class 1 A - Nonrotative Astereochirotopolysis**

Quartet Mode	Product Composition	Composition Description
q1	H	1 achiral substance
q22	D,F	2 achiral diastereomers
q44	D,F,M	2 achiral diastereomers and 1 achiral astereomer
q45	D,F,X	2 achiral diastereomers and 1 achiral nonequimer
q18	E <sup>*</sup> / <sup>†</sup> E, N <sup>*</sup> / <sup>†</sup> N	2 astereomeric enantiomeric pairs
q19	E <sup>*</sup> / <sup>†</sup> E, Z <sup>*</sup> / <sup>‡</sup> Z	2 nonequimERIC enantiomeric pairs
q35	D,F,M,N	2 astereomeric achiral diastereomeric pairs
q36	D,F,X,Y	2 nonequimERIC achiral diastereomeric pairs

**Class 1B - Rotative Astereochirotopolysis**

q27	D <sup>*</sup> ,F <sup>*</sup> ,G <sup>*</sup> ,J <sup>*</sup>	4 chiral diastereomers
q37	D <sup>*</sup> ,F <sup>*</sup> ,M <sup>*</sup> ,N <sup>*</sup>	2 astereomeric chiral diastereomeric pairs
q38	D <sup>*</sup> ,F <sup>*</sup> ,X <sup>*</sup> ,Y <sup>*</sup>	2 nonequimERIC chiral diastereomeric pairs

**Class 2A - Nonrotative Stereochirotopolysis**

q1	H	1 achiral substance
q7	D,F	2 achiral diastereomers
q22	D,F	2 achiral diastereomers
q28	D,F,G	3 achiral diastereomers
q35	D,F,M,N	2 astereomeric achiral diastereomeric pairs
q36	D,F,X,Y	2 nonequimERIC achiral diastereomeric pairs

**Class 2B - Rotative Stereochemistry**

q23	D*,F*	2 chiral diastereomers
q37	D*,F*,M*,N*	2 astereomeric chiral diastereomeric pairs
q38	D*,F*,X*,Y*	2 nonequimERIC chiral diastereomeric pairs

**Chirotopomutation****Class 3A - Nonrotative Astereochirotopomutation**

Quartet Mode	Product Composition	Composition Description
q1	H	1 achiral substance
q6	D,F	2 achiral diastereomers
q7	D,F	2 achiral diastereomers
q22	D,F	2 achiral diastereomers
q28	D,F,G	3 achiral diastereomers
q26	D,F,G,J	4 achiral diastereomers
q35	D,F,M,N	2 astereomeric achiral diastereomeric pairs
q36	D,F,X,Y	2 nonequimERIC achiral diastereomeric pairs

**Class 3B - Rotative Astereochirotopomutation**

q2	H*	1 chiral substance
----	----	--------------------

**Class 4A - Nonrotative Nonchirotopomutation**

q1	H	1 achiral substance
q6	D,F	2 achiral diastereomers
q7	D,F	2 achiral diastereomers
q22	D,F	2 achiral diastereomers
q13	A,N	2 achiral astereomers
q14	A,X	2 achiral nonequimers
q12	E*/ $\Xi$ ,D	2 enantiomers and an achiral diastereomer
q28	D,F,G	3 achiral diastereomers
q44	D,F,M	2 achiral diastereomers and 1 achiral astereomer
q45	D,F,X	2 achiral diastereomers and 1 achiral nonequimer
q11	E*/ $\Xi$ , D*/ $\Delta$	2 diastereomeric enantiomeric pairs
q18	E*/ $\Xi$ , N*/ $\Pi$	2 astereomeric enantiomeric pairs
q19	E*/ $\Xi$ , Z*/ $\Sigma$	2 nonequimERIC enantiomeric pairs
q26	D,F,G,J	4 achiral diastereomers
q35	D,F,M,N	2 astereomeric achiral diastereomeric pairs
q36	D,F,X,Y	2 nonequimERIC achiral diastereomeric pairs

### Class 4B - Rotative Nonchirotopomutation

q2	H*	1 chiral substance
q8	D*,F*	2 chiral diastereomers
q9	D*,F*	2 chiral diastereomers
q23	D*,F*	2 chiral diastereomers
q20	A*,N*	2 chiral astereomers
q21	A*,X*	2 chiral nonequimers
q24	D*,F*,G*	3 chiral diastereomers
q29	D*,F,G	3 diastereomers -1 chiral and 2 achiral
q31	D*,F*,N*	2 chiral diastereomers and a common chiral astereomer
q32	D*,F*,X*	2 chiral diastereomers and a common chiral nonequimer
q42	D,F,N*	2 achiral diastereomers and a common chiral astereomer
q43	D,F,X*	2 achiral diastereomers and a common chiral nonequimer
q27	D*,F*,G*,J*	4 chiral diastereomers
q37	D*,F*,M*,N*	2 astereomeric chiral diastereomeric pairs
q38	D*,F*,X*,Y*	2 nonequimERIC chiral diastereomeric pairs
q39	D*,F*,M,N	2 astereomERIC diastereomeric pairs (1 pair chiral, 1 pair achiral)
q40	D*,F*,X,Y	2 nonequimERIC chiral diastereomeric pairs (1 pair chiral, 1 pair achiral)

### Class 5A - Nonrotative Stereochirotopomutation

q7	D,F	2 achiral diastereomers
q22	D,F	2 achiral diastereomers
q12	E*/ $\bar{E}$ ,D	2 enantiomers and an achiral diastereomer
q28	D,F,G	3 achiral diastereomers
q26	D,F,G,J	4 achiral diastereomers

### Class 5B - Rotative Stereochirotopomutation

q2	H*	1 chiral substance
q8	D*,F*	2 chiral diastereomers
q9	D*,F*	2 chiral diastereomers
q23	D*,F*	2 chiral diastereomers
q24	D*,F*,G*	3 chiral diastereomers
q31	D*,F*,N*	2 chiral diastereomers and a common chiral astereomer
q32	D*,F*,X*	2 chiral diastereomers and a common chiral nonequimer
q27	D*,F*,G*,J*	4 chiral diastereomers
q37	D*,F*,M*,N*	2 astereomERIC chiral diastereomERIC pairs
q38	D*,F*,X*,Y*	2 nonequimERIC chiral diastereomERIC pairs

## Chirotopogenesis

### Class 6A - Nonrotative Astereochirotopogenesis

Quartet Mode	Product Composition	Composition Description
q1	H	1 achiral substance
q3	E*/*E	2 enantiomers (racemate)
q4	E*/*E	2 enantiomers (racemate)
q5	E*/*E	2 enantiomers (racemate)
q6	D,F	2 achiral diastereomers
q7	D,F	2 achiral diastereomers
q22	D,F	2 achiral diastereomers
q13	A,N	2 achiral astereomers
q14	A,X	2 achiral nonequimers
q15	E*/*E,N	2 enantiomers and an achiral common astereomer
q16	E*/*E,X	2 enantiomers and a common achiral nonequimer
q10	E*/*E,D*/*D	2 diastereomeric enantiomeric pairs
q25	E*/*E,D*/*D	2 diastereomeric enantiomeric pairs

### Class 6B - Rotative Astereochirotopogenesis

Quartet Mode	Product Composition	Composition Description
q2	H*	1 chiral substance
q8	D*,F*	2 chiral diastereomers
q23	D*,F*	2 chiral diastereomers
q20	A*,N*	2 chiral astereomers
q21	A*,X*	2 chiral nonequimers
q17	E*/*E,N*	2 enantiomers and a chiral common astereomer
q31	D*,F*,N*	2 chiral diastereomers and a common chiral astereomer
q32	D*,F*,X*	2 chiral diastereomers and a common chiral nonequimer
q27	D*,F*,G*,J*	4 chiral diastereomers
q37	D*,F*,M*,N*	2 astereomeric chiral diastereomeric pairs
q38	D*,F*,X*,Y*	2 nonequimERIC chiral diastereomeric pairs
q39	D*,F*,M,N	2 astereomERIC diastereomeric pairs (1 pair chiral, 1 pair achiral)
q40	D*,F*,X,Y	2 nonequimERIC chiral diastereomeric pairs (1 pair chiral, 1 pair achiral)

### Class 7A - Nonrotative Stereochirotopogenesis

Quartet Mode	Product Composition	Composition Description
q1	H	1 achiral substance
q3	E*/*E	2 enantiomers (racemate)
q4	E*/*E	2 enantiomers (racemate)
q5	E*/*E	2 enantiomers (racemate)
q6	D,F	2 achiral diastereomers
q7	D,F	2 achiral diastereomers
q22	D,F	2 achiral diastereomers
q12	E*/*E,D	2 enantiomers and an achiral diastereomer
q15	E*/*E,N	2 enantiomers and an achiral common astereomer
q16	E*/*E,X	2 enantiomers and a common achiral nonequimer
q10	E*/*E,D*/*D	2 diastereomeric enantiomeric pairs
q11	E*/*E,D*/*E	2 diastereomeric enantiomeric pairs
q18	E*/*E,N*/*N	2 astereomeric enantiomeric pairs
q19	E*/*E,Z*/*Σ	2 nonequimERIC enantiomeric pairs
q25	E*/*E,D*/*D	2 diastereomeric enantiomeric pairs

### Class 7B - Rotative Stereochirotopogenesis

Quartet Mode	Product Composition	Composition Description
q2	H*	1 chiral substance
q8	D*,F*	2 chiral diastereomers
q9	D*,F*	2 chiral diastereomers
q20	A*,N*	2 chiral astereomers
q21	A*,X*	2 chiral nonequimers
q23	D*,F*	2 chiral diastereomers
q24	D*,F*,G*	3 chiral diastereomers
q31	D*,F*,N*	2 chiral diastereomers and a common chiral astereomer
q32	D*,F*,X*	2 chiral diastereomers and a common chiral nonequimer
q27	D*,F*,G*,J*	4 chiral diastereomers
q37	D*,F*,M*,N*	2 astereomeric chiral diastereomeric pairs
q38	D*,F*,X*,Y*	2 nonequimERIC chiral diastereomeric pairs
q41	D*,F*,M*,N	2 astereomERIC diastereomeric pairs (1 pair chiral, 1 pair achiral/chiral)

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## References & Notes

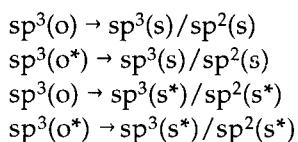
<sup>1</sup> Mislow, K. and Siegel, J., *J. Am. Chem. Soc.*, **1984**, *106*, 3319.

<sup>2</sup> Prof. James Brewster, private communication to this author, July 1993. The term "chirostereogenic" is not synonymous with "chirogenic".

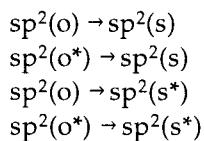
<sup>3</sup> Phantom atoms or sites do not count.

<sup>4</sup> In principle, stereogenizations may occur by disjunctive or substitutive processes. Disjunctive stereogenizations (distinct from disjunctive destereogenizations) are exemplified by the following transformations:

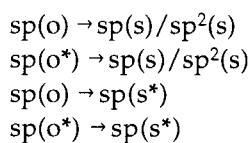
**1→3:**



**5→7:**

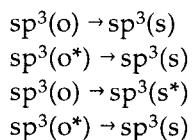


**9→11:**

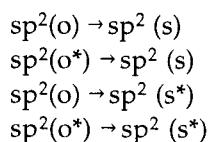


Substitutive stereogenizations are represented by:

**1→4:**



**5 → 8:**



<sup>5</sup> We prefer the term *chirogenization* over *chirotopization*.

<sup>6</sup> Mikami, K.; Narisawa, S.; Shimizu, M.; Terada, M., *J. Am. Chem. Soc.*, **1992**, *114*, 6566.

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<sup>7</sup> In Chapter 18, we develop an alternative classification on the basis of a net change of the number of chirotopic atoms  $\Delta c$ . The latter classification is based on the overall loss, no loss/gain, and gain of chirotopic atoms ( $\Delta c$ ), respectively: chirolysis ( $\Delta c < 0$ ), chirotopomutation (chiromutation) ( $\Delta c = 0$ ) and chirogenesis ( $\Delta c > 0$ ).

<sup>8</sup> A *rotative* substance (or mixture of substances) may be optically active or inactive. That is to say, the expected optical rotation may be finite, small or even accidentally zero (because of solvent, temperature, pH, or limited sensitivity of the measurement). A rotative substance consists of chiral molecules, and/or unequal numbers of enantiomorphic molecules. A *nonrotative* substance (or mixture of substances) is always optically inactive (at any wavelength). A nonrotative substance consists of achiral molecules, and/or equal numbers of enantiomorphic sets of molecules.

- <sup>9</sup> (a) Eliel, E. L.; Wilen, S. H.; Mander, L. N., *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; p. 1192.  
(b) *Ibid.*; p. 1198.  
(c) *Ibid.*; p. 1196.

<sup>10</sup> Zimmerman, H. E.; Singer, L.; Thyagarajan, B. S., *J. Am. Chem. Soc.*, **1959**, *81*, 108, footnote 16.

<sup>11</sup> Eliel, E. L., *Stereochemistry of Organic Compounds*; McGraw-Hill: New York, 1962, p. 436.

<sup>12</sup> The term *de novo* implies that bonds, defining the integrity of the stereogenic elements in the substrate and product(s), are broken/formed during the transformation for which the stereospecificity is being determined.

<sup>13</sup> The high-temperature addition of hydrogen bromide to 2-bromo-2-butene has been classified as being nonstereospecific, (ref. 11, pp. 436-437) because both *cis* and *trans* reactants give identical product mixtures - 75%-*dl* and 25%-*meso*. This is not necessarily so. By our new definition for stereospecificity, given above, this reaction is not nonstereospecific - a nonstereospecific reaction would have given a 50:50 *dl:meso* mixture. The above kinetically-controlled HBr addition involves latent thermodynamic equilibration – hence, the non-50:50 (75%-*dl* and 25%-*meso*) mixture. Ideally, the stereospecificity should be determined for transformations under kinetic control, and not, under thermodynamic control.

<sup>14</sup> Consider the following four scenarios:

- If  $S_1$  gives 100%  $P_1$ , while  $S_2$  yields 100%  $P_2$ , each of the reactions is said to display 100% stereospecificity.
- If  $S_1$  gives 100%  $P_2$ , and  $S_2$  gives 100%  $P_1$ , each of these two reactions also is said to exhibit 100% stereospecificity.
- If  $S_1$  gives 80%  $P_1$  and 20%  $P_2$ , while  $S_2$  yields 100%  $P_1$ , assuming kinetic control of the products, the reaction of  $S_1$  is 60% stereospecific and that of  $S_2$  is 100% stereospecific.
- If  $S_1$  gives 80%  $P_1$  and 20%  $P_2$ , and,  $S_2$  yields 100%  $P_2$  (instead of  $P_1$ ), assuming kinetic control of the products, the reaction of  $S_1$  is 60% stereospecific and that of  $S_2$  is 100% stereospecific.

In cases (a) vs. (b), the absolute sense of stereospecificity can be established clearly. However, in the case of (c) vs. (d), that absolute sense of stereospecificity cannot be ascertained.

<sup>15</sup> The quartet modes were defined in Volume 2, Chapter 12.

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<sup>16</sup>The molecules in question are intrinsically chiral ones, and whether there is preponderance of one type of chiral molecule over another is irrelevant here; thus, mixtures of enantiomers, in any proportions, consist of chiral molecules.

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