

Chapter 2

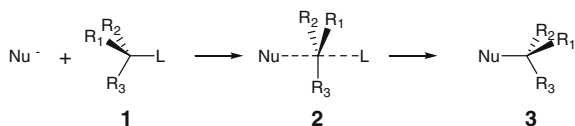
Reactions at Saturated and Unsaturated Carbons

Abstract This chapter covers the geometrical requirements for reactions at saturated and unsaturated carbons in both acyclic and cyclic systems with related stereochemical features. The nucleophilic attacks in S_N2 and S_N2' processes, involving the necessary geometrical requirements, are discussed. The resonance-driven activation of cyclopropane is of much significance in synthetic chemistry. The mode of activation and its consequences on the product profile are amply reasoned. The S_N2 -originated 1,2-migration within the geometrical constraints of the reactant and neighboring group participation under solvolysis conditions have been explained with emphasis on product distribution. The activation of oxiranes by Lewis acids, followed rearrangement with stereochemical effects, is elaborated. Given the suitable geometrical disposition of substituents and functional groups in a given molecule, many 1,2-migrations take place in tandem to generate fascinating skeletons. This chemistry has been described by the construction of several steroidal skeletons. Baldwin rules and the preferential 5-*exo*-trig over 5-*endo*-trig cyclization are demonstrated using kinetics and related product analysis with examples. The stereoelectronically controlled addition reactions have been highlighted.

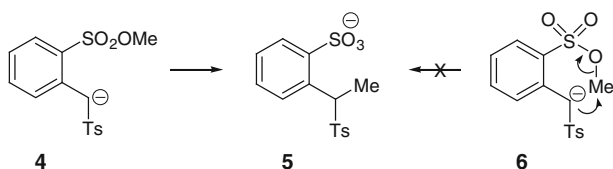
Keywords S_N2 and S_N2' reactions • Baldwin rules • Oxirane opening • Activation of a cyclopropane • 1,2-rearrangement • Ring contraction • Ring expansion • Solvolysis • Neighboring group participation • Oxirane rearrangement • Classical and nonclassical carbocations • 5-*exo*- vis-à-vis 5-*endo* cyclization • Addition and elimination reactions

The concerted bond formation and bond cleavage in S_N2 reactions proceeds with full stereoelectronic control. In the transition structure **2** for the reaction, both the nucleophile and the leaving group are bonded to the central carbon atom, which has acquired sp^2 character. One lobe of the p orbital on the carbon overlaps with the incoming nucleophile and the other lobe with the leaving group. Since the nucleophile approaches the carbon from the direction opposite to the leaving group, the result is Walden inversion or inversion of configuration. The reaction is, thus,

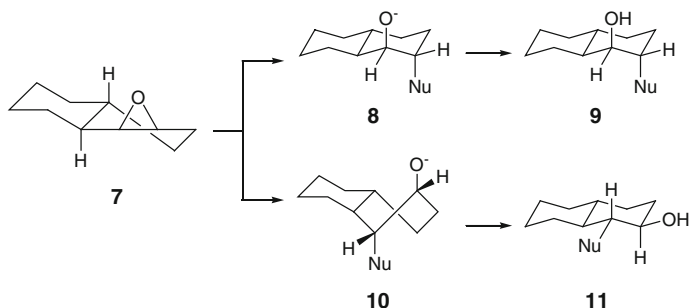
controlled by electronic effects that impose a definite geometrical restraint in the transition structure.



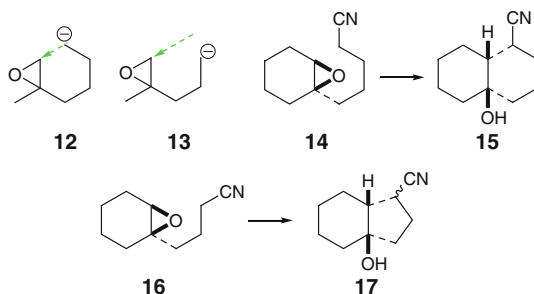
The evidence as to the fact that the nucleophile is indeed aligned in a collinear arrangement to the leaving group is provided from the transformation **4** \rightarrow **5**, which was discovered to take place via an intermolecular process rather than the formally appealing intramolecular version shown in **6**. The intramolecular version does not allow the said collinear arrangement [1]. The reaction was found indeed to be bimolecular.



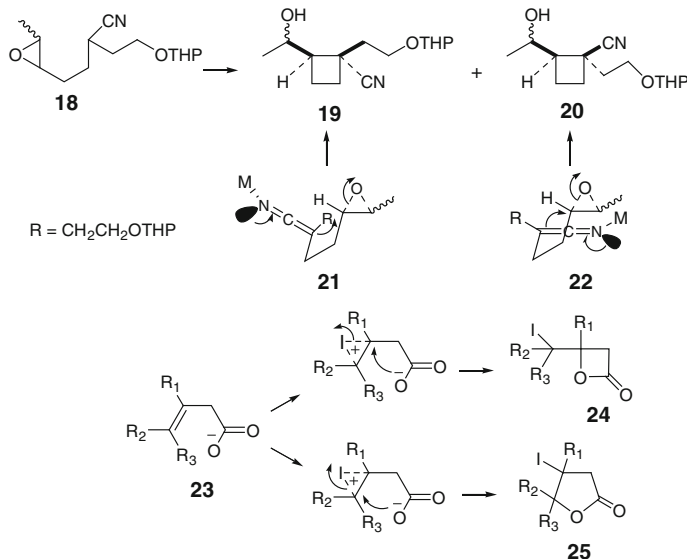
In accordance with the collinear requirement, epoxides react with nucleophiles and open up to give products of well-defined stereochemistry. We shall investigate this by considering the conformationally rigid unsymmetrical epoxide **7**, which may form two different products **9** and **11** by following different pathways. While the diaxial product **9** results from axial attack at C3 and proceeds through the chair-like intermediate **8**, the diequatorial product **11** results from equatorial attack at C2 and proceeds through the twist boat-like intermediate **10**. Since the equatorial attack at C2 proceeds through a higher energy twist-boat transition structure than the chair transition structure arising from axial attack at C3, the product **9** must form in preference to **11** under kinetically controlled conditions. It should be noted that the 1,2-diequatorial product is thermodynamically more stable than 1,2-diaxial product on account of the possible 1,3-diaxial interactions in the latter. Indeed, epoxide opening to give the diaxial product is very well known.



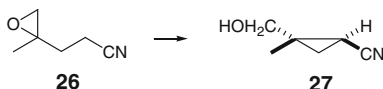
The intramolecular S_N2 opening of epoxides must also follow the above stereoelectronic requirement within the geometrical constraints of the system. It is solely based on the collinear requirement of the S_N2 reaction that Stork favored intramolecular opening leading to a six-membered ring more than that leading to a five-membered ring. While the nucleophile is perfectly aligned for a rear collinear attack in the formation of the six-membered in **12**, it is poorly aligned in the formation of the five-membered ring in **13**. The trajectory requires the nucleophile to be on the dotted line which, in turn, requires considerable bond distortion. From the reactions of the epoxynitriles **14** and **16** under basic conditions, it was indeed discovered that the transformation **14** \rightarrow **15** leading to a six-membered ring is significantly easier than the transformation **16** \rightarrow **17** leading to a five-membered ring [2].



A similar analysis of the transition state requirement allowed Stork to realize that it was easier to achieve collinearity in the formation of a four-membered ring than in the formation of a five-membered ring. Thus, for a given situation where both the four- and five-membered rings could form, the former was considered to prevail. Indeed, the reaction of the epoxynitrile **18** with a base (required for deprotonation to generate the requisite carbanion) in benzene furnished a 95:5 mixture of the isomeric cyclobutanes **19** and **20** only [3]. No five-membered ring product was formed. One may note that the major isomer **19** is less stable due to two large substituents being *cis* to each other than in the minor isomer **20**. This result indicates that the transition state structure **21**, leading to **19**, is of lower energy than the transition state structure **22** that leads to **20**. In the transition state structure **22**, the nitrogen atom along with the large solvated metal ion comes close to the far end of the epoxide carbon to cause significant van der Waals interactions. In yet another interesting example, iodolactonization of the β,γ -unsaturated carboxylic acid salts **23** were found to yield the butyrolactones **24** in preference to the otherwise more stable γ -lactones **25**. The internal opening of the three-membered ring iodonium ion (equivalent to an epoxide) by the carboxylate ion leading to a four-membered ring product, **23** \rightarrow **24**, is preferred over the opening leading to a five-membered ring product, **23** \rightarrow **25**.



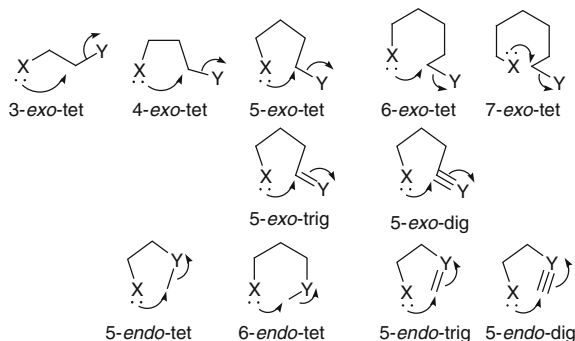
Finally, in regard to the internal opening of an epoxide ring, cyclopropane formation is preferred over cyclobutane formation, regardless of the relative degree of substitution of the ring. For instance, the reaction of **26** with a suitable base generated the cyclopropane **27** exclusively [3]. The transition state structure for this transformation resembles the transition state structure **21** above, but with one carbon less in the chain linking the nitrile group and the ring.



In summary, in internal epoxide ring opening, six-membered ring formation does not require bending of any of the σ bonds of the chain, while the formation of five-, four-, and three-membered rings requires the simultaneous bending of four, three, and two such σ bonds, respectively, in addition to the electron pair orbital of the carbanion. Though the degree of bending is more pronounced in the formation of the three-membered ring than in others, the number of bonds that must bend simultaneously is more important than the degree of bond bending. Thus, the simultaneous bending of three σ bonds leading to cyclobutane formation is less difficult than the simultaneous bending of four σ bonds leading to cyclopentane formation, but more difficult than the bending of two σ bonds leading to cyclopropane formation. In other words, the facility of ring formation in the internal opening of epoxides decreases in the order: six-membered ring > three-membered ring > four-membered ring > five-membered ring.

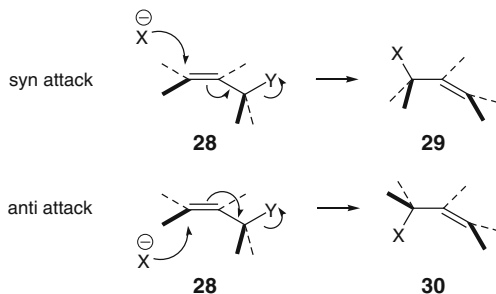
We shall now turn to the internal $\text{S}_{\text{N}}2$ reaction on a sp^3 carbon. Purely on account of geometrical constraints imposed in achieving the collinear alignment,

Baldwin proposed a set of rules for such ring closure reactions [4]. The reactions were designated by a numerical prefix which denotes the size of the ring to be formed, followed by the term *exo* or *endo* depending upon whether the bond breaking is exocyclic or endocyclic to the ring thus formed. Now, a suffix such as *tet* (for a tetrahedral or sp^3 carbon), *trig* (for a trigonal or sp^2 carbon), or *dig* (for a diagonal or sp carbon) describes the state of hybridization of the electrophilic carbon. A collection of many such reactions are given below.



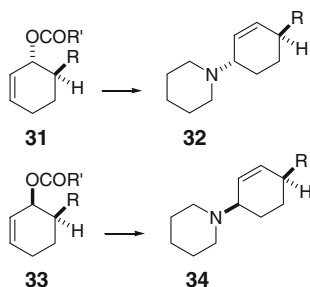
While all the reactions from 3-*exo-tet* to 7-*exo-tet* are favored, the 5-*endo-tet* and 6-*endo-tet* reactions are disfavored on stereoelectronic grounds, i.e., on account of the collinear requirement of S_N2 reactions. The relative ease of these processes is 3-*exo-tet* > 4-*exo-tet* < 5-*exo-tet* > 6-*exo-tet* > 7-*exo-tet*. It is important to recognize that the intramolecular S_N2 process proceeding through the transition structure resembling **6** constitutes a 6-*endo-tet* process and, hence, unfavorable.

The S_N2' reaction involves nucleophilic attack on the terminal sp^2 carbon with a shift in the position of the double bond. The nucleophile may attack either *anti* or *syn* to the leaving group as shown in the transformations **28** \rightarrow **29** and **28** \rightarrow **30**, respectively. The *syn* attack is preferred over the *anti* attack because the *syn* attack displaces the π electrons in the direction that is *anti* to the σ_{C-Y} bond and, thus, suitable for the next rear side attack.

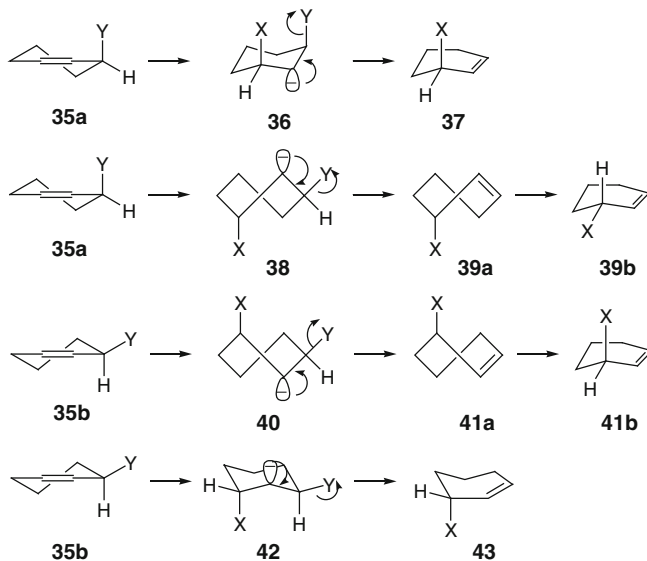


In confirmation of the above preferred *syn* attack, reactions of the cyclohexenyl dichlorobenzoates **31** ($R = \text{Me}$, $i\text{-Pr}$, $t\text{-Bu}$; $R' = \text{Cl}_2\text{C}_6\text{H}_3$) with piperidine afforded **32**. Likewise, the *trans* and *cis* mesitoates **31** and **33** ($R = i\text{-Pr}$, $R' = \text{C}_6\text{H}_2\text{Me}_3$)

reacted with piperidine to form **32** and **34**, respectively [5, 6]. The difference in the relative dispositions of the two substituents on the cyclohexene core should be noted.

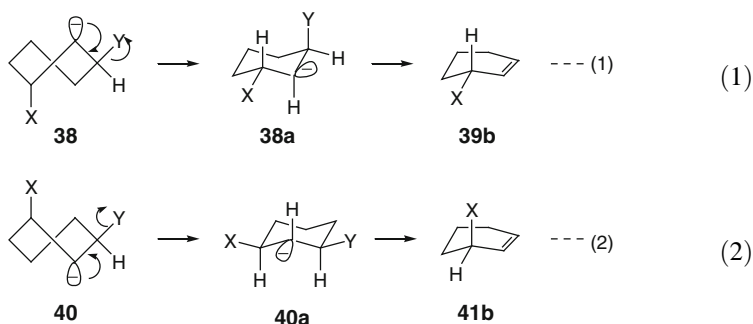


The story of the cyclohexenyl system is a little more complicated than from the above two reactions, because the cyclohexenyl system can exist in two conformations such as **35a** and **35b**. A *syn* attack on **35a** will proceed through the chair-like transition state resembling **36** and generate **37**. In the transition state structure **36**, the electron pair orbital is disposed *anti* to the leaving group *Y* and, thus, the subsequent elimination (or intramolecular S_N2 reaction) is facile. In the alternate *anti* attack, the transition state structure resembles the twist-boat structure **38**, wherein the electron pair orbital is *syn* to the leaving group and, thus, not facile. Thus, the difficulties in the transformation **35a** \rightarrow **39b** are: (a) energy-requiring twist-boat transition structure **38**, (b) stereoelectronically unsupported *syn* elimination leading to the transformation **38** \rightarrow **39a**, and (c) the energy requiring flip of the twist-boat olefin **39a** to the half chair product **39b**. Out of these two processes, the process **35a** \rightarrow **36** \rightarrow **37** appears to be the better choice.

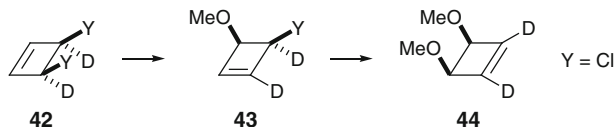


In the alternate conformer **35b**, the *syn* attack will proceed through the twist-boat conformer resembling **40**, wherein the axes of the electron pair orbital and σ_{C-Y} are *anti* but not antiperiplanar to allow a smooth elimination to **41a**, going over to **41b** through ring flip. However, in comparison, this transformation must be more facile than the transformation **35a** \rightarrow **39b**. Though the *anti* attack to **35b** does proceed through a chair-like transition structure resembling **42**, the final elimination reaction leading to **43** is not supported stereoelectronically for the *syn* dispositions of the electron pair orbital and the leaving group Y. Overall, the *syn* process **35a** \rightarrow **36** **37** is the most energy conserving process and it will be expected to prevail.

It is also conceivable that the twist-boat transition state structures **38** and **40** may undergo ring flip to **38a** and **40a** before collapsing through the elimination pathways to form **39b** and **41b** as shown in Eqs. 1 and 2, respectively.

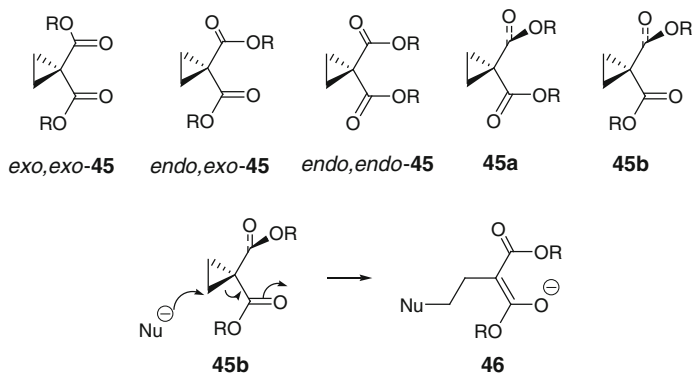


A fascinating example of two consecutive *syn* additions is expressed from the overall transformation **42** \rightarrow **44** via **43**, the product of the first *syn* addition, on reaction of **42** with sodium methoxide [7]. Note that the methoxy substituents in the product are *syn*, which could be easily established by nOe measurements.

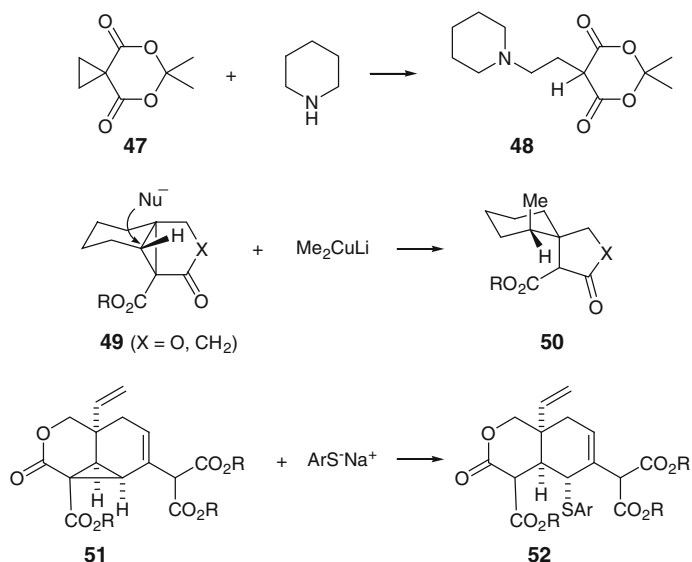


It is conceivable that cyclopropane 1,1-dicarboxylate can adopt either of the three conformations *exo,exo*-**45**, *endo,exo*-**45**, and *endo,endo*-**45**. When the carbonyl group and the cyclopropane ring are *anti* across the intervening σ_{C-C} bond, we will consider the orientation to be *exo*. Likewise, when the carbonyl group and the cyclopropane ring are *syn* across the intervening σ_{C-C} bond, we will consider the orientation to be *endo*. However, all the above conformations are disfavored on dipolar and/or steric grounds. It is therefore assumed that **45** adopts preferably the conformer **45a** or **45b** to avoid the said interactions, on one hand, and still have the *p* orbital of the in-plane carbonyl function parallel to the adjacent σ_{C-C} bond. This arrangement activates the σ_{C-C} bond and allows a nucleophilic attack on the remote carbon. The resultant carbanion delocalizes into the carbonyl group as shown in the

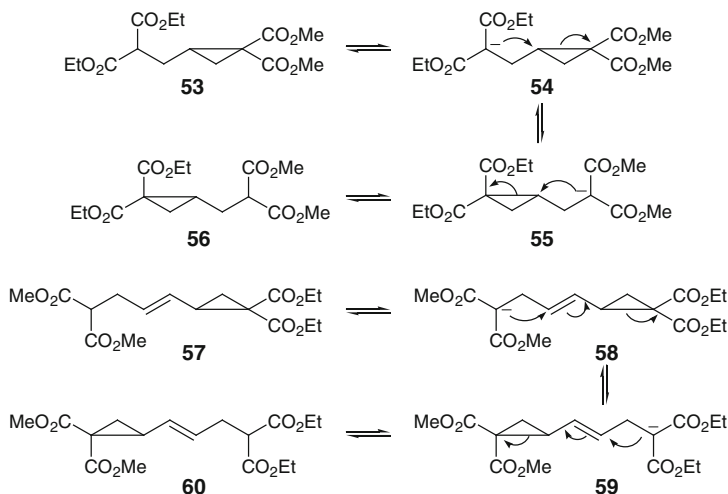
transformation **45b** \rightarrow **46**. The conformer **45b** is preferred over **45a** if one is to rely upon the anti-transition state structure theory. It is also evident that if the compound is locked in either of the conformations *exo,exo*-**45**, *endo,exo*-**45**, and *endo,endo*-**45** for geometrical reasons, it will display heightened reactivity toward nucleophiles.



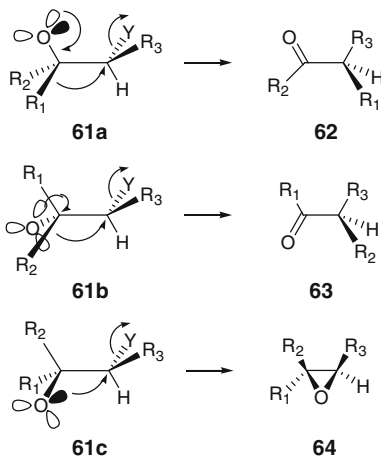
Indeed, when **47** is mixed with piperidine in benzene at room temperature, an exothermic reaction takes place to form the adduct **48** [8]. For substrates enjoying activation by a single carbonyl function, please see the transformations **49** \rightarrow **50** [9] and **51** \rightarrow **52** [10].



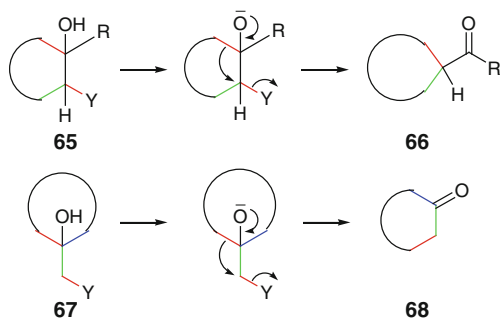
It is the consequence of the above activation mechanism that **53** equilibrates with **56** via **54** and **55**, and likewise, **57** equilibrates with **60** upon addition of a catalytic amount of $\text{CH}_3\text{S}(\text{O})\text{CH}_2\text{Na}$ in DMSO as the solvent [11, 12].



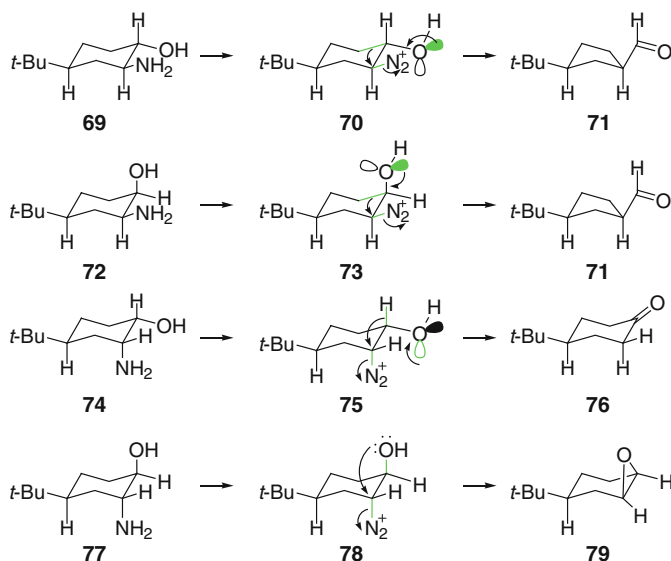
Now, we shall consider rearrangement reactions that involve two or more intramolecular $\text{S}_{\text{N}}2$ processes before reaching the product. Let us begin with the reaction of tertiary alcohols bearing a leaving group at the β carbon. Note that in the general transformation **61a** \rightarrow **62**, the group R_1 that migrates from the oxygen-bearing carbon to the carbon bearing the leaving group Y is disposed in an anti relationship with both $\sigma_{\text{C-X}}$ and electron pair orbital on the oxygen atom. If for some reason, steric or otherwise, the molecule adopts the conformation as in **61b**, it is R_2 that will migrate and yield the isomeric compound **63**. Finally, the conformer **61c**, wherein $\sigma_{\text{C-O}}$ is anti to the leaving group Y , will lead to the epoxide **64**.



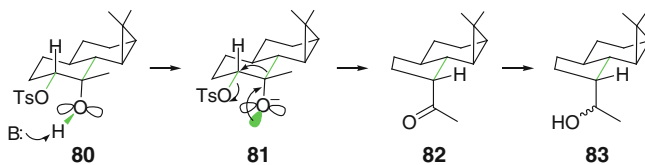
We can now apply the above general concepts to a system wherein both the hydroxyl group and the leaving group Y are located at positions 1 and 2 on a ring system, such as in **65**, and to a system wherein the hydroxyl function is located on a ring carbon and the leaving group Y on a carbon outside the ring, such as in **67**. We shall notice ring contraction in the transformation **65** \rightarrow **66** and ring expansion in the transformation **67** \rightarrow **68**. The carbon bearing the hydroxyl group in **65** comes out of the ring in the product **66** and, thus, the number of atoms in the ring gets reduced by one. In contrast, the carbon outside the ring in **67** becomes part of the ring in the product **68** and, thus, the ring gets enlarged by one.



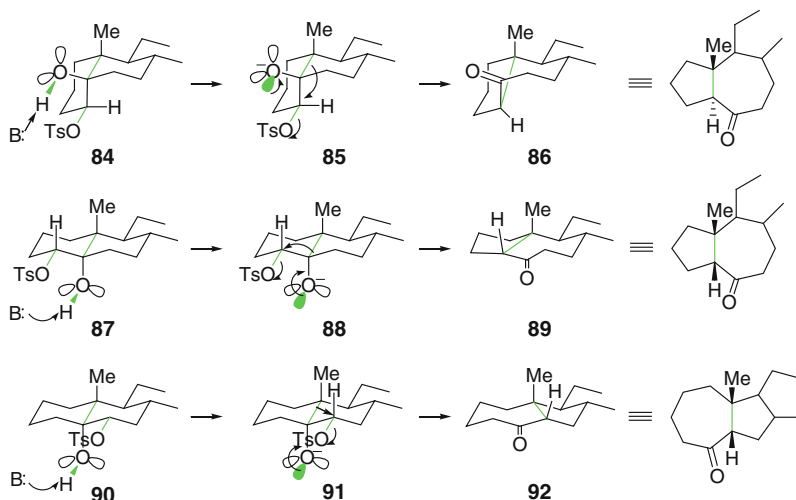
Let us now apply the above concepts to the deamination of vicinal aminoalcohols on a cyclohexane backbone. Four different situations arise from the structures of **69**, **72**, **74**, and **77**. The amino group is transformed into a diazonium species to act as a leaving group as in structures **70**, **73**, **75** and **78**, respectively. It is easy to note the antiperiplanar relationship of the ring bond in green color with an electron pair orbital on the oxygen in green color and the σ_{C-N} bond, also in green color, in structures **70** and **73**. The rearrangement, as shown, occurs to furnish the ring-contracted aldehyde **71** in each instance. In the diazonium species **75**, it is the axial hydrogen on the carbinol carbon that is antiperiplanar to the σ_{C-N} bond and, thus, the hydrogen migrates and the cyclohexanone **76** is formed. In the species **78**, the carbinol oxygen itself is antiperiplanar to the σ_{C-N} bond, which allows an intramolecular nucleophilic displacement of the diazonium group and the epoxide **79** is formed. It is important to recall that the transformations **70/73** \rightarrow **71** and **75** \rightarrow **76** are typical of the transformations **61a/b** \rightarrow **62/63** and, likewise, the transformation **78** \rightarrow **79** is typical of the transformation **61c** \rightarrow **64**.



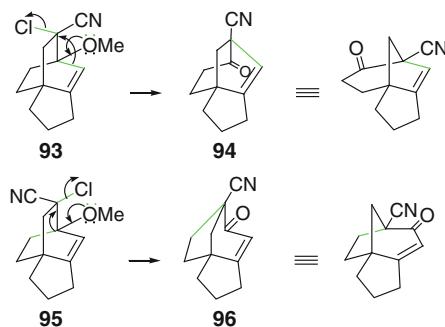
We will now consider some more such examples. Attempted reduction of **80** with LiAlH_4 furnished the ring-contracted product **83** [13]. The basic character of LiAlH_4 was responsible for deprotonation of the carbinol to generate the corresponding oxy anion **81**, which triggers the rearrangement to **82**. The carbonyl product **82** is reduced further by the hydride to yield the observed alcohol **83**.



The transformations **84** \rightarrow **86**, **87** \rightarrow **89** and **90** \rightarrow **92** are some of the other steroid-based examples wherein one ring is contracted and the other is enlarged by virtue of the structural design of the substrates [14].



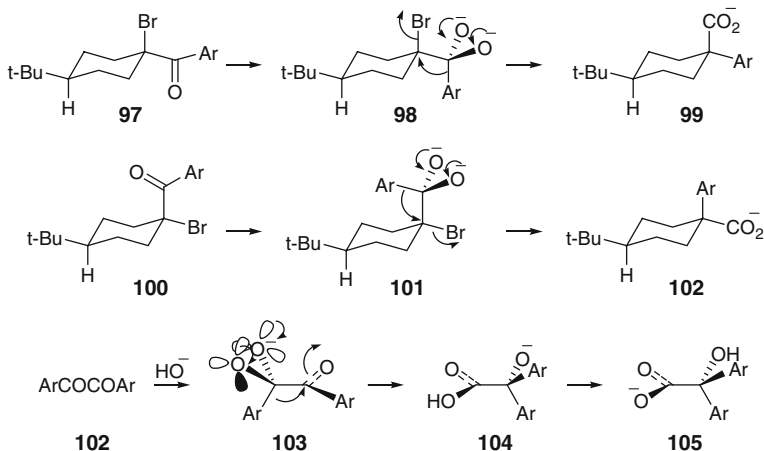
A consequence of the relative orientational differences could also be seen from the changes **93** \rightarrow **94** and **95** \rightarrow **96** [15]. These changes are brought about upon treatment with a silver salt, AgBF_4 , which weakens the $\sigma_{\text{C-Cl}}$ bond to allow the $\sigma_{\text{C-C}}$ bond antiperiplanar to it (green color bonds in the bicyclic system) to migrate. Of course, in each substrate, one electron pair orbital on the oxygen atom is antiperiplanar to the migrating bond as well to provide the much necessary push.



We learnt above that an oxygen atom (for that matter, a heteroatom) on one carbon and a leaving group on the adjacent carbon constituted a situation for bond migration from the oxygen-bearing carbon to the carbon bearing a leaving group with the loss of the latter. Throughout, an electron pair orbital on the oxygen was antiperiplanar to the migrating bond and the migrating bond, in turn, was antiperiplanar to the bond connecting the leaving group to the adjacent carbon. Let us consider a situation wherein there are two oxygen atoms on the same carbon and

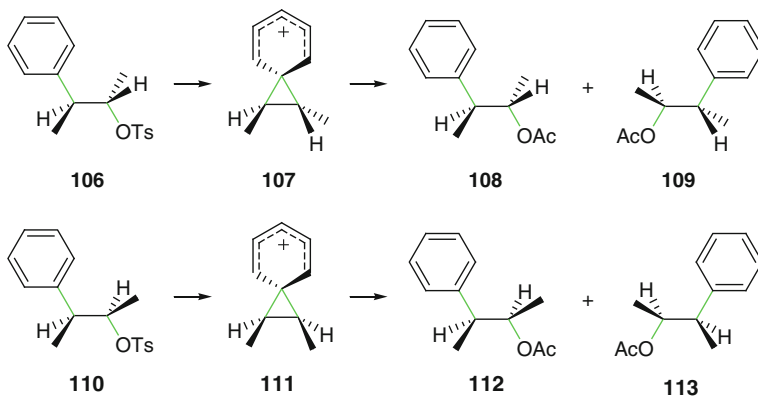
each oxygen atom has one electron pair orbital antiperiplanar to the migrating bond on the same very carbon. This allows the migration to occur faster, probably twice as fast as the migration in a case with just one oxygen atom. Such situations arise in reactions of α -halo ketones and aryl-substituted 1,2-dicarbonyl compounds with oxygen-based nucleophiles such as the hydroxide ion.

For instance, **97** generates **98** on reaction with sodium hydroxide, wherein each oxygen has one electron pair antiperiplanar to the $\sigma_{\text{C-Ar}}$ bond and, thus, making it labile for cleavage. Further, the $\sigma_{\text{C-Ar}}$ bond is antiperiplanar to the $\sigma_{\text{C-Br}}$ bond on the adjacent carbon. The combined consequence of these two geometrical dispositions is cleavage of the $\sigma_{\text{C-Ar}}$ bond and attack of the aryl group on the carbon bearing bromine in $\text{S}_{\text{N}}2$ fashion in quick succession to form **99** as the sole product. The reaction is, therefore, stereoelectronically controlled. The story with the transformation **100** \rightarrow **102** is similar. The transformation **102** \rightarrow **105** constitutes what we know as benzil-benzilic acid rearrangement, and it proceeds by following the same stereoelectronic principles as the other rearrangements.

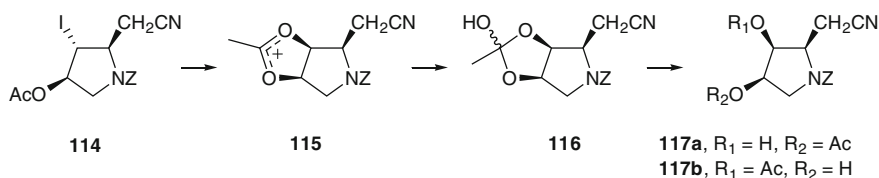


Solvolysis with neighboring group participation in the presence of a nucleophile may be viewed as a reaction on a saturated carbon. There is, however, a difference: the carbon under attack by the external nucleophile in the present instance carries substantial positive charge on account of charge distribution through the neighboring group. We will understand this process by considering the solvolysis of the *erythro*-tosylate **106** in comparison with the solvolysis of the *threo*-tosylate **110** in acetic acid. Neighboring group participation in **106** leads to the chiral phenonium ion **107**, which is captured by acetate ion on either of the two carbon atoms of the three-membered ring, as shown, and a 50:50 mixture of the *erythro*-acetates **108** and **109** is formed. Please note that **108** and **109** are one and the same (try

superimposing one onto the other) and, thus, the resultant product is optically active. A similar analysis of the solvolysis of **110** allows us to arrive at the two *threo* products **112** and **113** through the achiral phenonium ion **111**. Since **112** is mirror image of **113**, the resultant product mixture is optically inactive overall.

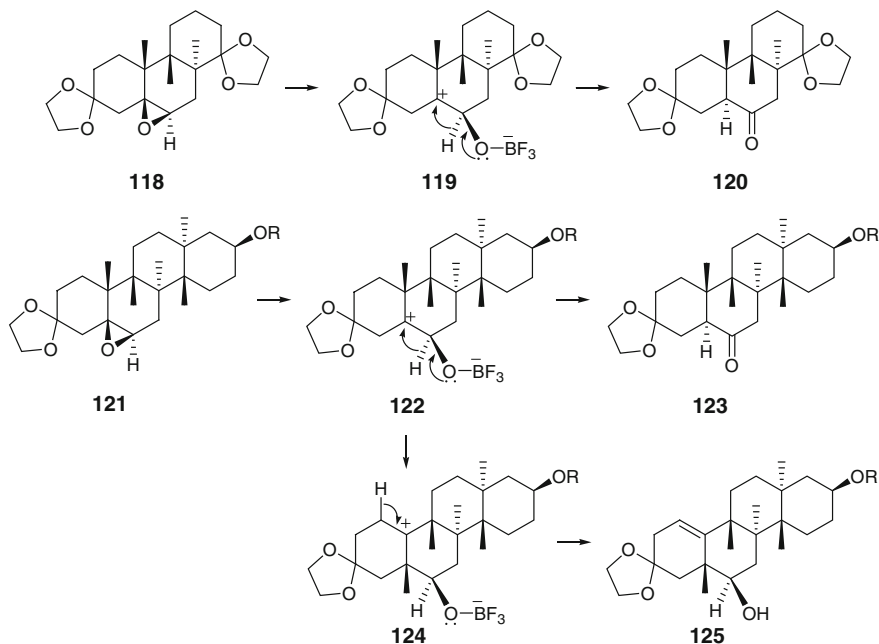


When the iodoacetate **114** was subjected to solvolysis in wet acetic acid containing silver acetate, the products were the *cis*-diol monoacetates **117a** and **117b**. Weakening of the $\sigma_{\text{C-I}}$ bond through association of silver ion with the iodine atom is closely followed by the intramolecular capture of the incipient carbocation by the acetoxy group on the adjacent carbon to generate the acetoxonium ion **115**. This is captured by water to generate **116**, which collapses to a mixture of **117a** and **117b**. The compound **117** was used in the synthesis of (+)-crotanecine, a naturally occurring alkaloid [16].

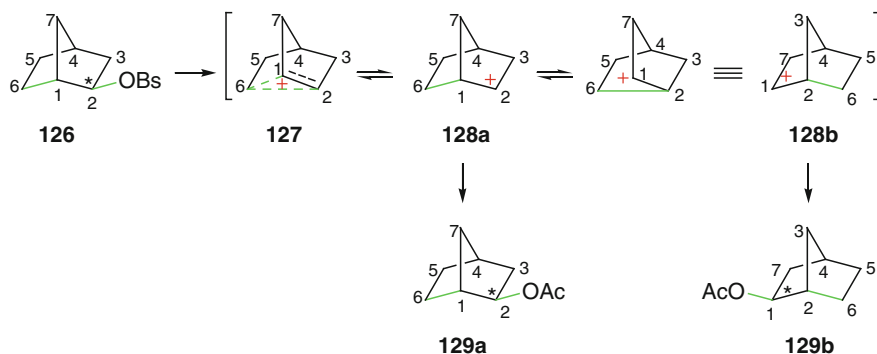


The rearrangement of oxiranes to carbonyl species on treatment with Lewis acids provides yet another elegant example of neighboring group participation that culminates into excellent diastereocontrol. For instance, the oxirane **118** is smoothly transformed into **120** on treatment with $\text{BF}_3 \cdot \text{OEt}_2$. The key to the formation of a single product is concurrent heterolysis of the $\sigma_{\text{C-O}}$ bond from the β -face and migration of the hydrogen as a hydride on the α -face is as shown. Contrast to this is the formation of both **123** and **125** from **121**. In this case, a small time lag between

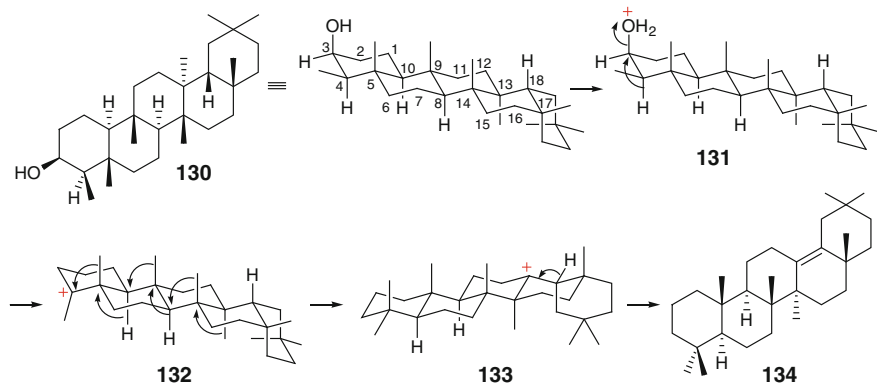
the cleavage of the $\sigma_{\text{C-O}}$ bond and the migration of hydrogen allows transient formation of the discrete carbocation **122**, which allows migration of the angular methyl group, as shown, and the new carbocation **124** is formed. The loss of a proton from **124** leads to the formation of **125**.



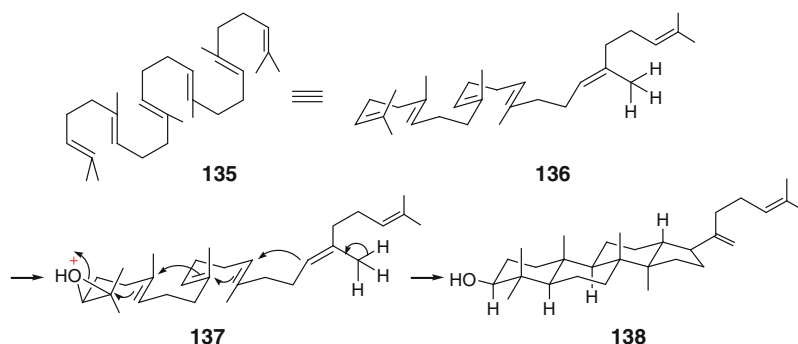
In the *exo*-2-norbornyl brosylate **126**, the $\sigma_{\text{C-OBs}}$ bond is antiperiplanar to $\sigma_{\text{C1-C6}}$ bond. This allows acetolysis to proceed with neighboring group participation, as shown, leading to the formation of a 50:50 mixture of **129a** and **129b** from an optically active brosylate. Since **129a** is mirror image of **129b**, the product is optically inactive overall. The cleavage of $\sigma_{\text{C-OBs}}$ bond under neighboring group participation of $\sigma_{\text{C1-C6}}$ bond allows formation of the nonclassical carbocation [17, 18] **127** which could be viewed as a fast equilibrating 50:50 mixture of the classical carbocations [19] **128a** and **128b**, one being mirror image of the other. The *exo*-capture of **128a** and **128b** forms **129a** and **129b**, respectively.



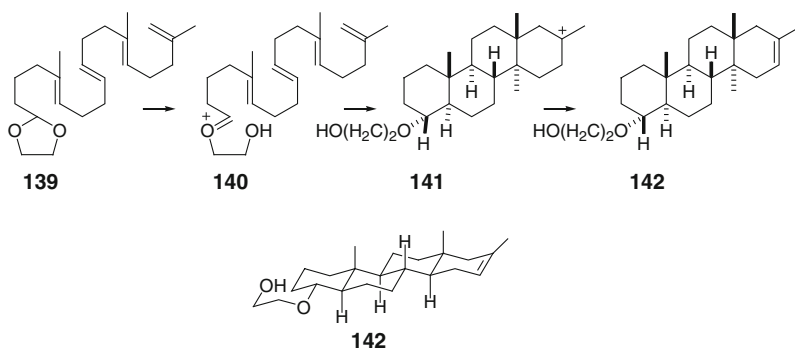
The effect of an antiperiplanar arrangement of an electron-deficient bond and an electron-rich bond is so dramatic that several rearrangements can occur one after the other in quick succession. The acid-catalyzed 3- β -friedelanol (**130**) \rightarrow 13(18)-oleanene (**134**) transformation is one such example among many. Protonation of the carbinol oxygen converts it into a strong leaving group. The α -hydrogen on C4, which is anti to the σ_{C-O} bond, migrates, leading to the tertiary cation **132**. Soon after, many angular group migrations take place to arrive at the angular tertiary cation **133**, whose fate is only to undergo deprotonation, as shown, to form **134**.



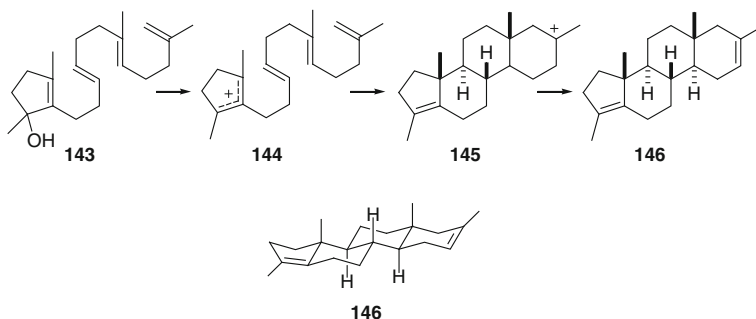
The enzyme-catalyzed polycyclization of squalene **135** produces dammaradienol **138**, which is known to be the precursor of cholesterol. In the process, squalene oxide is the intermediate, which adopts the conformation as shown in **137**, and rearranges, under acid catalysis, to **138** [20, 21]. Note that in the transformations **131** \rightarrow **133** and **137** \rightarrow **138**, many S_N2 reactions take place in tandem for the sole reason of stereoelectronically driven well-organized geometrical orientations of the reacting functional groups. Note that all the double bonds are *trans*, and also that two such consecutive bonds are 1,5-related to each other.



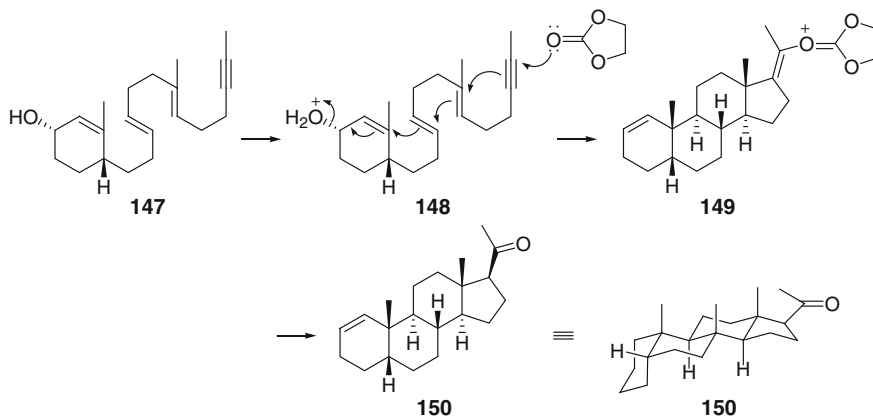
A cationic center may be derived from a variety of other sources such as acetal and alcohol on mixing with an acid. Treatment of the polyolefinic acetal **139** with stannic chloride in pentane gives an almost 50:50 mixture of the two racemic D-homosteroidal tetracyclic isomers **142**. The first formed cationic species **140** is not chiral and, hence, the two faces of the nearest olefinic bond can react with it at equal ease. The conversion of the open chain **139** having no chiral centers into the tetracyclic species **142** having seven such centers and yet producing only two out of the total possible 64 racemates (i.e., four out of $2^7 = 128$ diastereomers) is a striking tribute to the power of stereoelectronic effects [22].



The allylic alcohol **143** furnishes the tetracyclic product **146** on treatment with stannic chloride in nitroethane at $-80\text{ }^{\circ}\text{C}$. The first formed allylic cation **144** undergoes tandem cyclization with the remaining olefinic bonds to form the tertiary cation **145**, which loses a proton to generate **146** [23].

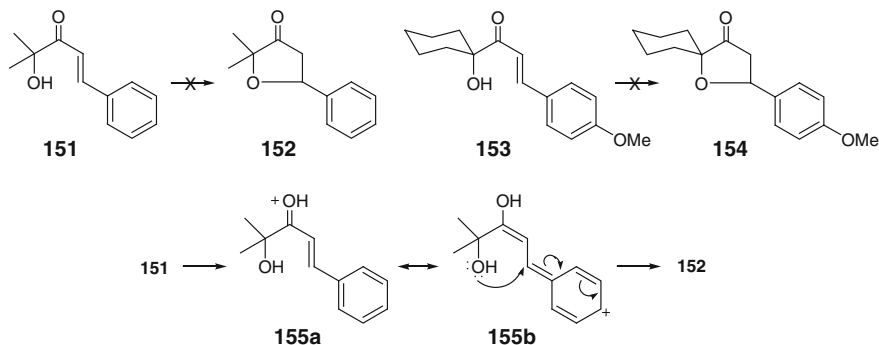


In a more impressive polyene cyclization, reaction of the optically active allylic alcohol **147** with trifluoroacetic acid and ethylene carbonate followed by workup with K_2CO_3 in aqueous methanol furnished the optically active product **150**. The reaction is initiated by a *syn*-selective S_N2 reaction with allylic rearrangement (S_N2') and proceeds through the carbonate-trapped intermediate **149**. Likewise, the reaction of the enantiomer of **147** furnished the enantiomer of **150**. The cyclization step was essentially enantiospecific. The process involves total asymmetric synthesis due to a single chiral center in the starting allyl alcohol [24].

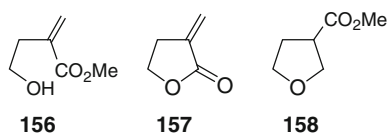


We have learnt that (a) the dihedral angle requirement for S_N2 reactions is 180° or close to it, (b) the 5-*exo*-trig reaction is favored over the 5-*endo*-trig reaction, and (c) axial electrophilic or nucleophilic attack on a double bond present in cyclohexene is favored over the corresponding equatorial attack. Keeping these principles in mind, we can proceed to analyze a few reactions that involve attack on a sp^2 center. Substrates such as **151** and **153** fail to react under basic conditions to form the furanones **152** and **154**, respectively. Obviously, the oxy anion formed from the alcohol does not react with the enone in 5-*endo*-trig manner, a pathway that one

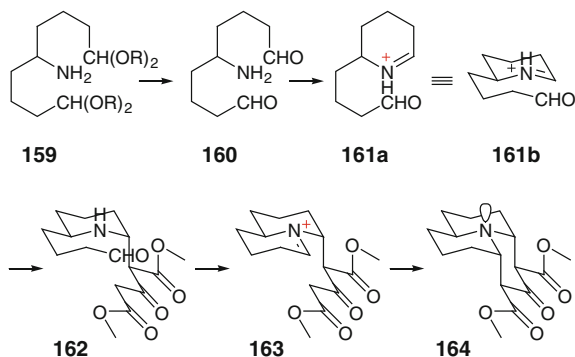
finds formally very appealing. Remember that oxy anions add rapidly to enones in bimolecular processes under otherwise similar reaction conditions. In contrast, **152** and **154** are formed readily under acidic conditions, and we must understand the compelling reason for the same. Under the acidic conditions of the reaction, protonation of the carbonyl oxygen in **151** leads to a resonance mixture of **155a** and **155b**. It is this **155b** that allows now the 5-*exo*-trig closure, as shown, and the product **152** is formed with a great facility [25, 26].



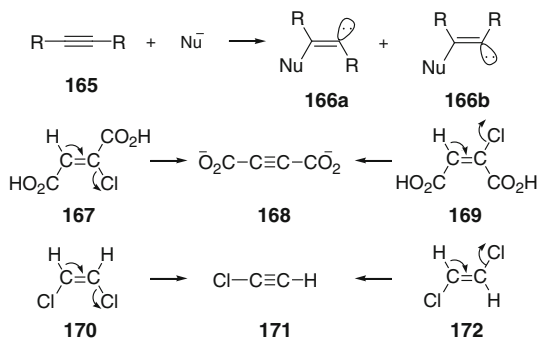
In further revelation of the strong stereoelectronic requirement for the intramolecular S_N2 reaction, the hydroxy ester **156** furnished the lactone **157** only and none of the tetrahydrofuran product **158** on reaction with a base. Whereas the product **157** arises from the 5-*exo*-trig process involving attack of the oxy anion on the ester carbonyl function, the difficult 5-*endo*-trig process involving attack of the oxy ion at the olefinic carbon in conjugate fashion is required for the formation of **158** [25, 26].



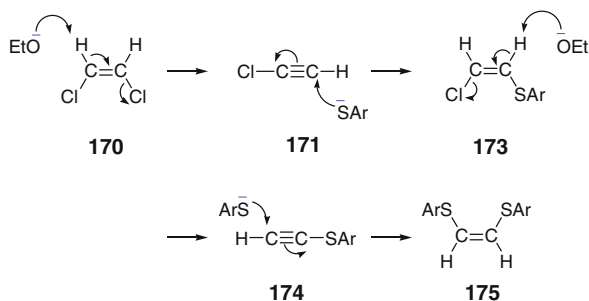
When the species **159** and dimethyl 3-oxo-pentan-1,5-dicarboxylic acid (dimethyl acetone dicarboxylate) are taken together in aqueous acid, **164** is formed as the sole product. Hydrolysis leads to the dialdehyde **160**, which undergoes intramolecular condensation to generate the iminium ion **161a**, rewritten as **161b** in the three-dimensional form. The enol from the dicarboxylate acts as a nucleophile and reacts with the above iminium ion on the axial face to generate **162**, releasing the secondary amine function simultaneously. Intramolecular condensation of this secondary amine with the other aldehyde function forms the iminium ion **163**, which is captured by the other enol form of the dicarboxylate, again on the axial face, and **164** is formed [27].



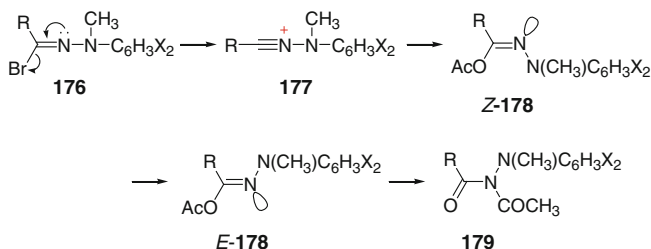
Addition of a nucleophile to a triple bond as in **165** may, in principle, lead to two different products **166a** and **166b**. The added nucleophile is anti to the released electron pair orbital in **166a** and *syn* in **166b**. The stereoelectronic effects favor the formation of **166a**. That being the case, the process **166a** \rightarrow **165** must also be faster than the process **166b** \rightarrow **165**; both of these processes are E1cB reactions. Following this, the transformation **167** \rightarrow **168** under basic conditions was indeed discovered to be 50 times faster than the corresponding transformation **169** \rightarrow **168** [28, 29]. Also, *cis*-dichloroethylene **170** is transformed into chloroacetylene **171** about 20 times faster than *trans*-dichloroethylene **172** [30].



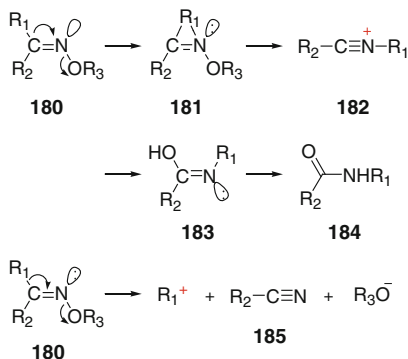
The *cis*-dichloroethylene **170** reacts with sodium *p*-toluenethiolate ($p\text{-CH}_3\text{C}_6\text{H}_4\text{SNa}$) in the presence of sodium ethoxide to give *cis*-1,2-*bis-p*-tolyl-mercaptoethylene **175**. This is in contrast to the behavior of *trans*-dichloroethylene which is recovered unchanged. The transformation **170** \rightarrow **175** proceeds as shown, and there is evidence in favor of **171**, **173**, and **174** as the intermediates during the course of the reaction [31–33]. *Trans*-elimination is therefore favored over *cis*-elimination, indicating a decisive role of the stereoelectronic effects in such reactions.



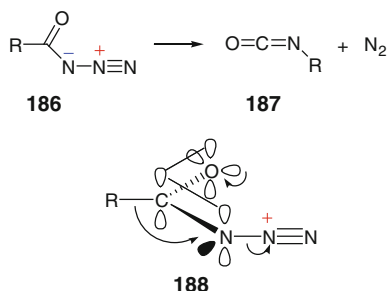
Addition of a nucleophile to a nitrilium ion generates a product in which the released electron pair occupies the position on the nitrogen that is *anti* to the nucleophile. For instance, the *N*-anilininitrilium ion **177**, formed from solvolysis of the hydrazoneyl bromide **176** in the presence of sodium acetate, gives *Z*-**178**. On heating, *Z*-**178** is rapidly transformed into the amide **179** via isomerization to *E*-**178** [34, 35]. Note that the acyl group migration from oxygen to nitrogen takes place in the last step of the whole process.



In the widely used Beckman rearrangement [36] that converts oximes and derivatives into amides, the group that migrates is the one that is *anti* to the $\sigma_{\text{N-O}}$ bond. Also, the stereochemical integrity of the migrating group is completely retained in the product. Thus, the migration of R_1 in **180** generates the nitrilium ion **182**, which hydrolyses, via **183**, to form the amide **184**. When the migrating group can form a stable cation, fragmentation to the corresponding nitrile such as **180** \rightarrow **185** takes place instead of the above migration.



In the Curtius rearrangement in which the acylazide **186** is transformed into the isocyanate **187** and molecular nitrogen, the migrating group retains its stereochemical integrity just as in the Beckman rearrangement. Stereoelectronic effects therefore control the reaction because the migrating group is necessarily anti to the $\sigma_{\text{N}-\text{N}_2^+}$ bond and, also, the migrating group is anti to an electron pair orbital on the carbonyl oxygen as illustrated in **188**.



Thus, both the *trans*-addition and *trans*-elimination are strongly favored over the corresponding *cis*-variants due to stereoelectronic effects. In 1,2-migrations, the migrating group is always anti to the leaving group on the adjacent carbon.

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