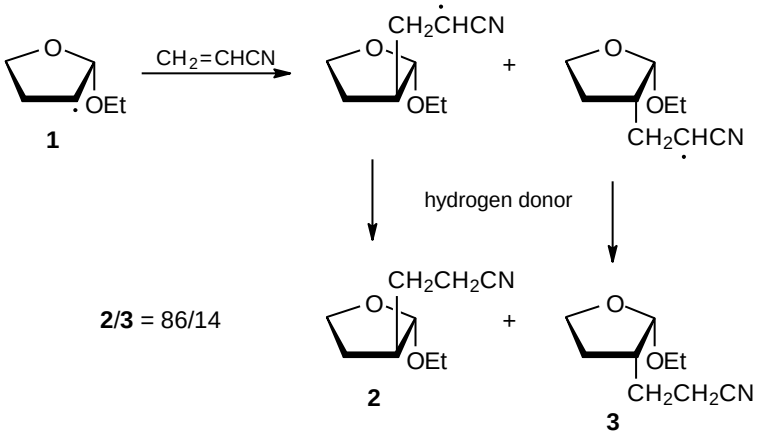
Chapter 11
Stereoselectivity

I. Introduction

A. Definitions

Stereoselectivity is "the preferential formation of one stereoisomer over another in a chemical reaction".[1] This selectivity can be divided into diastereoselectivity and enantioselectivity. "Enantioselectivity in a reaction is either the preferential formation of one enantiomer of the product over the other or the preferential reaction of one enantiomer of the (usually racemic) starting material over the other...Diastereoselectivity is the preferential formation in a reaction of one diastereoisomer of the product over others."[2] Although diastereoselectivity almost always refers to product formation, it also can apply to preferential consumption of one diastereomer.[3]

Scheme 1

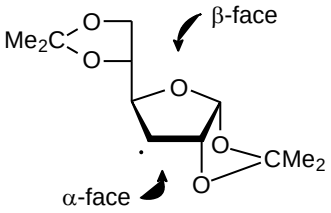


B. Factors Affecting Stereoselectivity

Stereoselectivity in radical reactions is determined by a combination of factors that includes steric, stereoelectronic, conformational, torsional, and configurational effects as well as reaction temperature.[4] Each of these effects can be linked to a particular aspect of structure. Steric effects are the repulsive interactions that develop between closely approaching species (e.g., a neutral molecule and a free radical) or between two groups within the same structure. Stereoelectronic effects are geometry-dependent, orbital interactions that favor formation or consumption of one stereoisomer over another. Conformational effects are differences in stereoselectivity due to differences in the population of various conformers. Torsional effects are the destabilizing interactions that develop as electrons in bonds on adjacent atoms move closer to each other. Finally, configurational effects in radical reactions are differences in stereoselectivity due to pyramidal radicals that undergo reaction faster than inversion of configuration.

Although stereoselectivity in a reaction often results from a combination of the effects just described, it is possible to identify three important situations where a particular effect appears to be dominant. First, in addition and abstraction reactions, where the radical center is not adjacent to a

ring oxygen atom, the greater role of steric effects causes reaction to occur along the least-hindered pathway. When a radical is centered on an atom adjacent to a ring oxygen atom (as occurs in pyranos-1-yl and furanos-1-yl radicals) orbital interactions become the factor most frequently determining stereoselectivity. Finally, in reactions that form new five- and six-membered rings, stereoselectivity usually is determined by maximizing stability of a chair-like or boat-like transition state



4

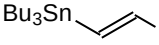
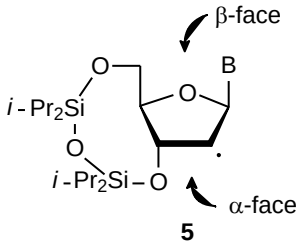
unsaturated reactant or deuterium donor	β-face reaction / α-face reaction	yield	ref
	73/27	40%	6,7
	68/32	57%	8
	67/33	60%	9
	87/13	83%	10
Bu_3SnD	85/15	-	11,12

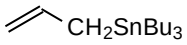
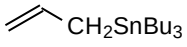
Table 1. Stereoselectivity in reactions of the radical **4**

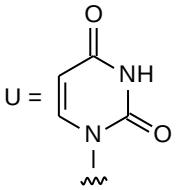
II. Minimizing Steric Interactions: The Least-Hindered Pathway

As mentioned in the previous section, stereoselectivity in reactions of carbohydrate radicals depends on the location of the radical center. When a radical is centered on a carbon atom adjacent to a ring oxygen atom, a combination of stereoelectronic, conformational, and steric effects determines stereoselectivity, but reactions of radicals centered on other carbon atoms are controlled primarily by steric effects. For the latter group the major stereoisomer in a bimolecular reaction is the one produced by a molecule and a radical approaching each other along the least-hindered pathway.



5

yield	B	unsaturated reactant or deuterium donor	β-face reaction / α-face reaction	ref
84%	U		0/100	13
80%	U		0/100	14
89%	A	Bu_3SnD	12/88	15,16
94%	U	Bu_3SnD	10/90	17
93%	U	$(Me_3Si)_3SiD$	3/97	17



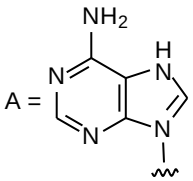


Table 2. Stereoselectivity in reactions of the radical **5**

A. Shielding of Radical Centers

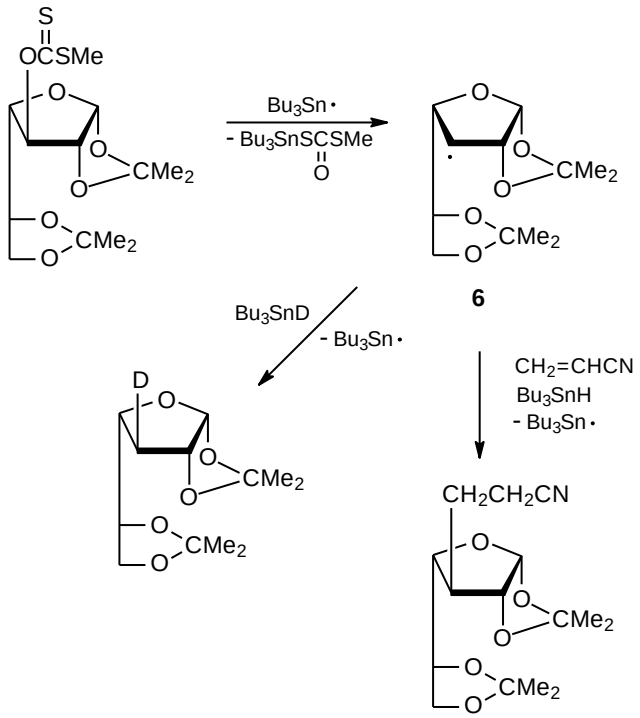
Although the least-hindered pathway for reaction between a molecule and a cyclic radical depends on the steric requirements of each reactant, the way in which the radical center is shielded by nearby groups is often the deciding factor in determining stereoselectivity. The substituents on carbon atoms adjacent to the radical center usually are the most important in the shielding process. The radical center in **1**, for example, has a single, adjacent substituent, one that directs reaction to the opposite face of the ring system (Scheme 1).[5,6] Shielding groups more remote from the radical center also may contribute, although usually in a less significant way, to determining the least-hindered pathway for reaction. With this potential for complex shielding patterns, it is useful to analyze some common group arrangements to see how they affect the least-hindered pathway.

1. Groups on Opposite Faces of a Cyclic Radical

A common situation for a carbon-centered radical in a cyclic carbohydrate is to have two adjacent carbon atoms, each with an attached substituent. If these substituents are on opposite faces of the ring system, uncertainty often exists concerning the least-hindered approach to the radical center. The radicals **4** and **5** (Tables 1 and 2, respectively) provide examples. Each has two shielding groups adjacent to the radical center, and for each radical these groups are on opposite faces of the ring system. Due to this shielding pattern it is difficult to predict what stereoselectivity to expect from reactions of these radicals. This uncertainty is well founded because addition to unsaturated molecules[6–10] and abstraction from tri-*n*-butyltin deuteride[11,12] by the radical **4** occurs preferentially on the β face of the ring system (Table 1), but for the radical **5** these reactions take place on the α face (Table 2).[13–17]

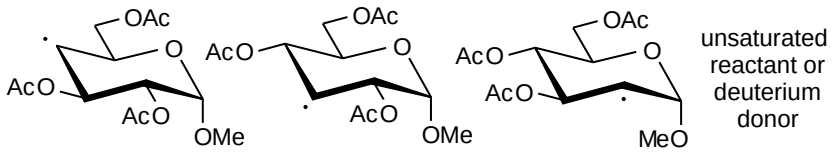
The information in Tables 1 and 2 demonstrates that stereoselectivity depends on both the radical and the molecule that are undergoing reaction. Although the steric requirements for reactions of radicals **4** and **5** are sufficiently great that the least-hindered pathway to each of them remains the same, regardless of the participating molecule, the data in Tables 1 and 2 show that the extent of stereoselectivity (i.e., the ratio of α-face to β-face reaction) depends upon the reactant molecule.

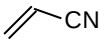
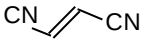
Scheme 2



2. Groups on the Same Face of a Cyclic Radical

Predicting stereoselectivity for reactions of radicals can be done with confidence when a radical center has two adjacent carbon atoms each with a group that projects onto the same face of the ring system; for example, in reactions of the radical **6** the least-hindered pathway approaches the face of the furanoid ring opposite that bearing the two shielding groups (Scheme 2).[7,11,12] There is no indication of reaction on the other face of the ring system.



	7	**8**	**9**	
eq/ax	82/18	76/24	55/45	
eq/ax	>98/2	>95/5	84/16	
eq/ax	58/42	53/47	-	Bu_3SnD

eq = new substituent adopts an equatorial position
ax = new substituent adopts an axial position

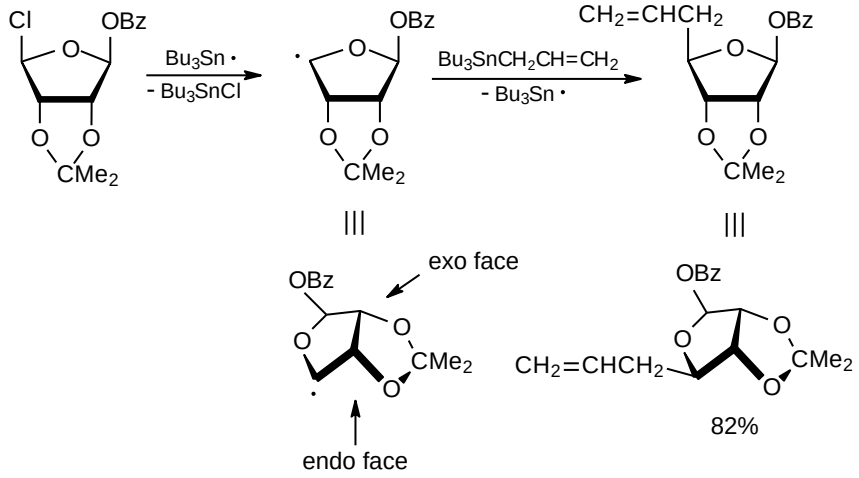
Table 3. Stereoselectivity of reactions of the radicals **7**-**9**

The reactions mentioned thus far have been ones in which the radical center is in a furanoid ring. When this center is located on an atom other than C-1 in a pyranoid ring, group shielding remains the primary factor controlling stereoselectivity. The radicals **7** and **8**, for example, react with acrylonitrile from the face of the ring opposite that containing the shielding groups on atoms adjacent to the radical center (Table 3).[6] [Although the configurations at the radical centers in **7** and **8** are not known, they are pictured as being pyramidal. From the discussion on radical structure in Chapter 6 (Section III.A.) it is reasonable to assume a pyramidal, but not fully tetrahedral, configuration for these radicals (**7** and **8**).]

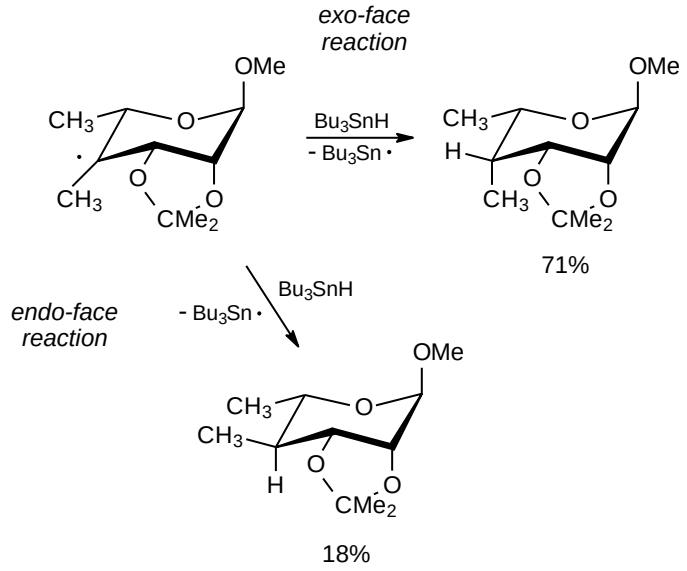
3. Fused and Bridged Ring Systems

If a radical center is located on an atom that is part of a *cis*-fused ring system, the radical will be more accessible from its exo (convex) face than from its endo (concave) face. The normal situation for a carbohydrate is that the *cis*-fusion is either between two five-membered rings (Scheme 3[18]) or between a five-membered and a six-membered ring (Scheme 4[19]).

Scheme 3

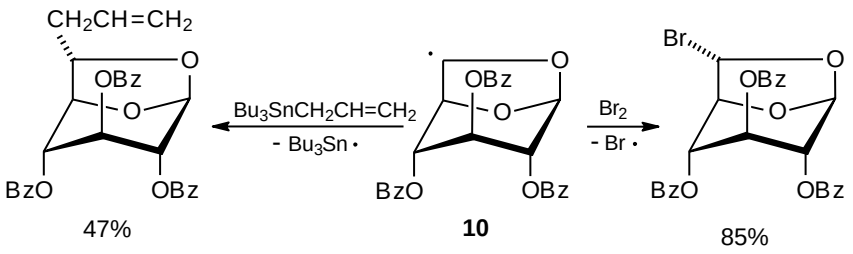


Scheme 4



Bridged ring systems are capable of forming radicals with a rigid structural framework. A radical center located in such a system reacts stereoselectively when a ring substituent is held in a position that blocks access to one face of the ring. The radical **10**, for example, reacts in the highly stereoselective fashion shown in Scheme 5 due to presence of the 3-*O*-benzoyl group.[20]

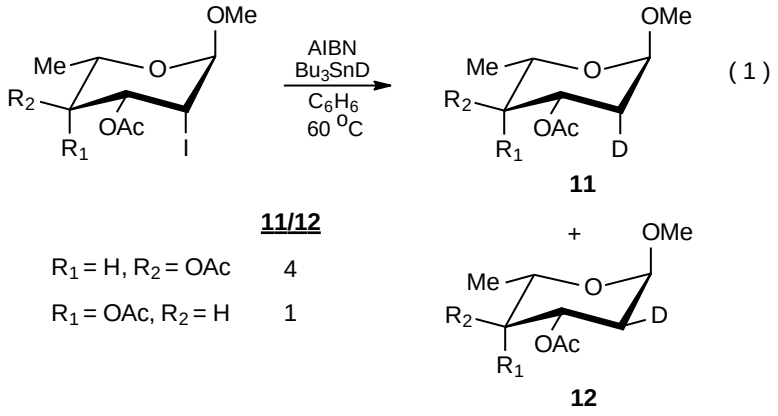
Scheme 5



(no C-6 epimers dectected in either reaction)

4. Groups not Adjacent to the Radical Center

A shielding group does not have to be adjacent to a radical center to affect stereoselectivity. The reaction shown in eq 1 provides an example of shielding by a remote substituent. In this reaction an axial acetoxy group at C-4 directs more reaction at C-2 to the opposite face of the pyranoid ring than does the same substituent in an equatorial orientation (eq 1).[21] There is the complicating factor in these reactions (eq 1) that the change in C-4 configuration also may affect ring conformation enough that differences in stereoselectivity may not be due entirely to shielding effects.



B. Steric Effects in Reactant Molecules

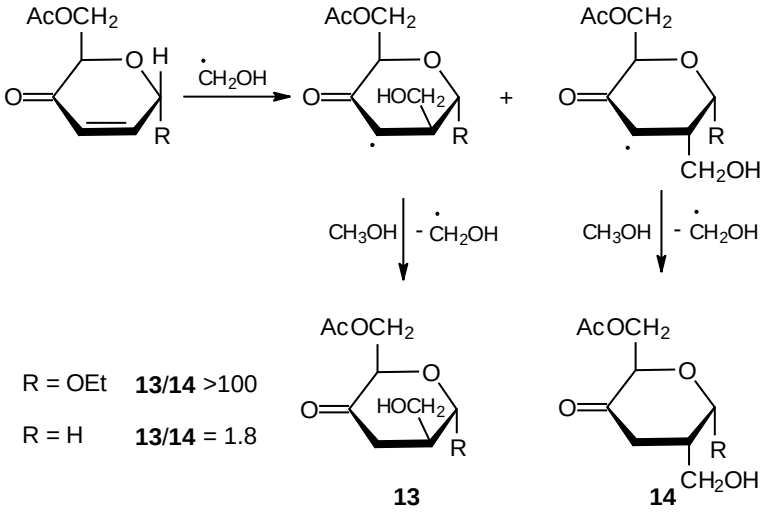
1. Radical Addition Reactions

A distinct change in stereoselectivity occurs when radicals **7**-**9** react with fumaronitrile rather than acrylonitrile (Table 3). This change in reactants causes each reaction to favor to a greater extent the product with an equatorial substituent at the carbon atom that previously was a radical center.[6] The rate constants for all reactions decrease as a result of the fumaronitrile-for-acrylonitrile substitution, but those for reactions leading to products with an axially oriented group

decrease to a greater extent. The net effect of this unequal shift in reactivity is to increase stereoselectivity, that is, the relative amount of those products with a new equatorial substituent (Table 3).

The reason for the change in reactivity upon replacing acrylonitrile with fumaronitrile has to do with steric effects. The presence of a second cyano group in fumaronitrile increases steric hindrance during the addition process for all reactions, but transition states are higher in energy and rate constants smaller for formation of isomers with new axial substituents (more hindered) than for those with new equatorial substituents (less hindered).

Scheme 6



The reaction pictured in Scheme 6 offers a view of the importance of steric effects to stereoselectivity when the roles of the radical and the unsaturated compound change, that is, when an unsaturated carbohydrate reacts with a noncarbohydrate radical.[22] Once again it is the least-hindered pathway that is followed. When R is an ethoxy group (Scheme 6), stereoselectivity of the reaction is consistent with the shielding of the R group directing the hydroxymethyl radical to the β-face of the ring system (**13**/**14** > 100). If, however, the ethoxy group is replaced by a hydrogen atom, the shielding group is gone and the stereoselectivity of the reaction is dramatically reduced (Scheme 6).

2. Hydrogen-Atom Abstraction Reactions

Since increasing the steric size of the molecules reacting with radicals **7**-**9** (Table 3) increases the relative amounts of products with equatorial substituents, it is reasonable to expect that reducing the size of the approaching molecule should have the opposite effect. Hydrogen-atom donors generally have reduced steric requirements because the hydrogen atom to be abstracted is on the periphery of the donor molecule (Figure 1). As long as a hydrogen-atom (or deuter-

ium-atom) donor is not required to react with a well shielded radical center, hydrogen-atom transfer is not very sensitive to steric effects; for example, the rate constants for reaction of simple primary, secondary, and tertiary radicals with Bu_3SnH are nearly the same.[23] The reactions of radicals **7** and **8** with tri-*n*-butyltin deuteride further illustrate this fact because products with axial and equatorial substituents at the former radical center are generated with little stereoselectivity (Table 3).[6]

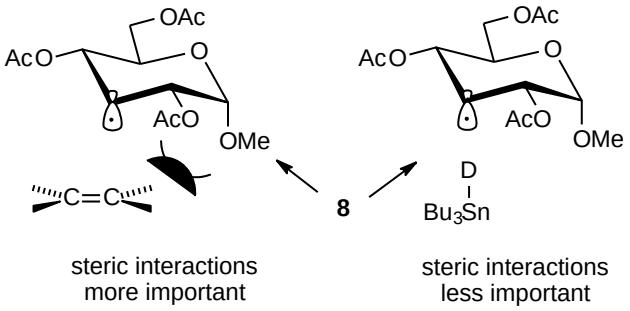
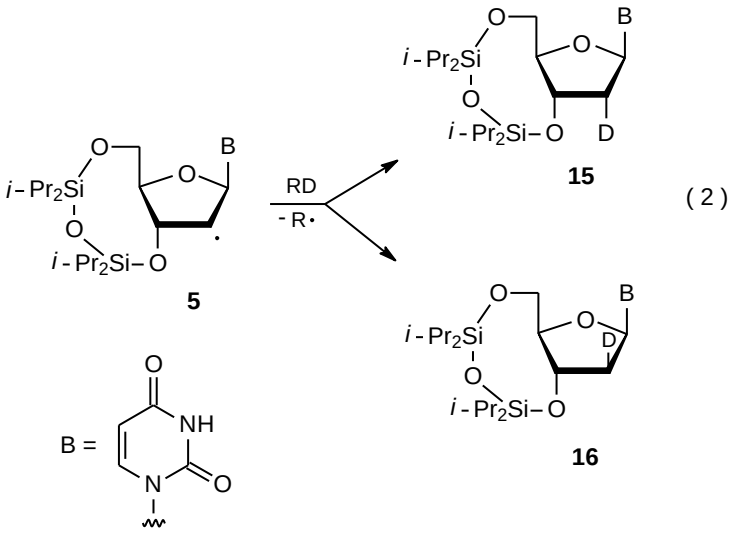


Figure 1. Steric interactions during reactions of **8**



(2)

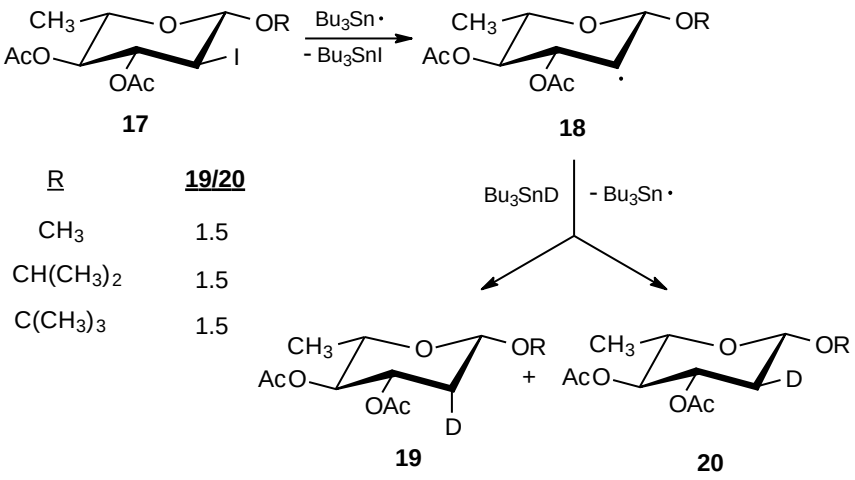
R	% yield	**15**/**16**
Bu_3Sn	87%	11
$(Me_3Si)_3Si$	90%	76

Although the indication from reactions of radicals **7** and **8** is that the steric requirements for atom transfer from tri-*n*-butyltin deuteride are small, these requirements can become significant when well protected radical centers are involved. Reactions of radicals **4** (Table 1) and **5** (Table 2) with tri-*n*-butyltin deuteride provide examples in which one face of a ring system is so well shi-

elded that the steric size of the deuterium donor becomes a factor in determining reaction stereoselectivity. In reacting with the radicals **4** and **5**, tri-*n*-butyltin deuteride encounters greater steric hindrance on one face of each radical (α face for **4** and β face for **5**) because the deuterium donor must penetrate to the interior of each radical by negotiating its way past effective shielding groups.

Another demonstration that deuterium-atom (and hydrogen-atom) donors have substantial steric requirements in some reactions comes from the difference in deuterium donating ability of Bu_3SnD and $(Me_3Si)_3SiD$. Although both reagents react stereoselectively with the shielded radical **5**, the selectivity of the silicon-containing compound is greater (eq 2).[17] The difference in stereoselectivity of these two donors has been attributed to molecular shape and flexibility; that is, the flexible alkyl chains in Bu_3SnD make it less sterically demanding than the spherical, more rigid shape found in $(Me_3Si)_3SiD$.[24]

Scheme 7



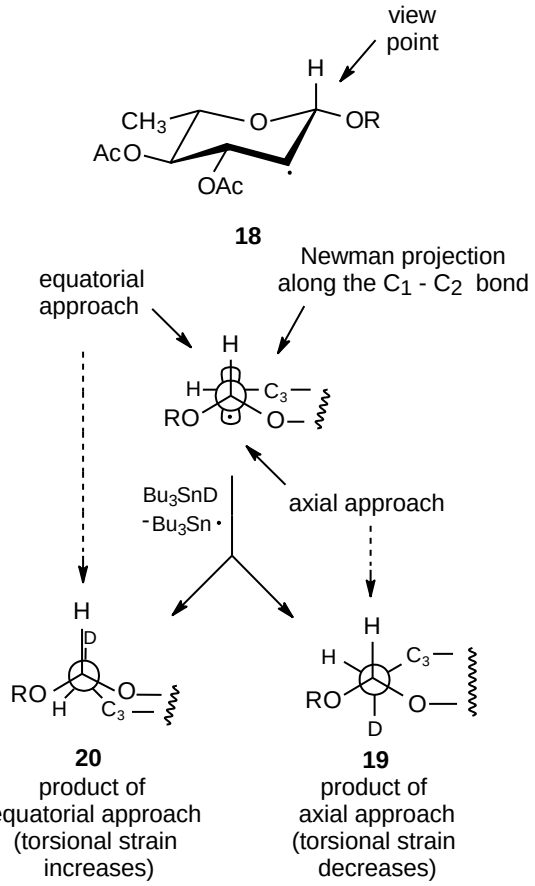
C. Torsional Effects

It would be valuable in further understanding stereoselectivity to know what would happen if steric effects were reduced to the point that they became inconsequential. In the reaction shown in Scheme 7[21] this point appears to have been reached because increasing the steric size of the R group has no effect on stereoselectivity. The shielding groups at C-1 and C-3 should cause an equatorial carbon-deuterium bond to form at C-2, but the expected product (**20**) turns out to be a minor one. The stereoselectivity in this reaction, therefore, must be due to a phenomenon that is normally overshadowed by steric effects.

Torsional strain occurs when electrons in bonds on adjacent carbon atoms repel each other. The destabilization caused by this type of interaction is normally much smaller than that arising from steric effects. Although steric effects usually favor the formation of new equatorial bonds over new axial ones in pyranoid rings, torsional effects do not; rather, torsional strain increases

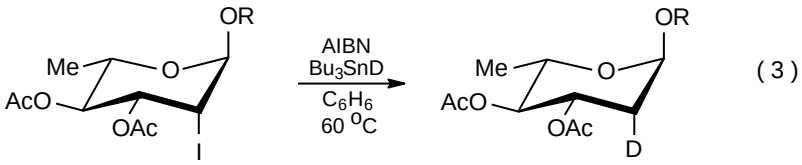
when equatorial bonds are formed (Scheme 8). If steric effects were a significant factor in the stereoselectivity of reactions of the radical **18**, the relative amount of the product **20** would increase as the OR group becomes larger. Since this does not happen (see data in Scheme 7) and since the axial orientation of the bond to deuterium in the major product (**19**) is that predicted if torsional effects were controlling, the products from the reaction of the iodide **17** with Bu_3SnD (Scheme 7) are consistent with torsional interactions being the primary factor in determining reaction stereoselectivity.

Scheme 8



19/**20** = 1.5

When the stereochemistry at C-1 is changed so that the OR group is axial, steric effects reassert themselves in influencing the stereoselectivity of reaction of C-2 radicals (eq 3).[21] As the shielding group at C-1 becomes progressively larger, more reaction occurs on the less hindered face of the ring in the intermediate radical. Torsional effects in these reactions contribute little to reaction stereoselectivity.



(3)

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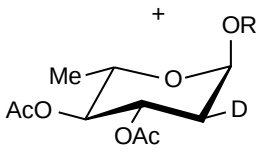
R	**21/22**
CH_3	4
$CH(CH_3)_2$	9
$C(CH_3)_3$	19



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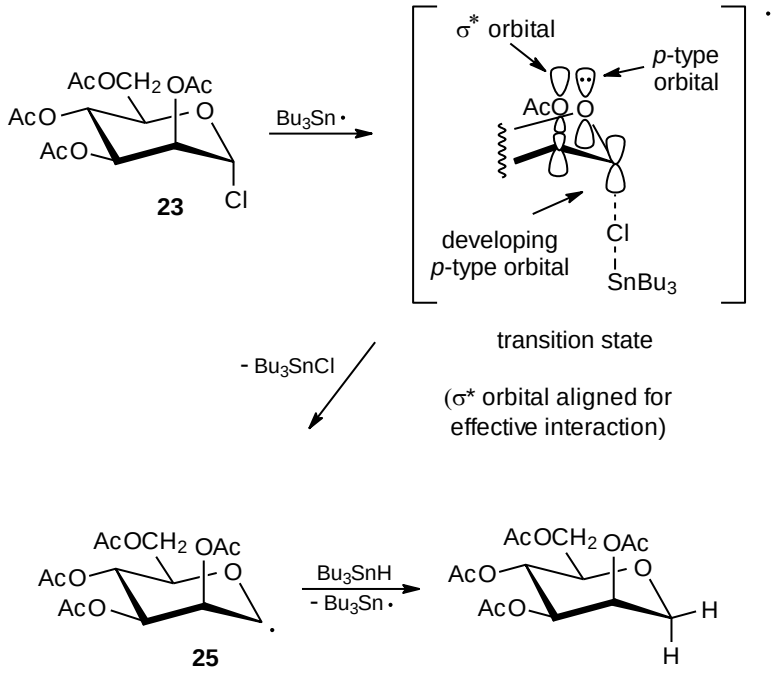
Scheme 9



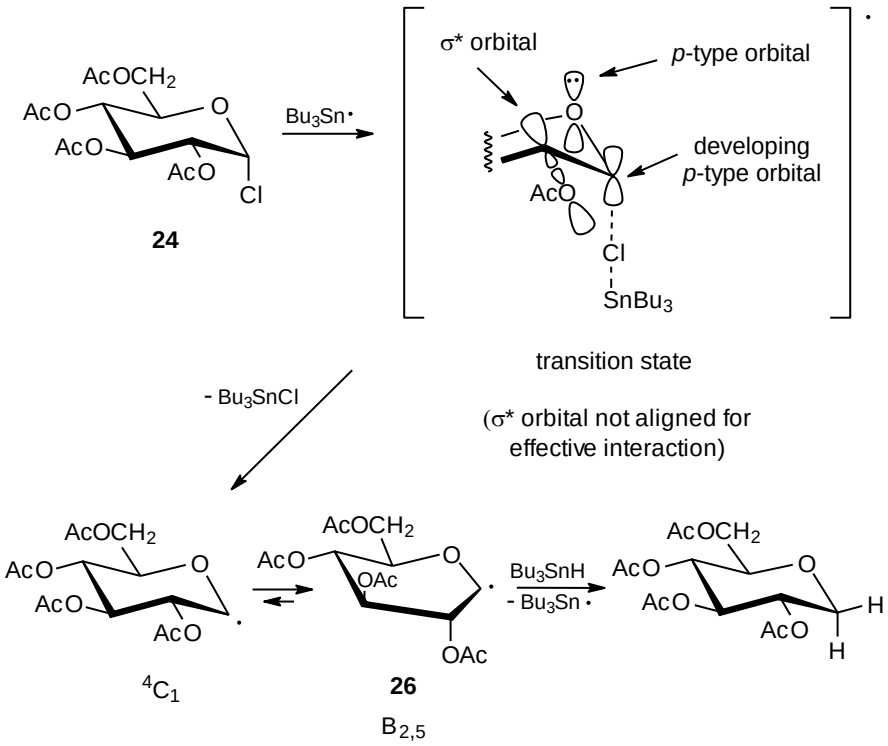
III. Maximizing Transition-State Stabilization by Orbital Interactions: The Kinetic Anomeric Effect

A. Radical Formation

The reactions of the glycosyl chlorides **23** and **24** provide examples of stereoselectivity in pyranos-1-yl radical formation that depends on orbital interactions (Schemes 9 and 10).[25,26] The difference in their reaction rates is linked to the orientation of the C_2–O bond in each of these

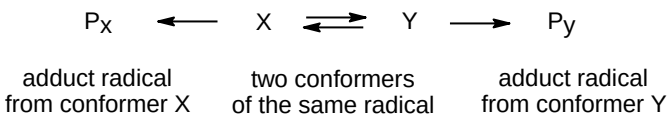
stereoisomers. The D-mannopyranosyl chloride **23** reacts with tri-*n*-butyltin hydride 7.8 times more rapidly than does the epimeric D-glucopyranosyl chloride **24**. For **23** the C-2 acetoxy group has an orientation that allows transition-state stabilization by the orbital interactions shown in Scheme 9. These are the same interactions associated with the quasi-anomeric effect. (The quasi-anomeric effect, discussed in Section V of Chapter 6, provides an explanation for the conformations adopted by pyranos-1-yl radicals.[27,28]) Since these orbital interactions are developing at the transition state, they should be responsible, at least in part, for the greater reactivity of **23** when compared to **24**. Such stabilization is minimal for reaction of **24** because the σ* orbital associated with the C_2–O bond does not have the proper, transition-state orientation to assist significantly in stabilization (Scheme 10).

Scheme 10



A critical assumption about the reactions shown in Schemes 9 and 10 is that the first step (chlorine-atom abstraction by the tri-*n*-butyltin radical), rather than the second step (hydrogen-atom abstraction from tri-*n*-butyltin hydride by the carbohydrate radical) is rate-determining. Such an assumption is reasonable because chlorine-atom abstraction in free-radical dehalogenation of alkyl chlorides is known to be rate-determining,[29] but it is not a certainty because for reaction of iodides, bromides, and some very reactive chlorides, hydrogen-atom abstraction from tri-*n*-butyltin hydride is the rate-determining step.

Scheme 11



B. Radical Reaction

1. The Role of Radical Conformation

a. The Curtin-Hammett Principle

Consider conformations X and Y of a radical that is undergoing an addition reaction to give the products P_x and P_y (Scheme 11). One possibility is that interconversion of X and Y is rapid compared to their reactions. In this situation the Curtin–Hammett principle applies; that is, the ratio of the products depends only on the relative energies of the transition states leading to their formation. (A more detailed statement of the Curtin-Hammet principle is "the relative amounts of products formed from two pertinent conformers are completely independent of the relative populations of the conformers and depend only on the difference in free energy of the transition states, provided the rates of reaction are slower than the rates of conformational interconversion".[30]) An energy diagram showing a situation in which the Curtin-Hammet principle applies is found in Figure 2. If in this reaction P_x and P_y are stereoisomers, the overall process will form P_y stereoselectively, even though conformer X is present in greater amount.

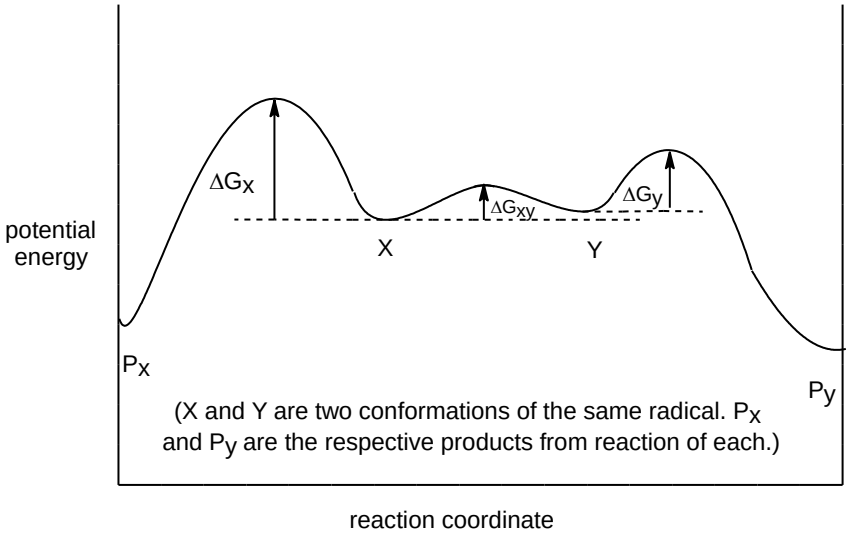


Figure 2. Potential energy diagram for reaction of readily interconvertable radical conformers X and Y.

A different situation exists for the reaction shown in Figure 3. In this case the interconversion of radicals X and Y is slow compared to their reactions. Under these conditions (the Curtin–Hammett principle not in effect) the conformation present in greatest amount determines the stereoselectivity of the reaction; thus, if X is the major conformer, P_x will be formed preferentially.

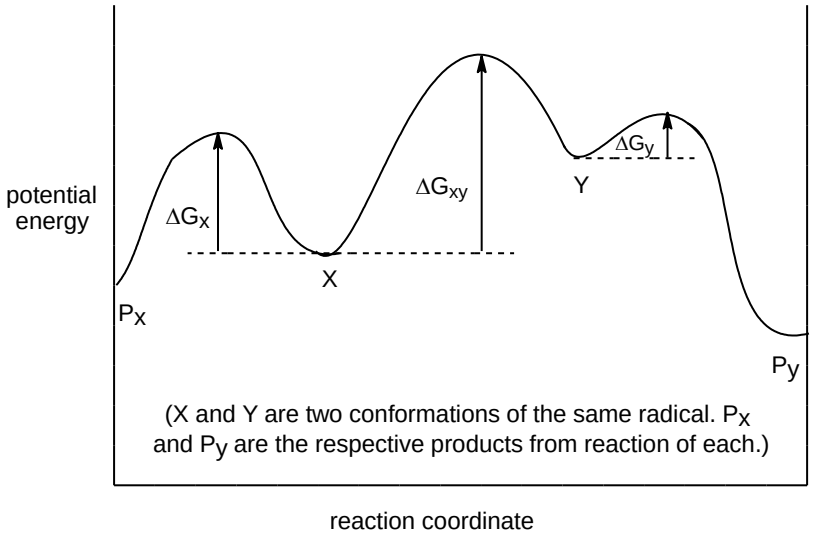
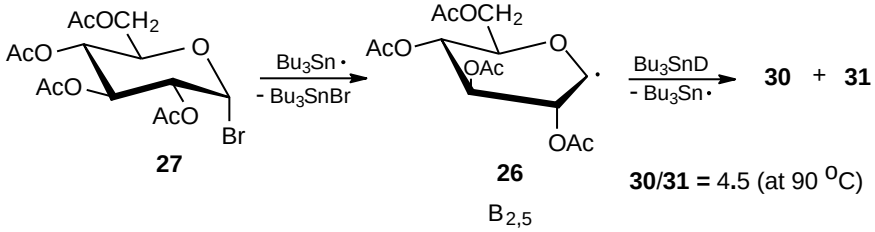


Figure 3. Potential energy diagram for reaction of radical conformations (X and Y) that react more rapidly than they interconvert.

Scheme 13

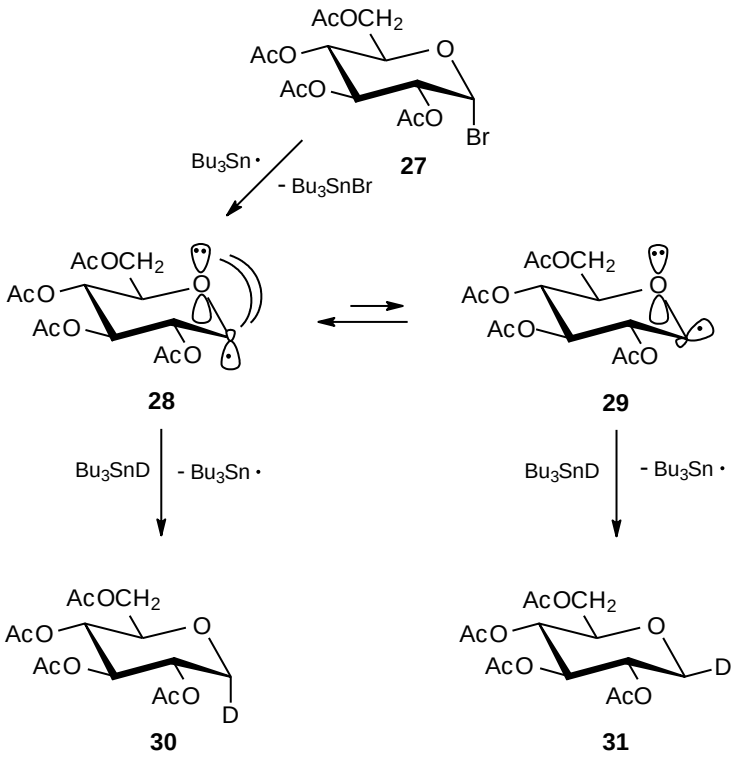


b. An Initial Proposal

The explanation for the stereoselectivity of the reactions of pyranos-1-yl radicals has changed over time as new information about radical structure has become available. The first proposal for the stereoselective formation of the reduction products **30** and **31** from reaction of the D-glucopyranosyl bromide **27** with tri-*n*-butyltin deuteride was that product yields reflected the relative amounts of **28** and **29** present in the reaction mixture (Scheme 12).[31] (Inherent in this proposal was the assumption that **28** and **29** were the most stable structures for this pyranos-1-yl radical and that they reacted more rapidly than they equilibrated.) The major component in this

proposed pseudoequilibrium was thought to be **28** because this radical would be stabilized more effectively than **29** by interaction of the orbital centered on C-1 with the *p*-type orbital on the ring oxygen atom (Scheme 12). This interpretation subsequently had to be revised because ESR spectral analysis showed that neither **28** nor **29** was as stable as the distorted $B_{2,5}$ boat conformation **26** (Scheme 13).[27,28]

Scheme 12



30/31 = 4.5 (at 90 °C)

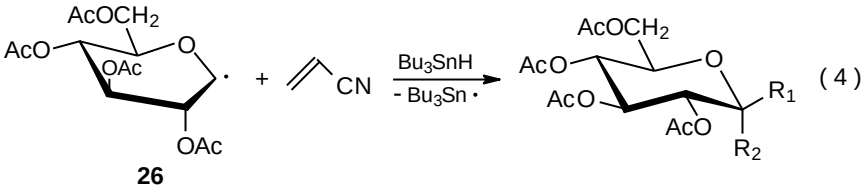
c. A Revised Explanation

(1). Steric Effects

One possible explanation for stereoselectivity in reactions involving the D-glucopyranos-1-yl radical **26** is that steric effects are determining this selectivity just as they do in the reactions of many other carbohydrate radicals. For this explanation to be correct, approach to C-1 by Bu_3SnD from the α face of **26** would have to be less hindered than a similar approach to its β face. With the neighboring 2-*O*-acetyl group shielding α-face reaction at C-1 (Scheme 13), it is difficult to see how the least hindered pathway to C-1 would involve approach to the α face of the radical.

Another view of the difficulty with steric interactions being the controlling factor in stereoselectivity of the reactions of **26** comes from comparing these reactions with those of the pyran-

os-4-yl radical **7** and the pyranos-3-yl radical **8** (Table 3). For neither **7** nor **8** is the stereoselectivity of reaction with Bu_3SnD large, but for each the major stereoisomer comes from reaction on the face of the radical opposite to that containing the shielding groups on the adjacent carbon atoms. This result stands in contrast to the reaction of the pyranos-1-yl radical **26**, where the stereoselectivity is not only much larger, but Bu_3SnD approaches this radical from the face containing the only shielding group on a neighboring carbon atom. The α-face stereoselectivity of **26** is not limited to reaction with Bu_3SnD. Addition of this radical to acrylonitrile also is stereoselectively from the more hindered α face (eq 4).

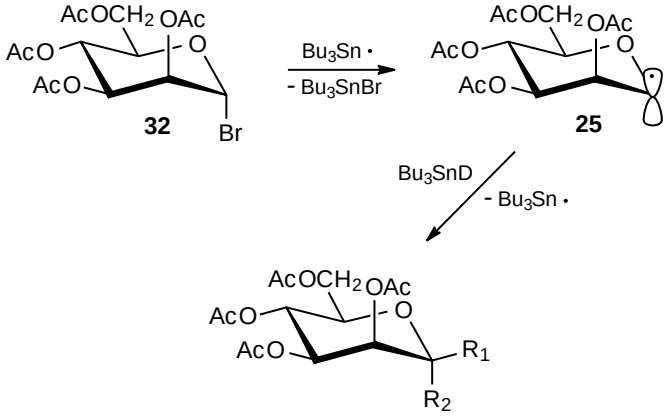


(4)

R_1 = H, R_2 = CH_2CH_2CN 58%

R_1 = CH_2CH_2CN, R_2 = H 5%

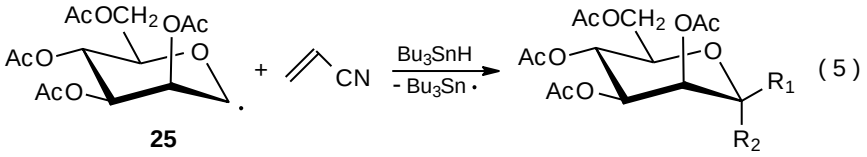
Scheme 14



33 R_1 = H, R_2 = D **33/34** = 19

34 R_1 = D, R_2 = H (at 90 °C)

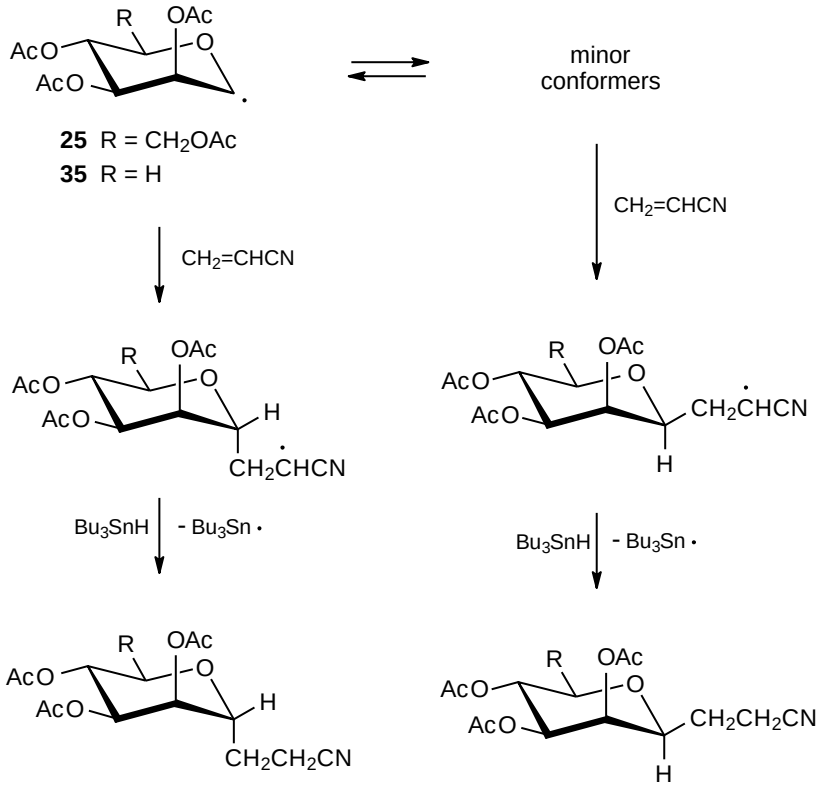
The D-mannopyranos-1-yl radical **25** exhibits even greater α-face selectivity in deuterium abstraction (Scheme 14) and addition to acrylonitrile (eq 5) than does its D-gluco epimer **26** (Scheme 13, eq 4). While steric effects could explain the stereoselectivity in the reactions of **25**, they are unable to rationalize the selectivity in the reactions of both **25** and **26**; however, for each of these radicals stereoselectivity does have a link to radical conformation.



R_1 = H, R_2 = CH_2CH_2CN 68%

R_1 = CH_2CH_2CN, R_2 = H 0%

Scheme 15



68% R = CH_2OAc 0%

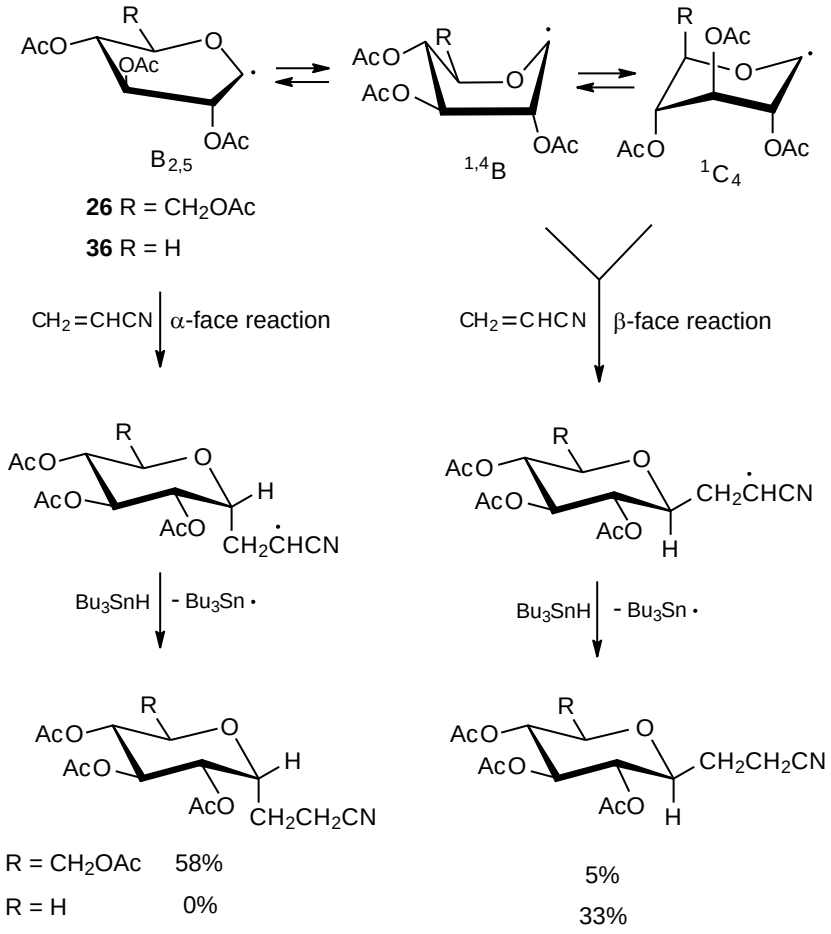
47% R = H 21%

(2). Interconversion of Conformations

For the D-mannopyranos-1-yl (**25**) and D-lyxopyranos-1-yl (**35**) radicals only the $^4C_1$ chair conformation can be detected in the ESR spectrum of each (Scheme 15).[27,28,32] Structurally these radicals differ only at C-5 where the equatorial CH_2OAc substituent in **25** is replaced by a hydrogen atom in **35**. Even though the structures **25** and **35** are quite similar in the vicinity of the radical center, the stereoselectivity of their reactions is quite different. The radical **25** adds

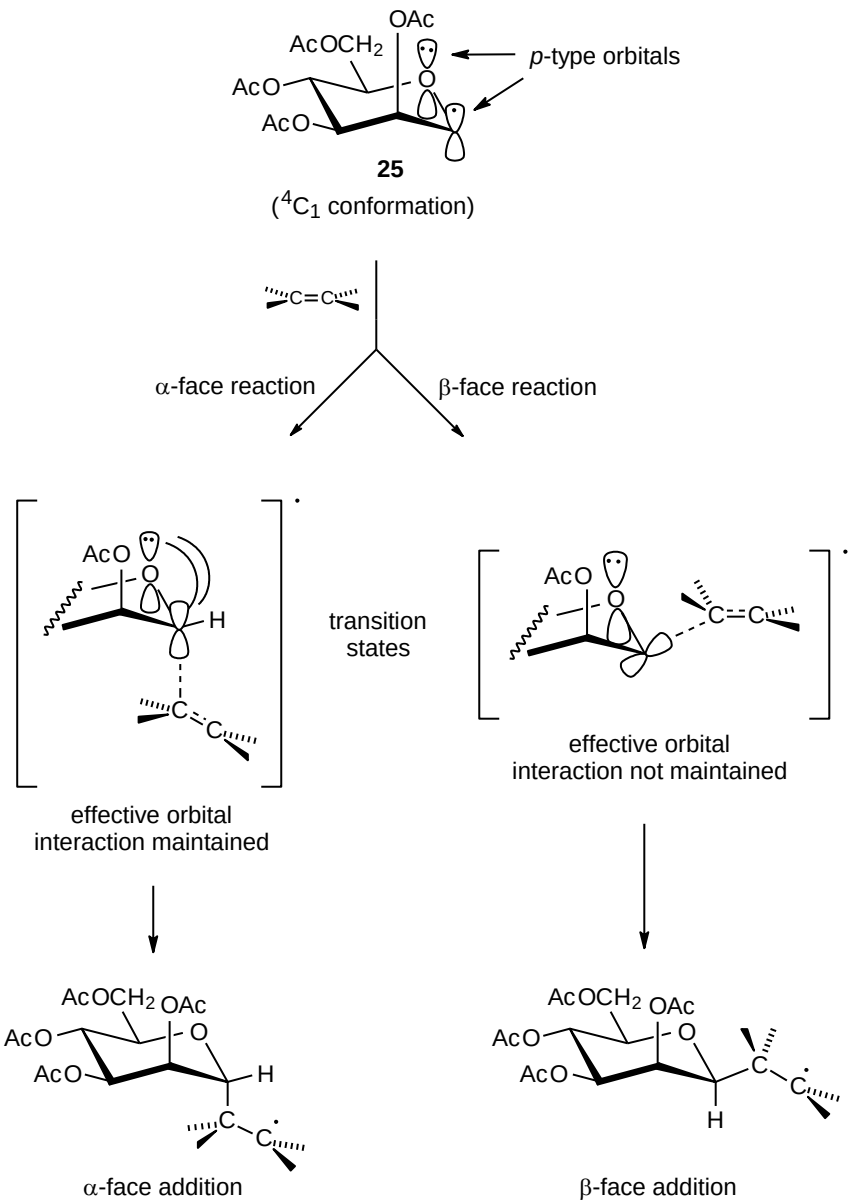
stereoselectively to acrylonitrile to give only the product arising from reaction at its α face, but the radical **35** reacts from both its α and β faces (Scheme 15).[32] Since an equatorial substituent at C-5 is remote from the reacting center at C-1, steric effects alone cannot explain the difference in reactivity between these two (**25** and **35**). Findings concerning the reactivity of **25** and **35** (Scheme 15) are echoed in the reactions of the D-glucopyranos-1-yl radical **26** and the D-xylopyranos-1-yl radical **36** (Scheme 16), further; observable conformations and reactivity **26** and **36** point to a possible explanation for the difference in stereoselectivity in the reactions of this pair (**26** and **36**) as well as the difference in stereoselectivity in the reactions of **25** and **35**.

Scheme 16



The ESR spectrum of **26** shows it to exist in a distorted $B_{2,5}$ boat conformation, but for **36** $B_{2,5}$ boat, $^{1,4}B$ boat, and $^{1}C_4$ chair conformations also can be detected.[6] Conformational population, therefore, changes considerable when the CH_2OAc substituent at C-5 in **26** is replaced by a hydrogen atom. This finding raises the possibility that the difference in stereoselectivity in the reactions of these radicals many be related to population and reactivity of conformational isomers (Scheme 16).

Scheme 17



(3). Conformational Mobility

If $B_{2,5}$ conformations react from their α face, and $^{1,4}B$ or $^{4}C_1$ conformers (or both) from their β face (Scheme 16), conformational population and mobility could explain the observed stereoselectivity in the reactions of radicals **26** and **36**.[6] According to this explanation, interconversion among conformers of the radical **36** would need to be more rapid than reactions of these radicals (Curtin-Hammet principle in effect). Since the assumption is that $^{1,4}B$ boat or $^{1}C_4$ chair conformers give β-face reaction products,[6] the conclusion is that one or both of these conformers is much more reactive than the $B_{2,5}$ conformation and that this very reactive conformation does so in a highly

stereoselective fashion. A further part of this argument is that the CH_2OAc substituent attached to C-5 in the radical **26** stabilizes the $B_{2,5}$ conformation and, in so doing, increases its population to the point that little reaction occurs from other conformers (Scheme 16).

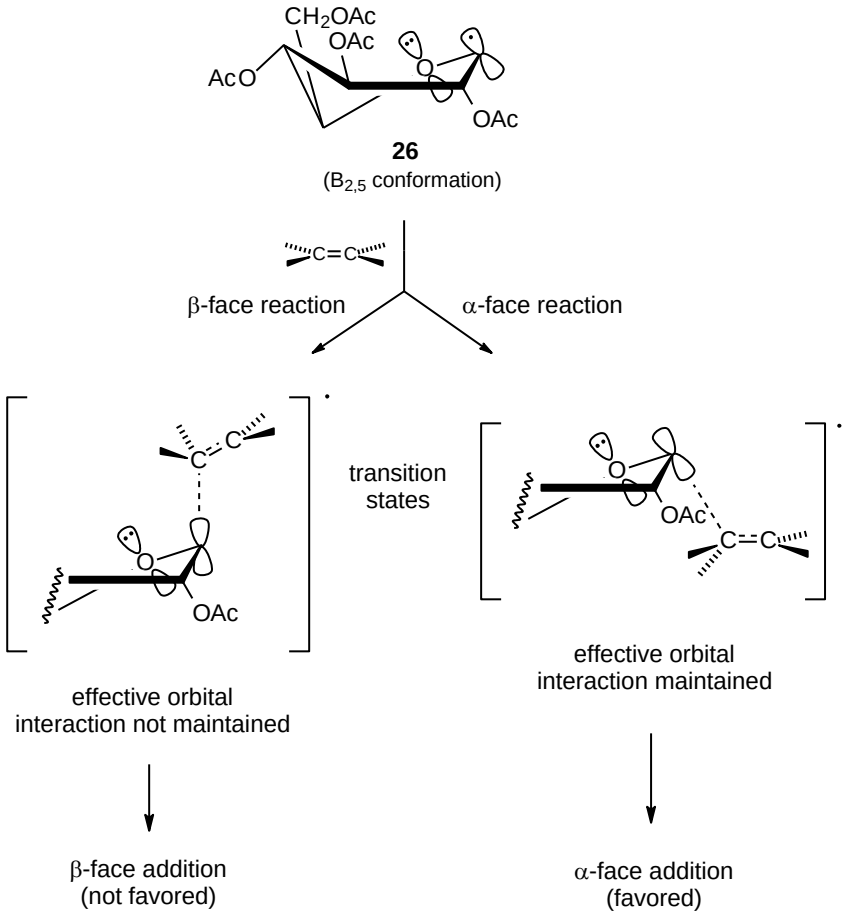
A similar explanation exists for the difference in stereoselectivity between radicals **25** and **35** (Scheme 15). If interconversion among the conformers of the radical **35** is faster than reaction with acrylonitrile, it is possible to form a β-*C*-glycoside by reaction with a minor conformer. For the radical **25** the equatorial CH_2OAc substituent at C-5 must stabilize the $^4C_1$ conformation sufficiently that the concentration of minor conformers is too small for them to account for significant product formation.

(4). Transition-State Stabilization: The Kinetic Anomeric Effect

To understand how radical conformation can have such a pronounced effect on stereoselectivity in the reactions of pyranos-1-yl radicals, it is instructive to examine transition-state stabilization. The major stereoisomer formed in these reactions results from a radical adopting a conformation that allows the stabilizing interaction between the *p*-type orbitals on C-1 and the ring oxygen atom to be maintained to the greatest extent in the transition-state. This conformation-dependent, stereoelectronic, transition-state stabilization is referred to as the kinetic[33,34] or radical[35,36] anomeric effect. (We will use "kinetic anomeric effect" in describing this phenomenon.)

The kinetic anomeric effect offers a rationale for the D-mannopyranos-1-yl radical **25** adding to acrylonitrile exclusively from the α face of the pyranoid ring (Scheme 15). Only for α-face reaction will stabilizing interaction between the *p*-type orbitals on the ring oxygen atom and the singly occupied orbital on C-1 be maintained in the transition state (Scheme 17). Predicting stereoselectivity in the reaction of a conformationally mobile radical can be a challenging task because more than one conformation is accessible and determining which conformation is the most reactive may be difficult. This means that minor conformers, even ones that cannot be detected by ESR spectroscopy, can play a major role in determining reaction stereoselectivity. For the D-glucopyranos-1-yl radical **26** the only conformation detectable by ESR spectroscopy is a distorted $B_{2,5}$ boat,[27,28] but $^{1,4}B$ and $^1C_4$ conformations may be only modestly higher in energy and, therefore, easily accessible. For the $B_{2,5}$ conformation, reaction from the α-face of the pyranoid ring maintains stabilizing orbital interaction more effectively than reaction from its β face (Scheme 18). Reaction does occur, however, to a small extent (5%) from the β face of the pyranoid ring in the radical **26**. The β anomer formed as a minor product could come from an accessible but undetected conformation, such as the $^1C_4$. Maintaining orbital interactions in a $^1C_4$ chair conformation would favor the β-face addition that leads to the minor product (Scheme 19). If this is the way in which β-face addition takes place, then stereoselectivity depends not only on which conformations are accessible and highly reactive but also on which face of a given conformer maintains the reaction-promoting orbital interaction that stabilizes the transition state.

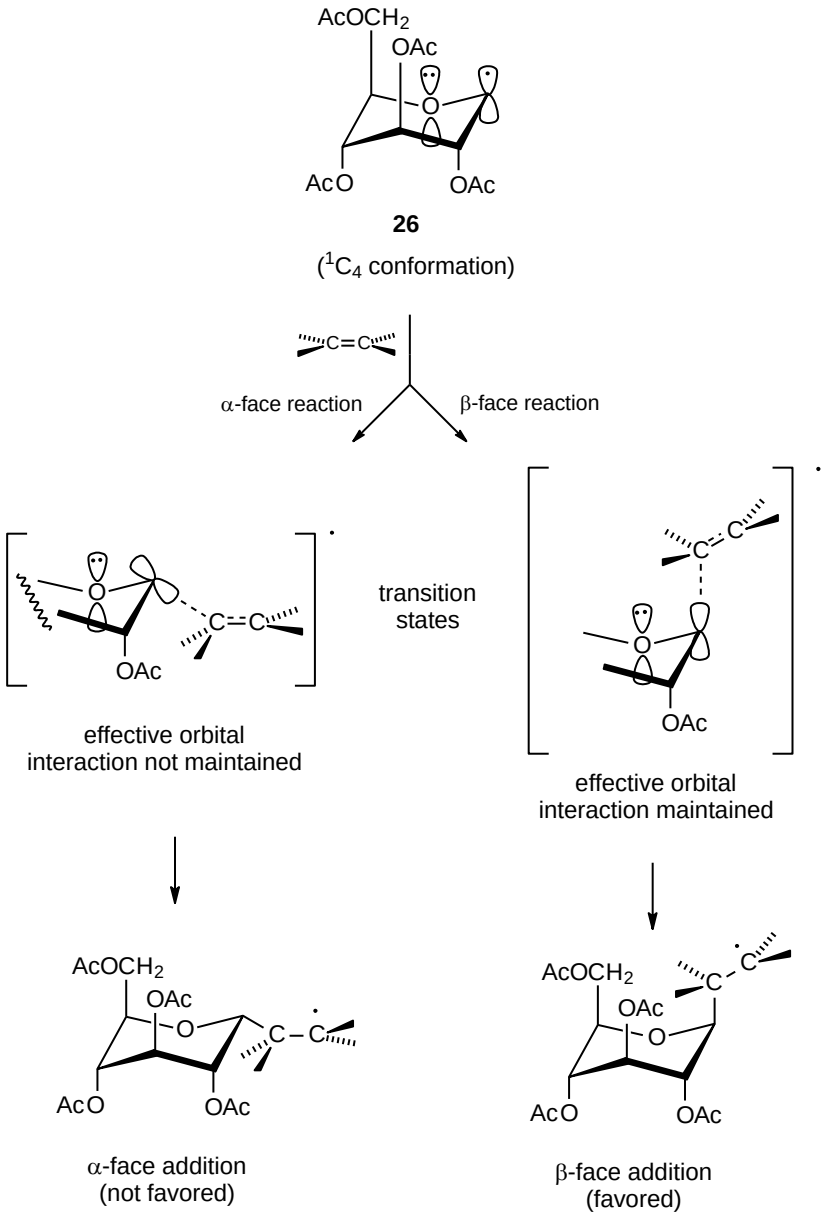
Scheme 18



Another explanation for the formation of the minor product in the reaction of the radical **26** is that this product results from a small amount of β-face addition to the radical in its $B_{2,5}$ conformation. Such an explanation, however, fails to explain greater β-face addition for the radical **36**, when compared to **26** (Scheme 16), and is incompatible with the information, discussed in the next section, on reactions of radicals with restricted conformations.

Although the case is strong for radical conformation playing a critical role in stereoselectivity of reactions of pyranos-1-yl radicals, uncertainty remains about how to identify the reactive conformation when several may be present and undergoing reaction. This uncertainty is effectively eliminated where radicals with restricted conformations are concerned. Study of such radicals has provided considerable insight into the power of the kinetic anomeric effect in determining reaction stereoselectivity.

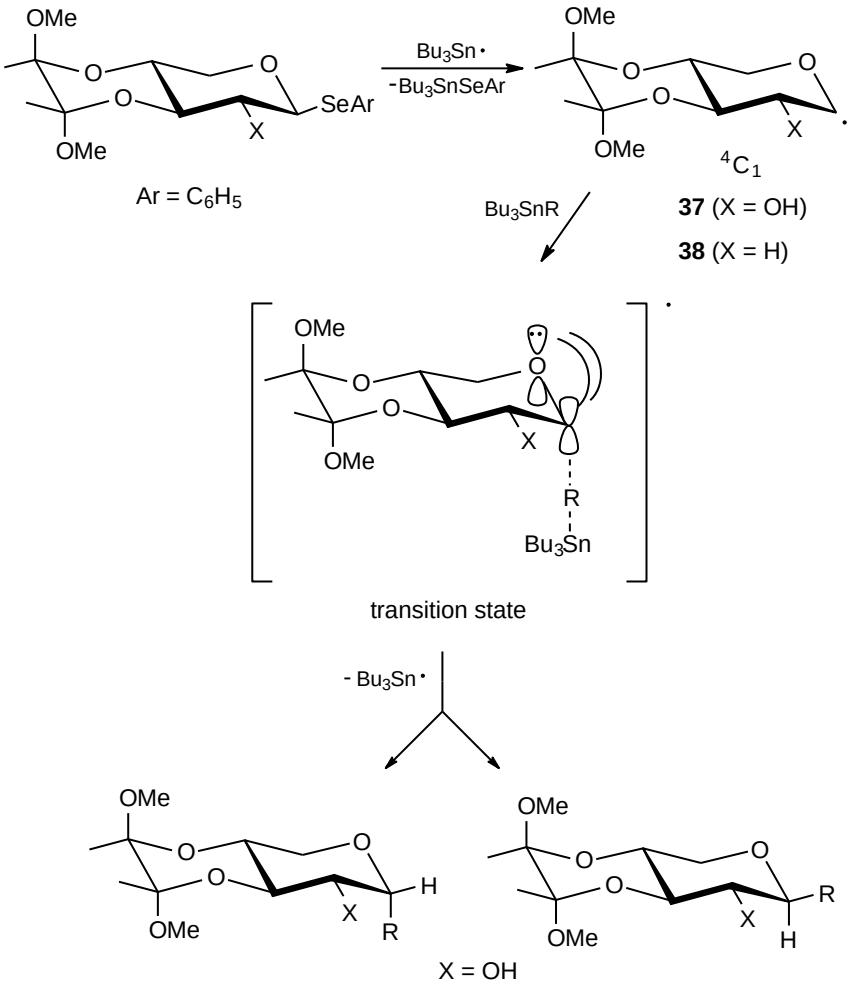
Scheme 19



(5). Restricted Conformations

A restricted conformation for a radical is one that is highly favored over others due to some structural feature, such as an additional ring system. The radicals **37** (Scheme 20) and **47** (Scheme 21) have pyranoid rings restricted to $^4C_1$ and $^1C_4$ chair conformations, respectively. This restriction is caused by the presence of appropriately placed, additional rings.[33] A second ring restricts conformational change in the radical **37** by creating a *trans*-decalin-type structure. For the radical **47** a bridge produces a bicyclic structure that creates a rigid, conformationally restricted system.

Scheme 20



39 R = D **39**/**40** = 97/3 **40** R = D

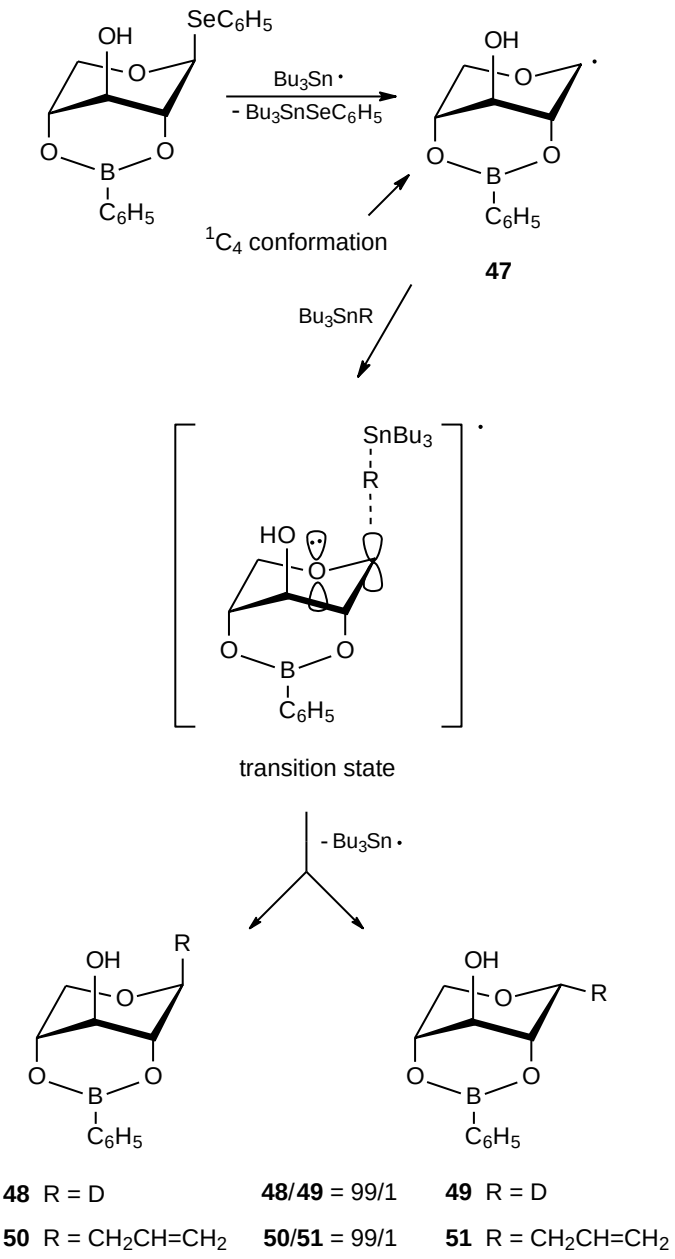
41 R = $CH_2CH{=}CH_2$ **41**/**42** = 91/9 **42** R = $CH_2CH{=}CH_2$

X = H

43 R = D **43**/**44** = 99/1 **44** R = D

45 R = $CH_2CH{=}CH_2$ **45**/**46** = 98/2 **46** R = $CH_2CH{=}CH_2$

Scheme 21



48 R = D **48**/**49** = 99/1 **49** R = D

50 R = $CH_2CH{=}CH_2$ **50**/**51** = 99/1 **51** R = $CH_2CH{=}CH_2$

(a). Explanation for Reaction Stereoselectivity

For the radical **47** maintaining stabilizing orbital interaction in the transition state requires approach of a reacting molecule, such as tri-*n*-butyltin deuteride, to the β-face of the pyranoid ring (Scheme 21). This means that reaction proceeding according to the kinetic anomeric effect will give a product (**48**) with an axial deuterium atom at C-1. The high stereoselectivity of this reaction (**48**/**49** = 99/1) supports the idea that conformational and stereoelectronic effects together have a

powerful influence on the reactions of pyranos-1-yl radicals. Such an idea is reinforced in a dramatic fashion by the reaction of the radical **37** (Scheme 20). In this case in order to benefit from kinetic anomeric stabilization, the deuterium donor must approach the radical from the α face of the pyranoid ring. α-Face selectivity (**39**/**40** = 97/3) in this reaction (the pyranoid ring restricted to a $^4C_1$ chair conformation) is nearly as great as the β-face selectivity (**48**/**49**= 99/1) in the reaction of **47** (pyranoid ring restricted to a $^1C_4$ chair conformation). Changing the radical conformation then completely changes reaction stereoselectivity;[33] furthermore, the selectivity observed in each case is that predicted by the kinetic anomeric effect.

When $Bu_3SnCH_2CH=CH_2$ replaces Bu_3SnD as the molecule reacting with the radical **37**, the stereoselectivity decreases somewhat, although it remains high.[33] [The ratio of α-face to β-face reaction decreases from 97/3 (**39**/**40**) to 91/9 (**41**/**42**) (Scheme 20).] This modest decrease in stereoselectivity disappears when the hydroxy group at C-2 is replaced by a hydrogen atom: that is, the stereoselectivity for the reaction of the 2-deoxy radical **38** with Bu_3SnD is essentially the same as that for reaction with $Bu_3SnCH_2CH=CH_2$ (Scheme 20). Steric hindrance associated with the C-2 hydroxy group, therefore, may be responsible for the small difference in stereoselectivity observed for reactions of the radical **37** with Bu_3SnD and $Bu_3SnCH_2CH=CH_2$. The overall picture, however, remains one in which steric effects have, at most, a minor role in determining stereoselectivity in the reactions of these two radicals (**37** and **38**).

(b). σ*-Orbital Interaction

The σ* orbital of the C_2–O bond in a pyranos-1-yl radical contributes to the stability of these radicals by interacting with the *p*-type orbitals on C-1 and the ring oxygen atom. Radical stabilization of this type plays a critical role in determining preferred radical conformation (see Section IV.A.2.d. of Chapter 6). A question raised by these orbital interactions concerns whether this type of stabilization also affects stereoselectivity in reactions of pyranos-1-yl radicals. The more rapid reaction of the D-mannopyranosyl chloride **23** (Scheme 9) when compared to the epimeric D-glucopyranosyl chloride **24** (Scheme 10) indicates that it may. Even for **24**, however, σ*-orbital interaction is not essential because reaction still takes place (although less rapidly) even with minimal participation from this orbital (Scheme 10). Study of radicals with restricted conformations helps to clarify the role of the C_2–O σ* orbital in stereoselectivity of reactions of pyranos-1-yl radicals.

Because the pyranoid rings in radicals **37** and **38** (Scheme 20) are restricted to $^4C_1$ conformations by their *trans*-decalin-like ring systems, the reactions of these radicals provide insight into the effect of a C_2–O bond (in particular, its σ*-orbital) on the stereoselectivity of the reactions of pyranos-1-yl radicals. The radical **37**, for example, reacts in a highly stereoselective fashion with tri-*n*-butyltin deuteride even though the σ* orbital of the C_2–O bond is not aligned to assist in transition-state stabilization (Figure 4). The radical **38** completely lacks a C-2 substituent; yet, it also undergoes highly stereoselective reaction (Scheme 20). σ*-Orbital interaction involving the C_2–O bond, therefore, is not essential to the stereoselectivity of the reactions of the radicals **37** and

38. The reactions of these radicals, however, point to the critical factor in determining reaction stereoselectivity, namely, maintaining effective interaction in the transition state between the singly occupied, *p*-type orbital on C-1 and the *p*-type orbital on the ring oxygen atom.

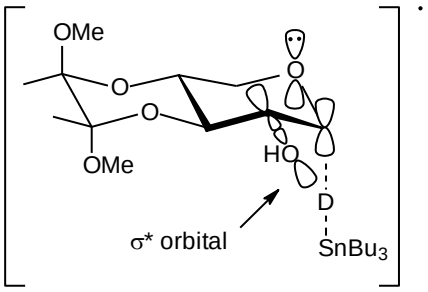
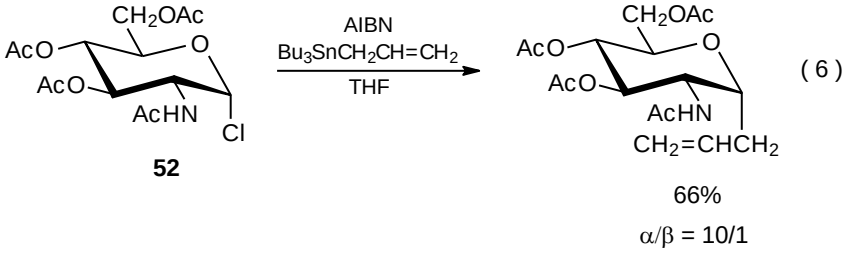


Figure 4. Allignment of the σ* orbital at C-2 during reaction of the radical **37** with Bu_3SnD

Study of the reactions of radicals with restricted conformations generates a powerful argument in favor of the control that conformational and stereoelectronic effects have on the reactivity of pyranos-1-yl radicals. Among the radicals of this type discussed thus far, there is little indication that steric effects have other than a minor role in determining stereoselectivity. Study of compounds that have particularly well shielded radical centers, however, shows that steric effects can be significant in the stereoselectivity of some pyranos-1-yl radical reactions.

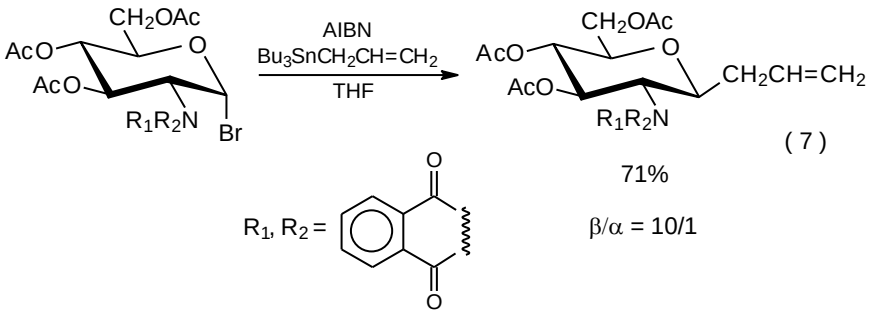


(6). Steric Effects Revisited

(a). Pyranos-1-yl Radicals

Even though conformational and stereoelectronic effects usually have the dominant role in determining stereoselectivity in the reactions of pyranos-1-yl radicals, comparing the reactions shown in equations 6 and 7 shows that steric effects can assert themselves when a sufficiently effective shielding group is present in a reacting molecule. Reaction of the glycosyl chloride **52** with allyltri-*n*-butyltin follows the now familiar pattern of α-face reaction that maintains transition-state interaction between orbitals on C-1 and the ring oxygen atom (eq 6).[37] This reaction stands in contrast to that shown in eq 7 where the sterically demanding phthalimido group at C-2

causes a reversal of stereoselectivity in *C*-glycoside formation. This second reaction (eq 7) is a striking example of steric effects overwhelming the conformational and stereoelectronic effects that normally control stereoselectivity in reactions of pyranos-1-yl radicals.[37,38]



(7)

71%

β/α = 10/1

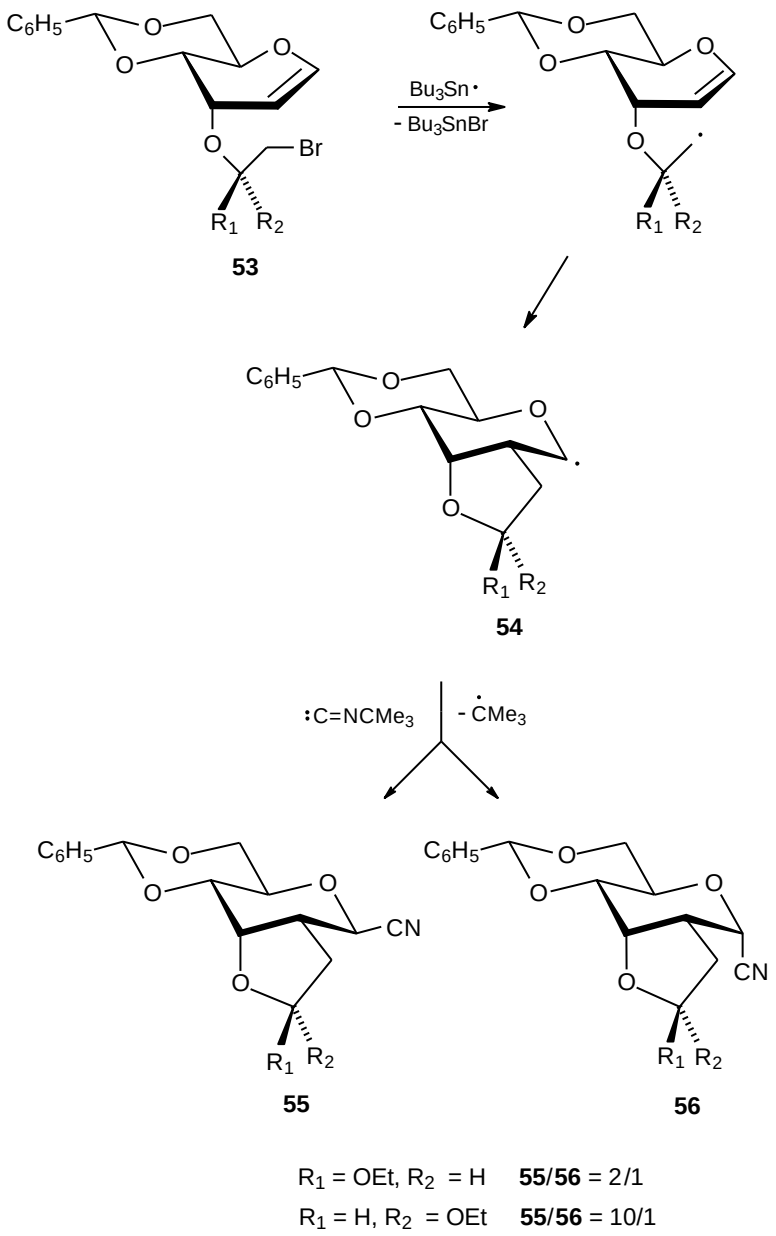
Reaction of the bromide **53** with *tert*-butyl isocyanide gives additional insight into the competition between steric and stereoelectronic effects in determining the stereoselectivity of reaction of pyranos-1-yl radicals (Scheme 22).[35] The C-1 configuration in products **55** and **56** is determined by the stereoselectivity of the reaction between the radical **54** and *tert*-butyl isocyanide. In this reaction steric effects, which favor β-face reaction of **54**, are more powerful than the stereoelectronic effects, which favor forming the product with an α configuration. In addition to shielding due to the methylene carbon atom attached to C-2, the shape of the radical in the vicinity of the ethoxy group has major impact on the steric effects directing the approach of *tert*-butyl isocyanide (Scheme 22).

(b). Furanos-1-yl Radicals

Study of pyranos-1-yl radicals has identified conformational mobility as a "key" factor in the stereoselectivity of their reactions. This selectivity depends not only on which conformation is the major one but also on the accessibility and reactivity of other conformations. For furanos-1-yl radicals the same factors are involved, but their relative importance may differ. Conformational mobility is greater for furanos-1-yl radicals than for their pyranos-1-yl counterparts. Also, due to the shape of the furanoid ring, maintaining effective, transition-state interaction between *p*-type orbitals on C-1 and the ring oxygen atom (i.e., the interaction necessary for kinetic-anomeric stabilization) in many conformations is possible during reaction from both α and β faces of the ring. These observations lead to the proposal that conformational and stereoelectronic effects may be less important in determining stereoselectivity in furanos-1-yl radical reaction than in reactions of pyranos-1-yl radicals. The available information on stereoselectivity of the reactions of furanos-1-yl radicals is not sufficient to draw a firm conclusion about the relative importance of the kinetic anomeric effect when compared to steric effects. Exclusive hydrogen-atom transfer to the less-hindered β face of the radical **57** is consistent with steric effects controlling stereoselectivity; in addition, the fact that the radical **58**, for which the β face is more hindered, is less stereoselective

in its reaction also is consistent with steric effects primarily determining reaction stereoselectivity (Scheme 23).[39]

Scheme 22

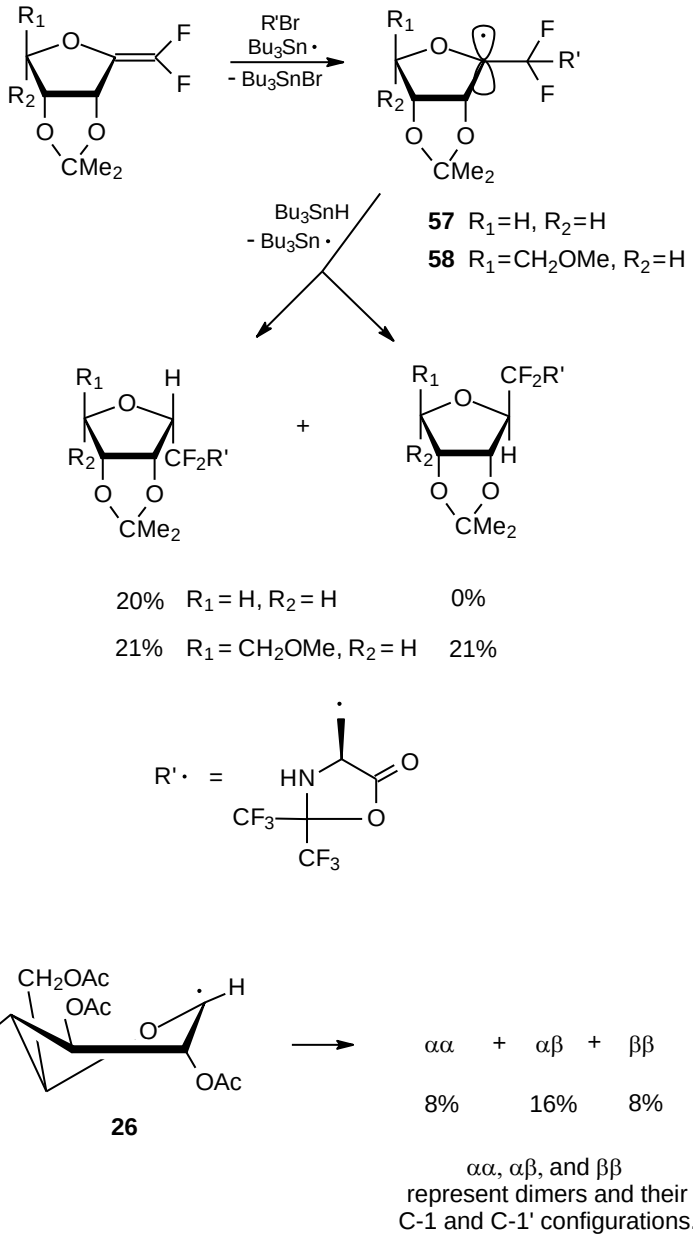


(c). Supersteric Radicals

Although bonding between two radicals normally is a rare event, such a reaction can become significant when other processes (e.g., hydrogen-atom abstraction or addition to an unsaturated

compound) take place too slowly. Bonding between two radicals begins at a sufficiently long distance that differences in transition-state energies leading to different products sometimes are too small to be of consequence; as a result, little or no stereoselectivity is observed (eq 8).[40]

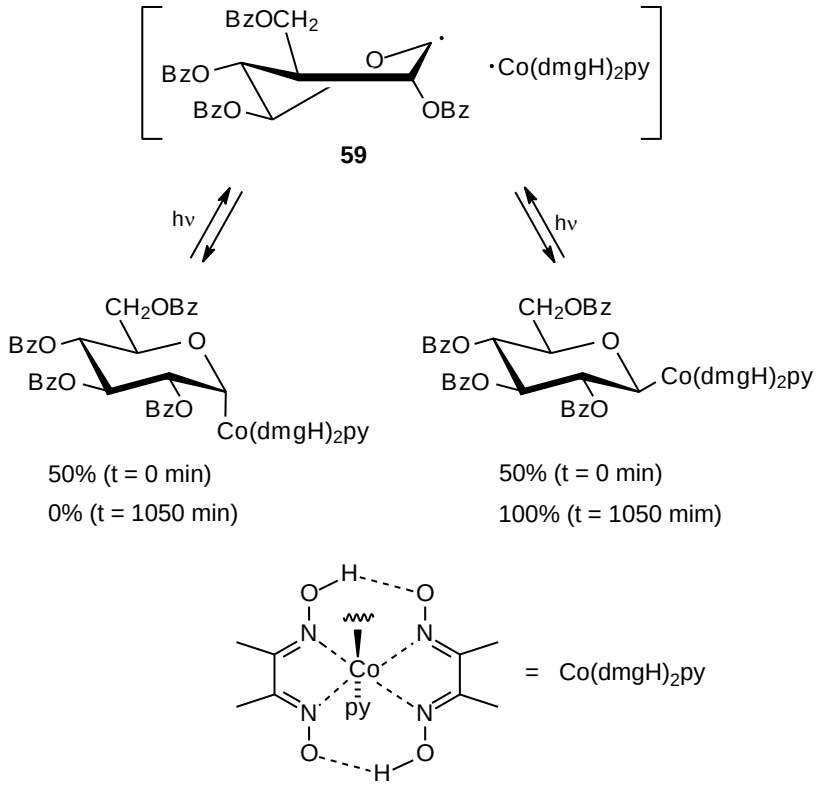
Scheme 23



If one of the radicals involved in a coupling process has steric requirements that are great enough, even radical coupling becomes stereoselective. The "supersteric" $Co(dmgH)_2py$ radical,

for example, has such a large steric requirement that its reaction with the pyranos-1-yl radical **59** occurs much more rapidly from the β face of the pyranoid ring in **59** than from its α face (Scheme 24).[41] Having the $Co(dmgH)_2py$ substituent in an equatorial position (β anomer) is so much more stable than having it in the more crowded axial orientation (α anomer) that this difference significantly affects the transition-state energies leading to these two anomers. The steric size of the $Co(dmgH)_2py$ substituent is so great that it overcomes the usually more important kinetic anomeric effect in determining reaction stereoselectivity.

Scheme 24

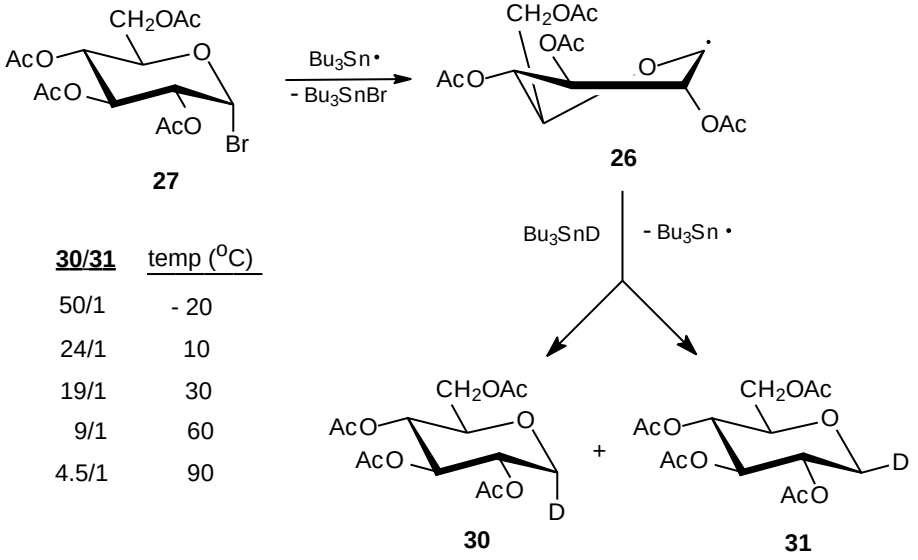


2. Effect of Temperature on Stereoselectivity

A final point with respect to stereoselectivity in bimolecular radical reactions concerns reaction temperature. In the process shown in Scheme 25 stereoselectivity is determined by the approach of Bu_3SnD to the intermediate pyranos-1-yl radical **26**.[31] According to the kinetic anomeric effect [Section III.B.1.c.(4).] stereoselective deuterium transfer to the α face of **26** (to give **30**) should have a lower transition-state energy than transfer to its β face (to give **31**). At low temperature the stereoselectivity is high, but as the temperature rises, stereoselectivity decreases because a progressively larger percentage of radicals are able to react with Bu_3SnD and transcend

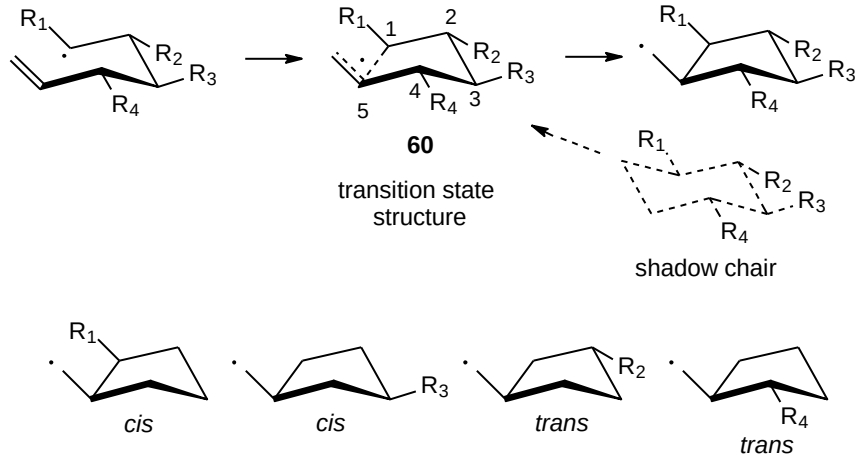
the barriers leading to both products (**30** and **31**). The results shown in Scheme 25 can be viewed as a general response of reaction stereoselectivity to changes in temperature.

Scheme 25



30/31	temp (^{o}C)
50/1	- 20
24/1	10
19/1	30
9/1	60
4.5/1	90

Scheme 26

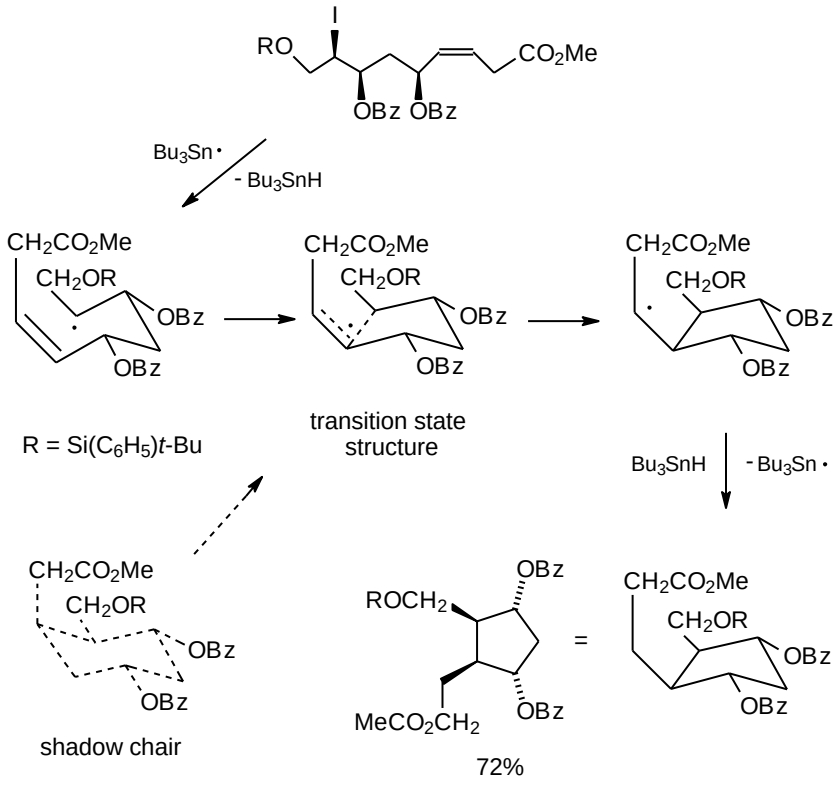


IV. Maximizing Transition-State Stability during Ring Formation

Whenever a radical center and the group with which it is reacting are part of the same molecule, new factors become important in determining both regio- and stereoselectivity.[42–44] Since the reaction taking place is an internal radical addition to a π system, the size of the ring being formed and the constraints placed on reactivity by existing structural features (e.g., other ring systems) both contribute to determining selectivity. Regioselectivity in ring formation is discussed

in Chapter 10 (Section III). The discussion here is concerned with the stereoselectivity of reactions that create new ring systems.

Scheme 27



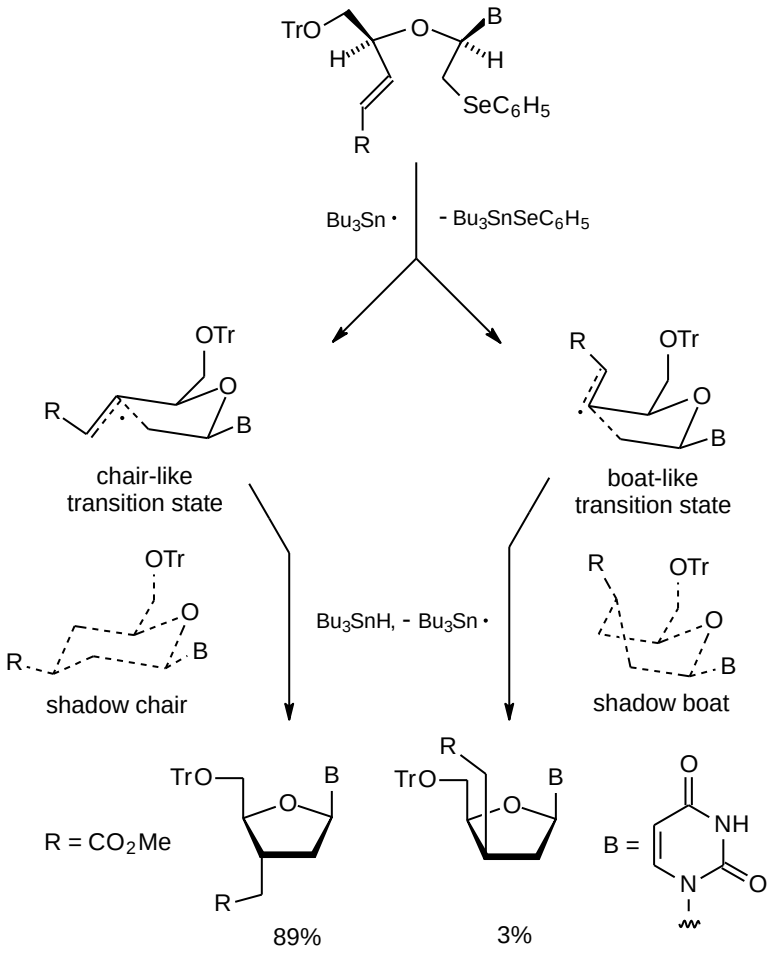
A. Five-Membered Ring Formation

1. Chair-like Transition State

The stereoselectivity of a radical cyclization reaction producing a five-membered ring often can be rationalized by assuming that a transition state is reached that resembles the chair form of a cyclohexane ring (Scheme 26).[45–48] In such a transition state (**60**) the lowest energy arrangement of the "ring substituents" has each group in a pseudoequatorial position. (Scheme 26 includes a shadow-chair representation to help in picturing the chair-like transition state and the ring substituents.) This transition-state model can be used to predict stereochemical outcomes of various types of radical cyclization reactions; for example, cyclization of 1- or 3-substituted 5-hexenyl radicals should give *cis*-disubstituted products, but 2- or 4-substituted radicals should give *trans*-disubstituted ones.[45–48] Even though the complex substitution patterns present in many carbohydrates introduce a variety of possibilities for steric and polar interactions, the chair-like transition state model typically predicts the stereoselectivity of a cyclization reaction. An example is shown in Scheme 27,[49] where if one assumes the reaction passes through a chair-like transition state that

maximizes the number of pseudoequatorial substituents, it is possible to explain completely the stereochemistry in the cyclic product.

Scheme 28



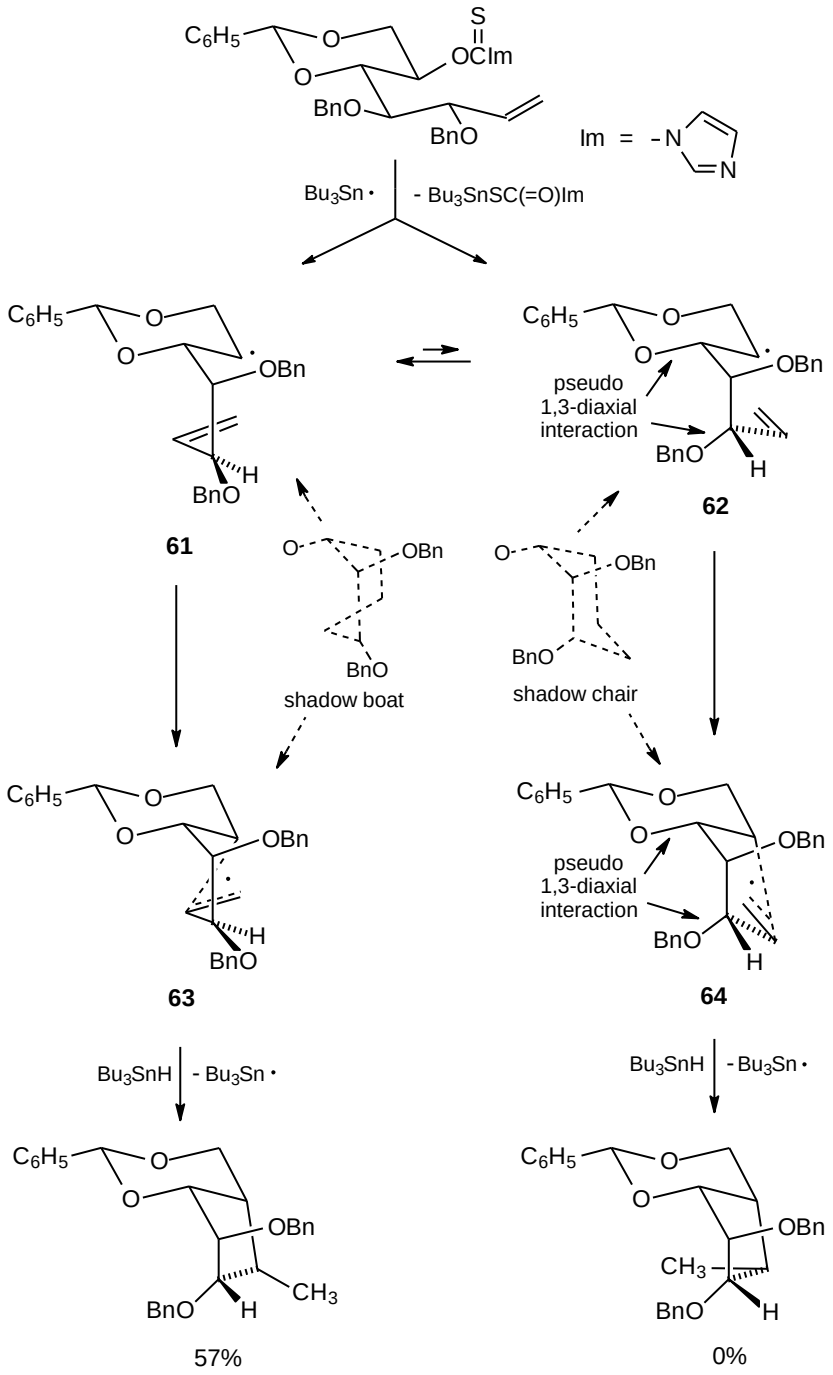
2. Boat-Like Transition State

Although chair-like transition states explain the stereoselectivity of most radical cyclization reactions, calculations on transition-state structures indicate that boat-like transition states should be included as possibilities.[44] These calculations show the boat-like transition state to be only 0.5 kcal/mol higher in energy than the chair-like one in the cyclization of the 5-hexenyl radical. This finding suggests that cyclization reactions may produce minor products via boat-like transition states. Such a transition state explains formation of the minor product in the reaction shown in Scheme 28.[50]

With the structural complexity of carbohydrates and the general similarity in energies between boat-like and chair-like transition states, it would not be surprising to find a cyclization

reaction of a carbohydrate in which formation of the major stereoisomer involves a boat-like transition state. Such a situation appears to exist in the reaction pictured in Scheme 29.[51,52] The stereochemistry in the only cyclic product formed is that expected from a boat-like transition state.

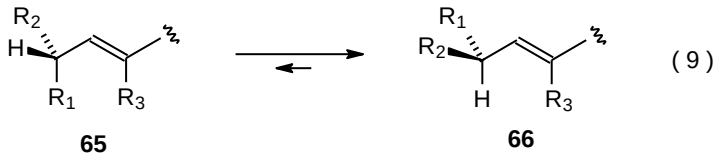
Scheme 29



3. Factors Affecting Transition-State Stability

a. Pseudo-1,3-diaxial Interactions

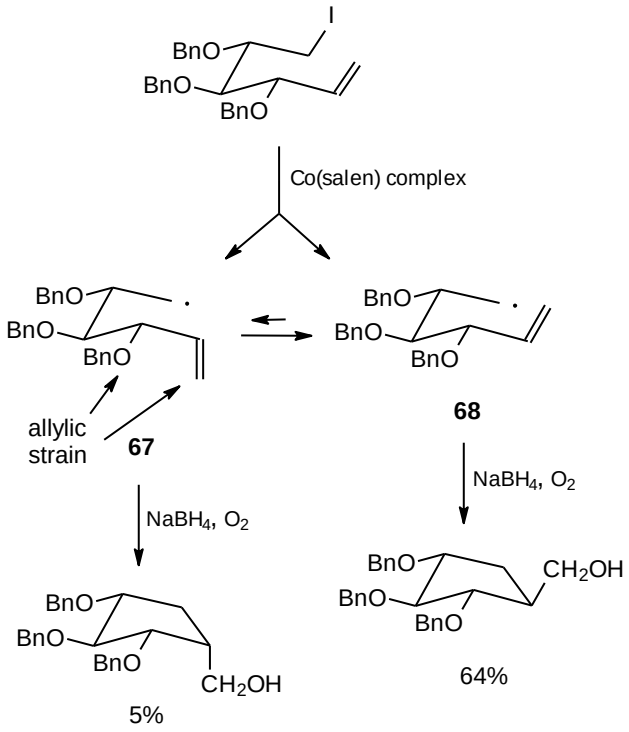
Pseudo-1,3-diaxial interactions can be a factor in transition-state stability in radical cyclization reactions. In the reaction shown in Scheme 29, for example, it is possible to identify a destabilizing, pseudo-1,3-diaxial interaction[53] in the intermediate radical **62** and the chair-like transition state **64**. In the radical **61** and the corresponding boat-like transition state **63** this destabilizing interaction does not exist. As mentioned in the previous paragraph, the stereochemistry of the product from the reaction pictured in Scheme 29 is consistent with a process occurring exclusively via a boat-like transition state.



(9)

R_1, R_2, R_3 are groups sterically larger than a hydrogen atom.

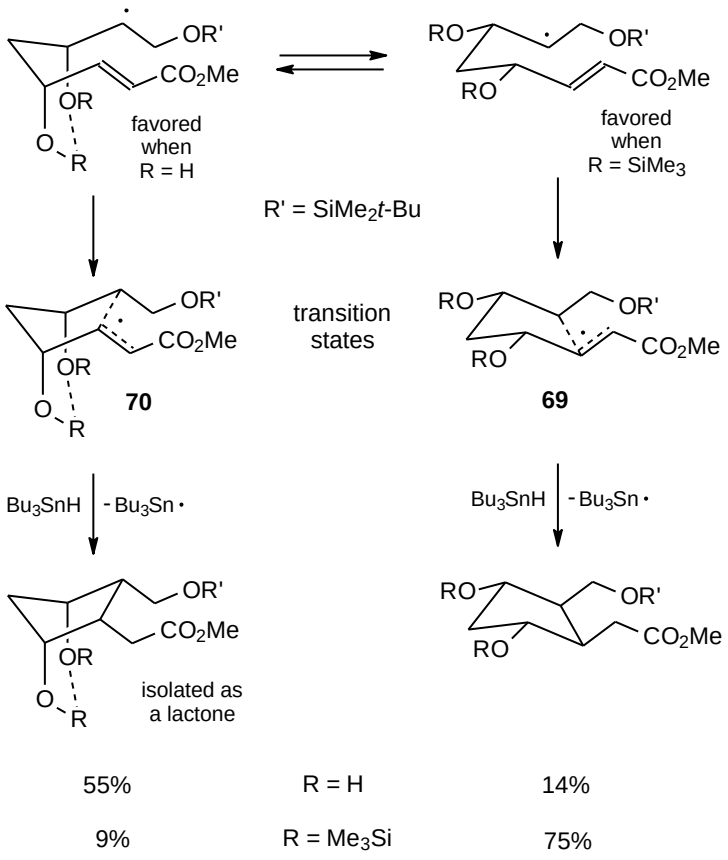
Scheme 30



b. Allylic Strain

Another factor that is credited with affecting transition-state stabilization in cyclization reactions is allylic strain. Allylic strain can be defined in terms of the partial structures shown in eq 9.[54] Conformation **66** is favored energetically over **65** because the destabilizing steric interaction between R_1 and R_3 in **65** is greater than the corresponding interaction between H and R_3 in **66**. Such interaction also affects the transition state energies for reactions from these two conformers; thus, reaction occurs preferentially, sometimes exclusively, from **66**. In the reaction shown in Scheme 30 allylic strain destabilizes conformation **67** and the boat-like transition state through which it reacts, but bond rotation relieves this strain and, thus, favors reaction via the chair-like transition state arising from conformer **68**.[55]

Scheme 31

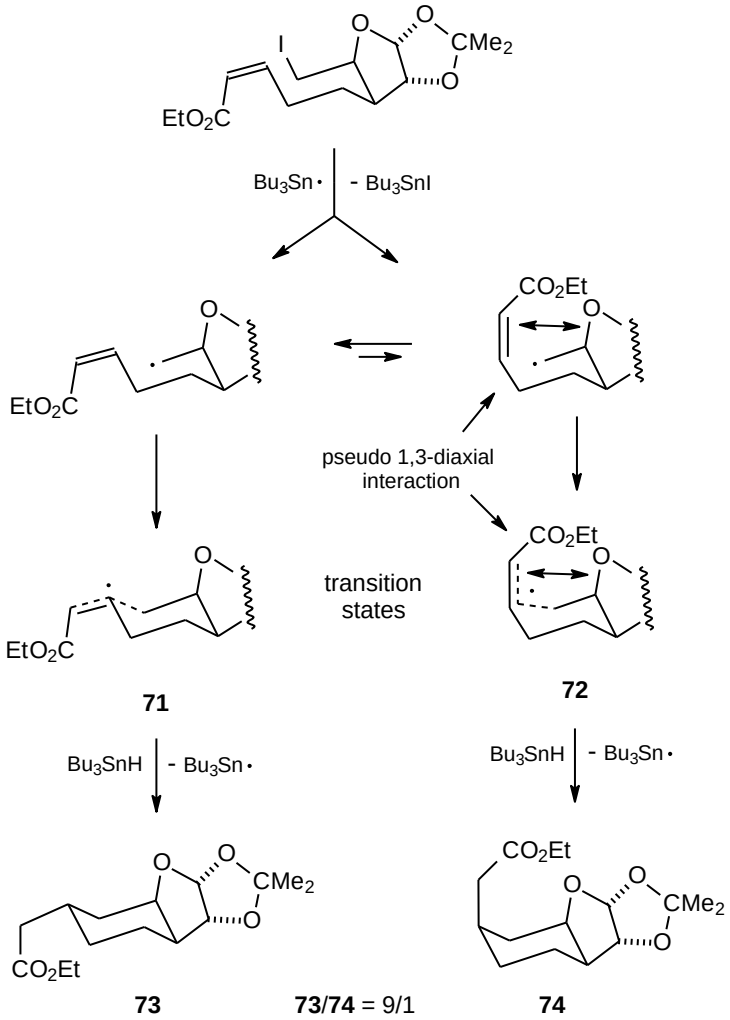


c. Hydrogen Bonding[56,57]

The lowest energy transition state in the reaction shown in Scheme 31 depends upon whether R is a hydrogen atom or a trimethylsilyl group. When the trimethylsilyl group is in place, the

chair-like transition state **69** is lower in energy because it places all substituents in pseudoequatorial positions.[56] If the trimethylsilyl groups are replaced by hydrogen atoms, a different transition state (**70**), one stabilized by hydrogen bonding, has lower energy. The reaction shown in Scheme 31 then illustrates the power of hydrogen bonding in determining a reaction pathway because interaction between the two hydroxyl groups controls the stereochemistry in the products.

Scheme 32



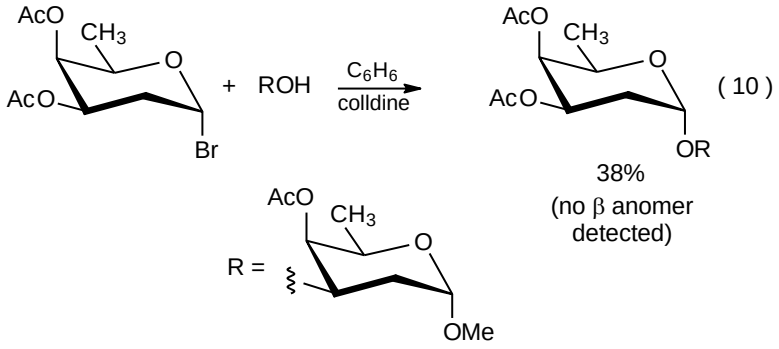
B. Six-Membered Ring Formation

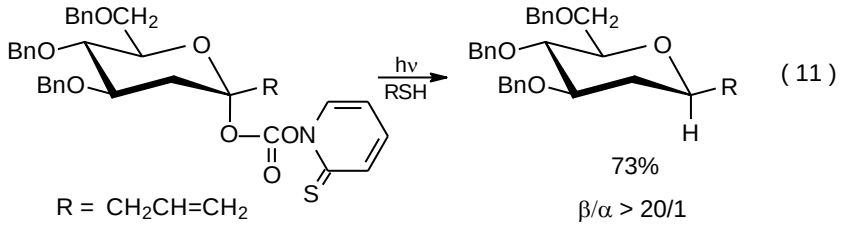
A chair-like transition state also explains the stereoselectivity of cyclization reactions producing six-membered rings. In the reaction shown in Scheme 32, product formation can be understood by assuming that two chair-like transition states (**71** and **72**) are accessible during reac-

tion.[58] The difference between these two is the developing stereochemistry at the carbon atom bearing the $CH_2CO_2CH_3$ group. Transition state **72** with its pseudo-1,3-diaxial interaction would be expected to be higher in energy than **71**. Product yields are consistent with such a difference in transition-state energies.

V. Stereoselectivity in Synthesis

The primary thrust of the discussion in this chapter is to understand the factors controlling stereoselectivity in radical reactions. Many of the reactions examined provide both basic understanding of radical-reaction stereoselectivity and examples of how stereoselectivity can achieve a particular synthetic goal. The emphasis in discussion in this part of the chapter shifts to reactions where the primary goal is to solve a particular synthetic problem by taking advantage of knowledge about stereoselectivity in radical reactions. Even though the purpose in conducting these reactions is synthetic, their investigation has increased basic understanding of radical-reaction stereoselectivity.

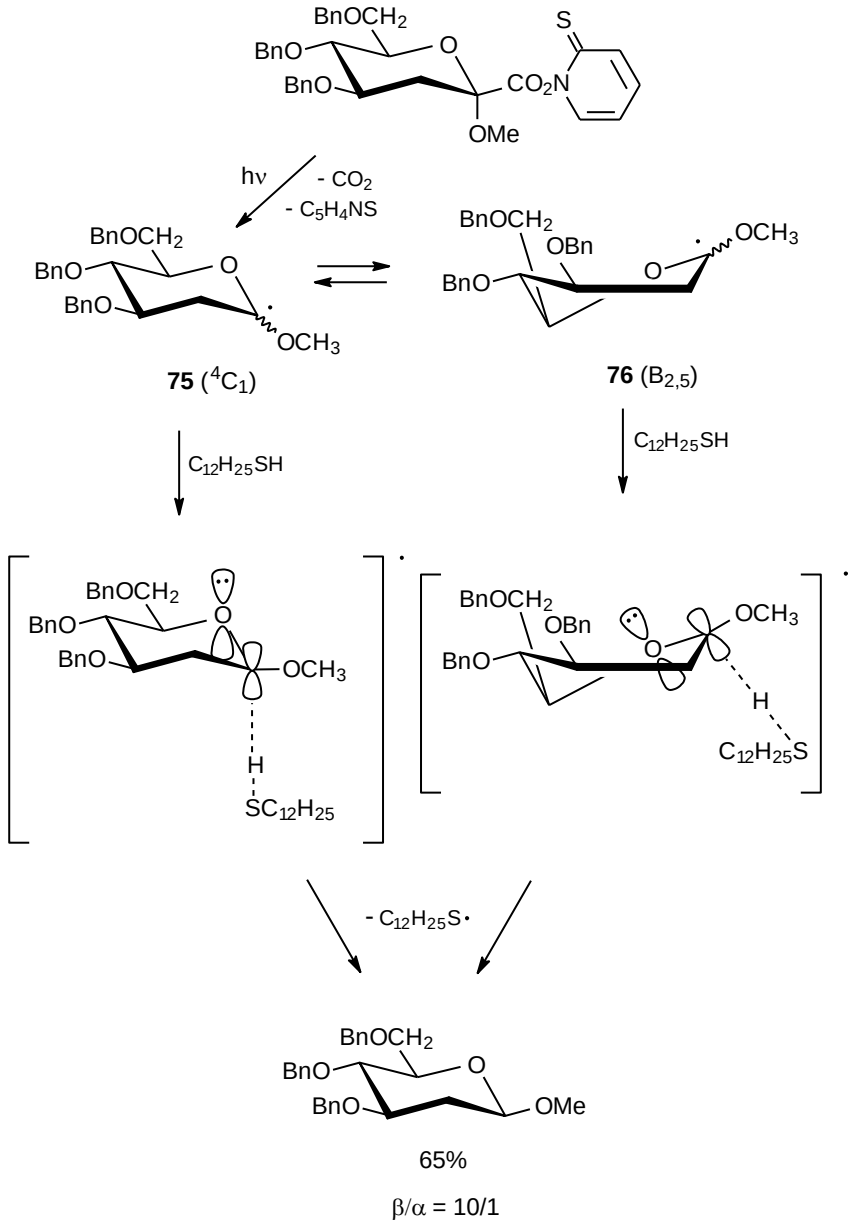




A. β-Glycoside Synthesis

2-Deoxy-β-D-glycopyranosides are difficult to prepare because common procedures for their synthesis give the thermodynamically more stable α-anomers as the major products (eq 10).[59,60] Stereoselective formation of β-glycosides traditionally depends upon a temporary, C-2 substituent anchimerically assisting β-glycoside formation. The disadvantage to this approach is that the C-2 substituent must be replaced by a hydrogen atom after the glycosidic linkage is established.

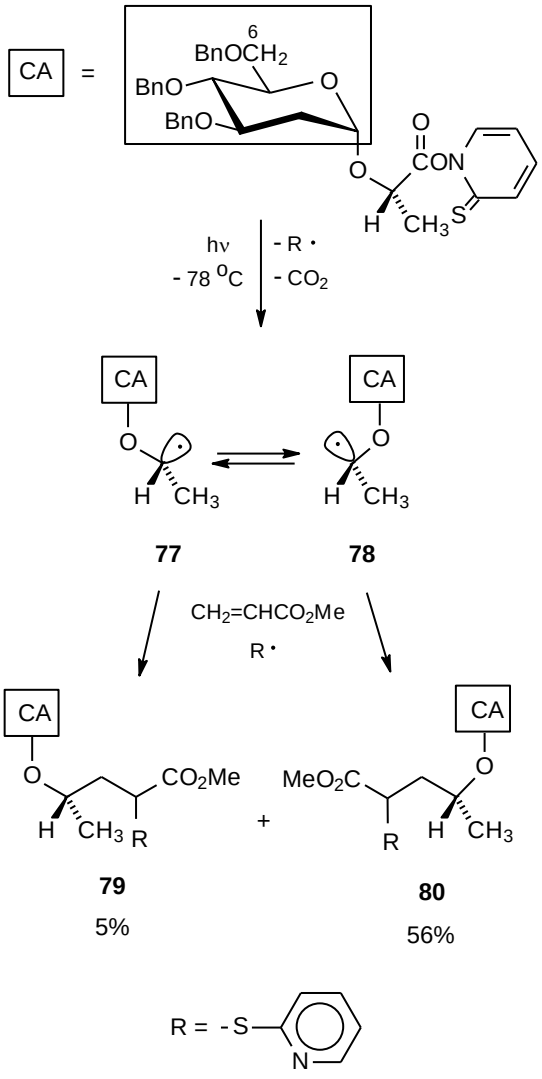
Scheme 33



Free-radical reaction provides a pathway to 2-deoxy-β-D-glycopyranosides that does not require participation of a substituent at C-2.[61–66] This method depends upon the kinetic anomeric effect controlling the approach of the hydrogen-atom donor to the radical center. In most instances stabilized approach occurs on the α face of the ring; thus, a β glycoside forms. In the reaction shown in Scheme 33[61] both $^4C_1$ chair (**75**) and $B_{2,5}$ boat (**76**) conformations are included because the conformation of the reacting radical is not known. In either case reaction based on the kinetic anomeric effect favors formation of the β glycoside.

Since the primary factor determining stereoselectivity in the radical-based synthesis of 2-deoxy-β-D-glycopyranosides is the stabilizing interaction between *p*-type orbitals on C-1 and the ring oxygen atom, it is reasonable to expect such interaction also to be important in the formation of *C*-glycosides. This turns out to be the case.[67–71] An example of stereoselective β-*C*-glycoside synthesis is give in eq 11.[67,68]

Scheme 34



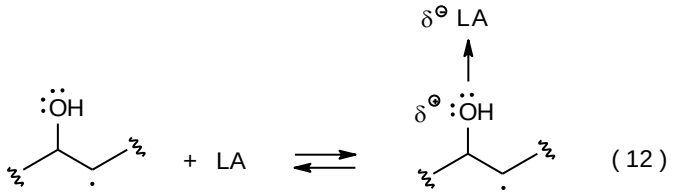
B. Reaction at Remote Radical Centers (Carbohydrates as Chiral Auxiliaries)

1. Substrate-Controlled Reactions

When a radical center is located on a chain of atoms to which a carbohydrate moiety is attached, the carbohydrate portion of the molecule can affect the stereoselectivity of reaction at the

radical center; that is, the carbohydrate moiety will function as a chiral auxiliary. The typical procedure is: a carbohydrate is coupled with a noncarbohydrate; stereoselective reaction takes place; and, finally, the link to the carbohydrate is broken to give a modified, stereoisomerically enriched product.

One way in which carbohydrates can function as chiral auxiliaries is in the addition of radicals to carbon–carbon double bonds.[72–77] The selectivity of the reaction shown in Scheme 34 illustrates the influence of the carbohydrate portion of the molecule on the relative ability of the equilibrating radicals **77** and **78** to add to methyl acrylate.[72] Since the energy barrier for interconversion of these two (**77** and **78**) is less than the barrier for either to add to methyl acrylate, the Curtin– Hammett principle is in effect; therefore, the difference in stereoselectivity is determined by the difference in activation energies for the reactions taking place.[77] Although the calculated energies of these radicals are nearly identical, when the calculations are extended to include energies of possible transition-state structures, the addition of **78** to methyl acrylate has a lower energy pathway than that for addition of **77**. This difference in energy is due to greater steric interactions at the transition state leading to **79** as opposed to that leading to **80**.[72,77] These interactions are primarily between the incoming methyl acrylate and the groups and atoms attached to C-6.



(12)

LA = Lewis acid

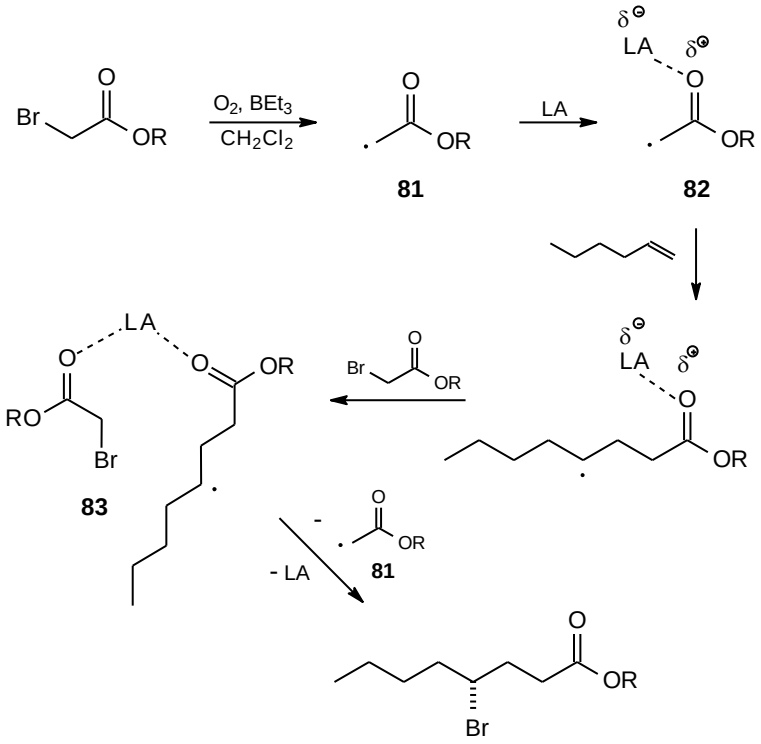
2. Complex-Controlled Reactions

Formation of a complex between a radical (or radical precursor) and a Lewis acid can change radical reactivity in several ways.[78,79] Complex formation can render a radical more electrophilic (eq 12),[79] accelerate radical formation,[80,81] or restrict a radical to a particular conformation.[79] Also, complex formation can bind together a radical and a molecule in a manner that leads to highly stereoselective reaction.

A Lewis acid is critical in more than one way to the reaction shown in Scheme 35.[82] First, reaction does not take place unless the Lewis acid is present. This suggests that the radical **81** is not sufficiently electrophilic to add to 1-hexene, but the complex **82** is. In addition, the stereoselectivity of the reaction depends on the identity of the Lewis acid. Among the seven acids tested, $Eu(OTf)_3$ was the most effective. The ability of $Eu(OTf)_3$ to promote stereoselectivity in this reaction is attributed to the formation of the Lewis acid complex **83** prior to bromine-atom transfer. When such a complex forms, the carbohydrate moiety is able to function as chiral auxiliary that controls the stereoselectivity of bromine-atom transfer.

Chelation control is another way in which complexation can affect the stereoselectivity of a radical reaction. (A chelate is "a ligand that is able to bond to a central metal atom simultaneously through more than one donor atom".[83]) In the reaction shown in Scheme 36 the intermediate radicals are bonded to samarium simultaneously through two oxygen atoms. This chelation insures that the two hydroxyl groups are *cis* related in the six-membered ring in each of the final products.[83]

Scheme 35



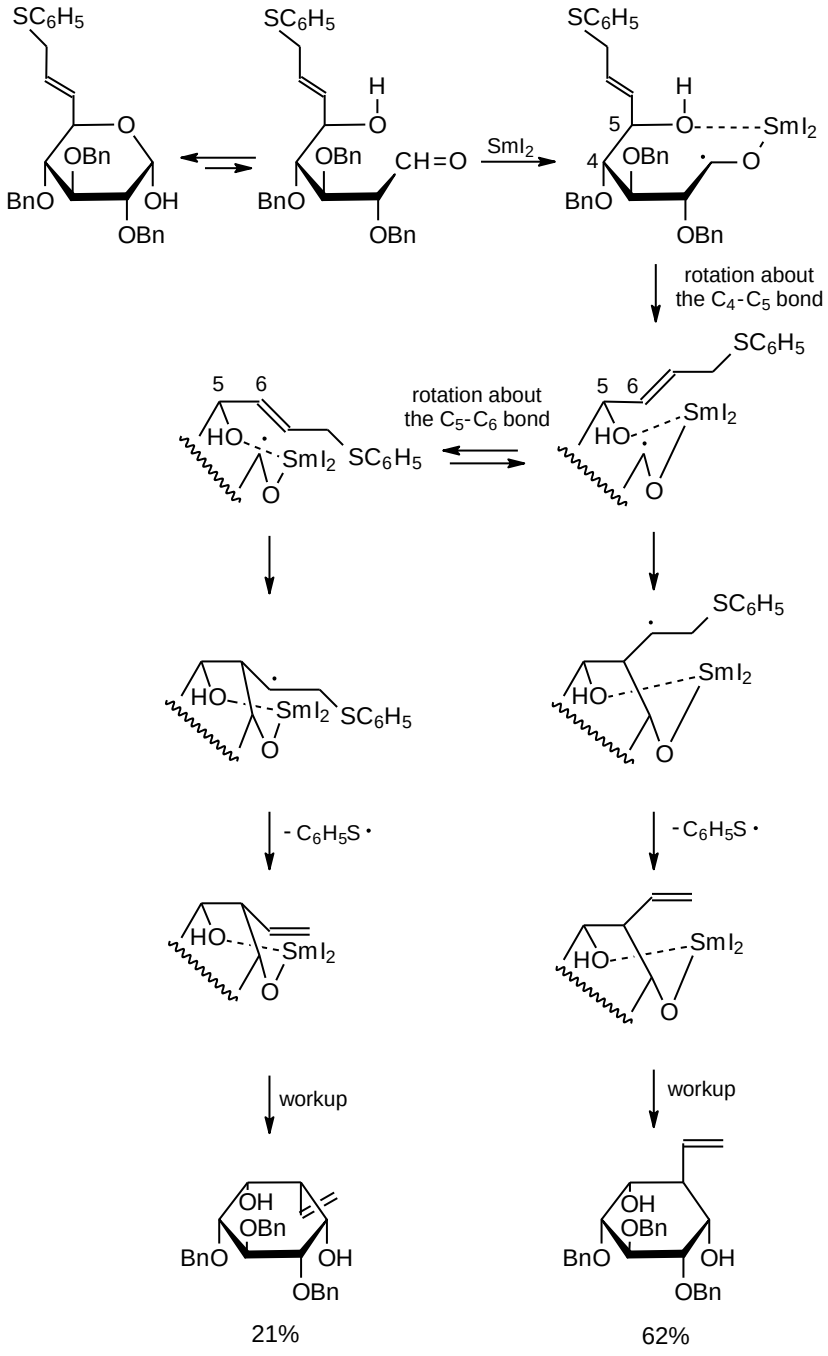
R =	LA = Lewis acid	yield	de	temp
	none	0%		
	$Eu(OTf)_3$	56%	1.7:1	25 °C
	$Eu(OTf)_3$	65%	2.8:1	0 °C
	$Eu(OTf)_3$	71%	12.5:1	-78 °C

C. Enantioselective Reactions

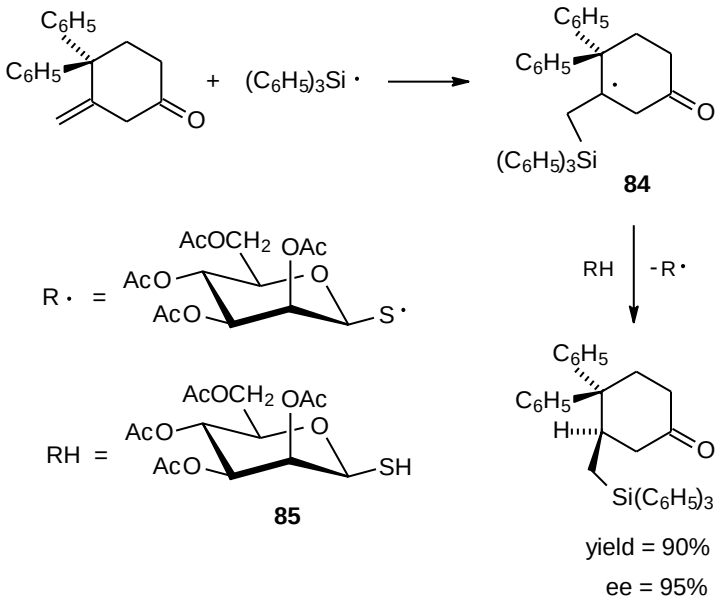
The reactions discussed thus far all have been diastereoselective. Enantioselective reactions involving carbohydrate radicals do take place, although they are far less numerous than diastereoselective ones in typical (nonenzymatic) laboratory reactions. In the reaction shown in Scheme

37 the carbohydrate thiol **85** is involved in an enantioselective reaction.[84,85] In this process **85** transfers a hydrogen atom to the radical **84** to give the final product in 90% yield with a 95% enantiomeric excess (ee).

Scheme 36



Scheme 37



VI. Summary

Stereoselectivity is the preferential formation or consumption of one stereoisomer rather than another in a chemical reaction. In radical reactions stereoselectivity is controlled by a combination of conformational, steric, stereoelectronic, and torsional effects. The stereoselectivity caused by these effects is generally increased by conducting reactions at lower temperature. For radicals not centered on C-1, steric effects direct reaction to occur along the least-hindered pathway. A primary factor in determining this pathway is the way in which various groups shield a radical center.

As the steric size of a molecule reacting with a carbohydrate radical increases, the extent to which the least-hindered pathway is followed also increases. As this size of reacting molecules becomes smaller, stereoselectivity decreases but does not completely disappear; rather, a low level of selectivity remains due to torsional interactions.

Stereoelectronic effects operate in conjunction with conformational effects to determine stereoselectivity in reactions of pyranos-1-yl radicals. The critical factor in forming a particular stereoisomer in a reaction is the ability of the reactants to maintain in the transition state a stabilizing interaction between orbitals on C-1 and the ring oxygen atom. Maintaining this interaction causes different conformations of a radical to yield stereoisomerically different products. This stereoelectronic, conformation-dependent, transition-state stabilization gives rise to a phenomenon known as the kinetic anomeric effect. This effect provides a basis for predicting and rationalizing stereoselectivity of pyranos-1-yl radical reactions.

Radical cyclization places additional requirements on reaction stereoselectivity. Prominent among these is that in most situations a reaction proceeds through a chair-like transition state that

has substituents located in pseudoequatorial positions. In some instances a boat-like transition state is lower in energy than a chair-like one. This is often the case when structural features such as allylic strain or pseudo-1,3-diaxial interactions destabilize a chair-like transition state. The stereoselectivity of radical reactions provides the basis for several synthetic processes. These include the synthesis of β-glycosides, the use carbohydrates as chiral auxiliaries, and the incorporation of carbohydrates into enantioselective syntheses.

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