

# Chapter 10

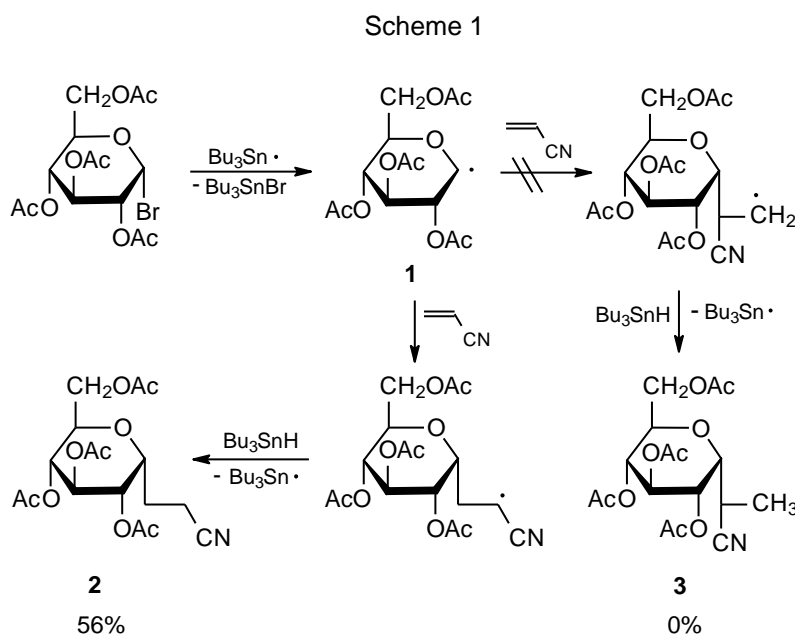
## Regioselectivity

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## I. Introduction

### A. Definitions of Regiospecific and Regioselective Reactions

When the terms regioselective and regiospecific were first introduced into organic chemistry, they were defined in the following way: "If a reaction proceeds without skeletal rearrangement to give exclusively (within experimental error) one of two or more possible isomers, it is called *regiospecific*. If there is a significant preponderance of one isomer formed, it is said to be *regioselective*."<sup>1</sup> Since a regiospecific reaction can be viewed as a special type of regioselective reaction (i.e., one that is totally selective), the term regioselective can be used to describe any reaction that produces one structural isomer in greater abundance than another.

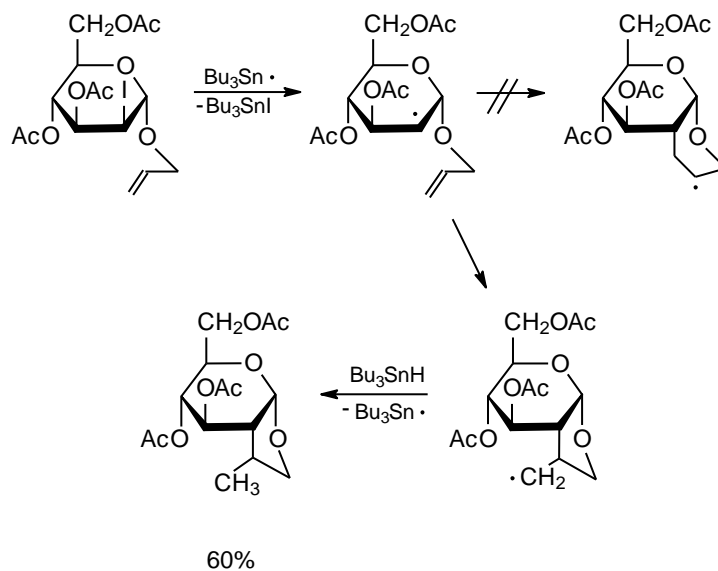


### B. Regioselectivity in Radical Reactions of Carbohydrates

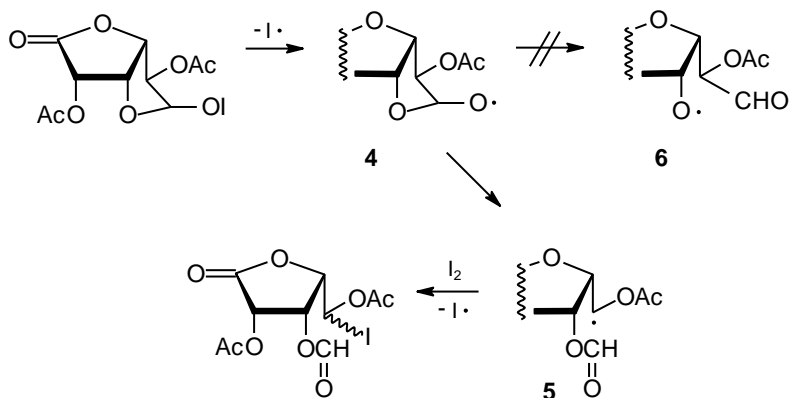
Among carbohydrates there are several types of radical reaction for which regioselectivity is an important consideration. The first of these (discussed in Section II) is the addition of a radical to the multiple bond in an unsaturated compound. An example of reaction of this type is found in Scheme 1, where addition of the pyranos-1-yl radical **1** takes place only at the unsubstituted carbon atom of the double bond in acrylonitrile.<sup>2,3</sup> A second type of regioselective reaction (described in Section III) is a variation on this addition process that occurs when the radical center and the multiple bond are part of the same molecule. In the reaction shown in Scheme 2, for example, regioselectivity arises because there is a choice between producing a five-membered or six-membered ring.<sup>4</sup> A third type of regioselective reaction, one involving  $\beta$ -fragmentation, is discussed in Section IV. An example is given in Scheme 3 where the oxygen-centered radical **4** undergoes ring

opening to generate the carbon-centered radical **5** rather than the oxygen-centered radical **6**.<sup>5</sup> An example of the final type of regioselective radical reaction is found in Scheme 4, where abstraction of H-5 from the pentaacetate **7** takes place even though there are other hydrogen atoms present in **7** that could have been abstracted to form isomeric products.<sup>6</sup> This type of regioselectivity, sometimes referred to as site-selectivity, is described in Section V.

Scheme 2



Scheme 3



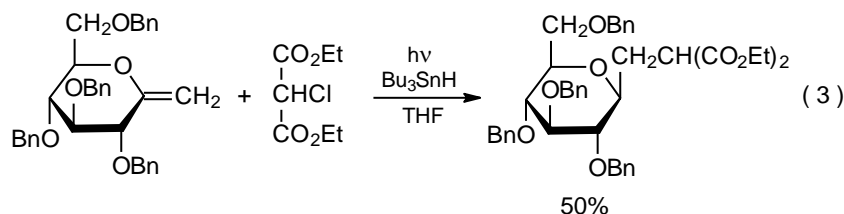
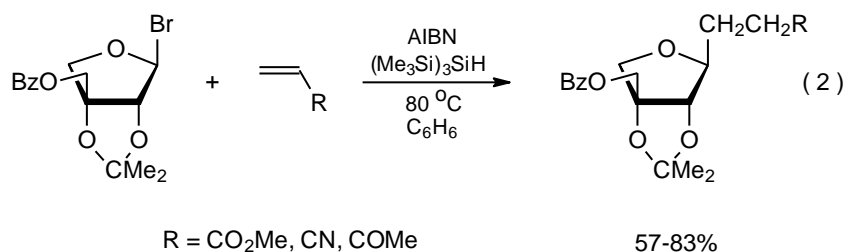
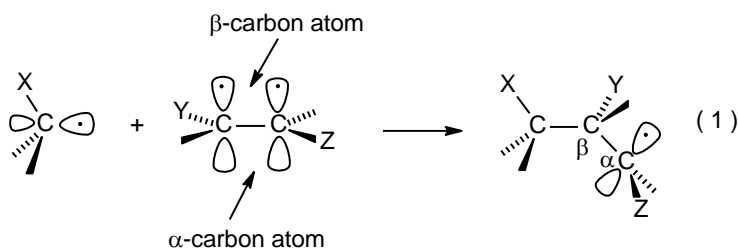
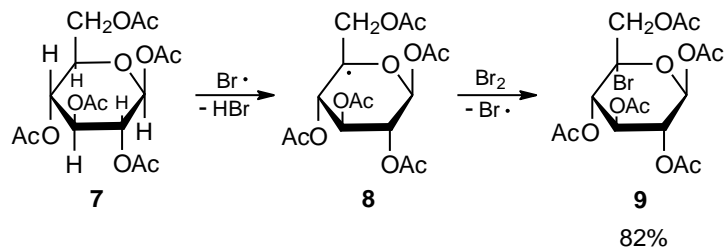
## II. Intermolecular Addition Reactions

### A. General Reaction Equation

A useful terminology for describing radical addition reactions is given in eq 1. According to this description, when a carbon-centered radical reacts with a carbon-carbon double bond, it adds

to the  $\beta$ -carbon atom and creates a new radical center on the  $\alpha$ -carbon atom. The letters X, Y, and Z in eq 1 represent substituents attached to the three carbon atoms directly involved in the reaction.

Scheme 4



## B. Reaction at the Less-Substituted Carbon Atom

A characteristic of radical addition reactions is that a carbon-centered radical adds regioselectively to the less-substituted atom in a C–C multiple bond.<sup>7–10</sup> The reaction shown in Scheme 1 provides a typical example. Other reactions involving double bonds with different substituents

(eq 2)<sup>11</sup> and double bonds with more than one substituent (eq 3)<sup>12,13</sup> exhibit similar regioselectivity. Explaining regioselectivity in addition reactions begins by noting that they usually are not reversible;<sup>14</sup> therefore, information about transition-state structures is critical to understanding the selectivity in these kinetically controlled reactions.

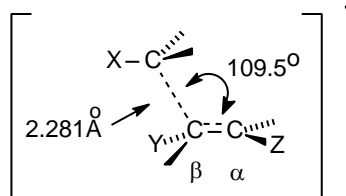


Figure 1. Transition-state structure for addition of a radical to an unsaturated compound. The numbers are calculated values for  $X = Y = Z = \text{H}$ .

### C. Transition-State Structure

The structure for the transition state in a radical addition reaction, as determined from molecular-orbital calculations, is shown in Figure 1.<sup>8</sup> Several aspects of this structure affect reaction regioselectivity. The first is that the structure is unsymmetrical.<sup>7,8</sup> An unsymmetrical transition state requires that radical addition to each carbon of the multiple bond represents a distinct reaction pathway; there is no common intermediate. Also, partial  $\sigma$ -bond formation between the  $\alpha$ -carbon atom and the incoming, carbon-centered radical causes the groups attached to each of these atoms to assume a decidedly pyramidal arrangement; thus, reaction causes the groups attached to each center to move closer together.

### D. Factors Controlling Regioselectivity

The unsymmetrical nature of the transition state structure shown in Figure 1 requires that addition to each carbon atom of an unsymmetrically substituted double bond has a different rate constant for reaction. Understanding regioselectivity in addition reactions then depends upon correctly analyzing the factors controlling these two rate constants. “The temperature dependence of the rate constants is well described by the Arrhenius equation  $k = A \exp(-E_a/RT)$ . Thus, at a given temperature, the rate variations with radical and substrate substitution can be caused by variations in the frequency factor ( $A$ ) and/or the activation energy ( $E_a$ ). For polyatomic radicals, the frequency factors span a narrow range... Hence, the large variation in the rate constants is mainly because of variations in the activation energy”.<sup>8</sup> The major factors determining activation energy [bond strengths, steric effects, stereoelectronic effects, and polar effects] are then the ones that need to be considered in determining reaction regioselectivity.<sup>8</sup>

$$E_a = C + \alpha H_r \quad (4)$$

$E_a$  = energy of activation

$H_r$  = reaction enthalpy

C and  $\alpha$  are constants.

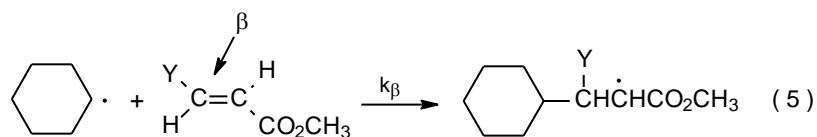
### 1. Bond Strengths

A characteristic of many reactions that are similar in nature is that their energies of activation ( $E_a$ ) can be determined from the Evans–Polanyi relation (eq 4).<sup>8,10</sup> (The Evans–Polanyi relation is discussed in Section I.A. of Chapter 7.) In such situations calculating these energies depends upon determining reaction enthalpies ( $H_r$ ) and establishing values for the two constants in eq 4. For the addition of carbon-centered radicals to C–C double bonds the values for the experimentally determined constants are  $C=50 \text{ kJmol}^{-1}$  and  $\alpha=0.25$ , when  $E_a$  and  $H_r$  are expressed in  $\text{kJmol}^{-1}$ .<sup>8,15</sup> The number 0.25 for the proportionality constant  $\alpha$  means that the enthalpy change, which depends on the difference in the strengths of the bonds being broken and formed, needs to be large for it to have a significant impact on the energy of activation for the reaction. The 0.25 value for  $\alpha$  is reasonable for a reaction with an early transition state.

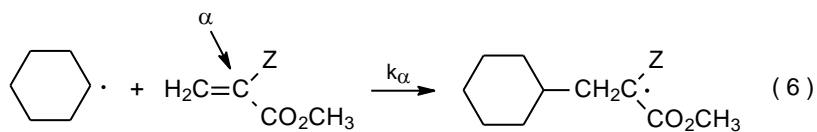
### 2. Steric Effects

Rehybridization of the  $\beta$ -carbon atom from  $sp^2$  to  $sp^3$  takes place during radical addition (eq 1). The necessary repositioning of groups that this rehybridization requires forces them closer together (i.e., causes group compression) as reaction proceeds. Any resistance to group compression caused by steric hindrance raises the energy required to reach the transition state for a reaction.<sup>8–10</sup> The transition state, therefore, becomes energetically more difficult to attain as the steric size of any of the groups attached to the  $\beta$ -carbon atom increases. A similar steric compression of the groups attached to the carbon atom bearing the radical center in the adding radical also takes place, but the effect should be smaller because a typical radical center has a structure that already is at an intermediate stage between  $sp^2$  and  $sp^3$  hybridization.<sup>8–10</sup>

In addition to group compression, steric interactions at the transition state also arise between groups attached to the  $\beta$ -carbon atom and those bonded to the adding radical (Figure 1). Experimental support for significant interaction comes from the finding that the rate constants for radical addition to the  $\beta$ -carbon atom of an alkene change dramatically when sterically demanding groups are introduced on this atom.<sup>7,16</sup> In the reactions represented in eq 5 increasing the steric size of the Y group significantly decreases the rate constant for  $\beta$  addition.<sup>7</sup> While it may be difficult to decide how much rate constant reduction is attributable to group compression and how much to interaction between groups on the  $\beta$ -carbon atom and the incoming radical, the relative rate constants shown in eq 5 leave little doubt that steric effects play a major role in determining the rates of radical addition reactions.<sup>7</sup>



$\underline{\text{Y}}$	$k_\beta$
H	20,000
CH <sub>3</sub>	220
CH <sub>3</sub> CH <sub>2</sub>	132
(CH <sub>3</sub> ) <sub>2</sub> CH	30
(CH <sub>3</sub> ) <sub>3</sub> C	1



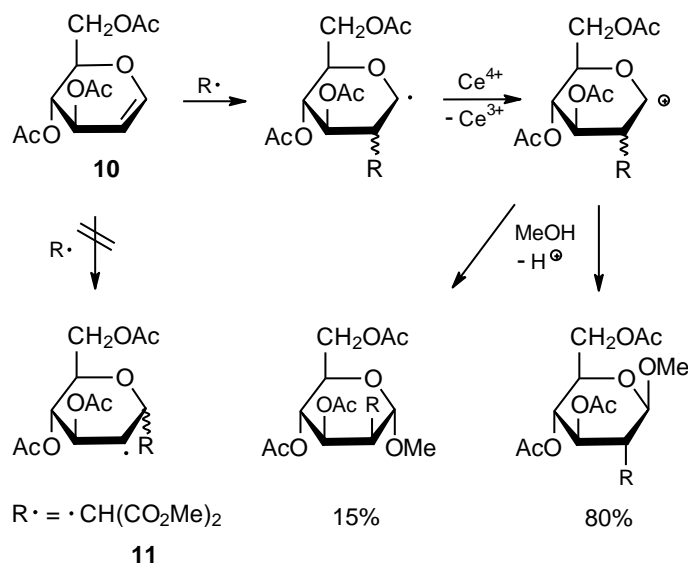
$\underline{\text{Z}}$	$k_\alpha$
H	4.2
CH <sub>3</sub>	3.0
CH <sub>3</sub> CH <sub>2</sub>	2.3
(CH <sub>3</sub> ) <sub>2</sub> CH	1.8
(CH <sub>3</sub> ) <sub>3</sub> C	1.0

Since the separation at the transition state between the adding radical and the  $\alpha$ -carbon atom in an addition reaction is considerable (Figure 1), it is reasonable to expect that any steric hindrance involving  $\alpha$ -substituents should be small.<sup>7,16</sup> The relative rate constants shown in eq 6 support this expectation because a dramatic change in the steric size of groups attached to the  $\alpha$ -carbon atom has only a small effect on the value of these constants; the largest and the smallest differ only by a factor of 4.2.<sup>7</sup>

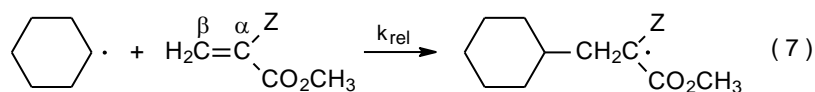
Steric effects have a more important role in determining addition-reaction regioselectivity than do the strengths of the bonds being broken or formed. The reason for this situation can be traced to the nature of the addition process. In the competing reactions that determine regioselectivity [i.e., addition to either the  $\alpha$  or  $\beta$  carbon atom in a multiple bond of an unsaturated compound] the same number and types of bonds are being broken and formed; consequently, there

should be little difference in activation energies for these two reactions based on bond strengths alone.

Scheme 5



Although the primary role of steric effects in determining regioselectivity in radical addition reactions is clear, these effects are not always the sole determining factor. It would be difficult, for example, to explain preferential addition to C-2 in the glycal **10** (Scheme 5) on the basis of steric effects alone because C-2 is, if anything, more hindered than C-1.<sup>17-19</sup> Clearly, another factor also affects regioselectivity in reactions of this type.



Z	$k_{\text{rel}}$	Z	$k_{\text{rel}}$
CN	1940	H	6
CO <sub>2</sub> CH <sub>3</sub>	940	CH <sub>3</sub>	5
Cl	75	CH <sub>3</sub> O	1

### 3. Polar Effects

Polar effects are influences on reactivity caused by unequal electron distribution within a molecule or reactive intermediate. In radical addition reactions these effects can originate with substituent groups and can be transmitted to the reacting atoms either through bonds or through



space. Polar effects also can arise from electron delocalization that produces unequal electron distribution.

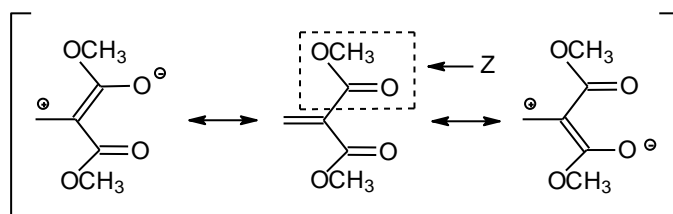
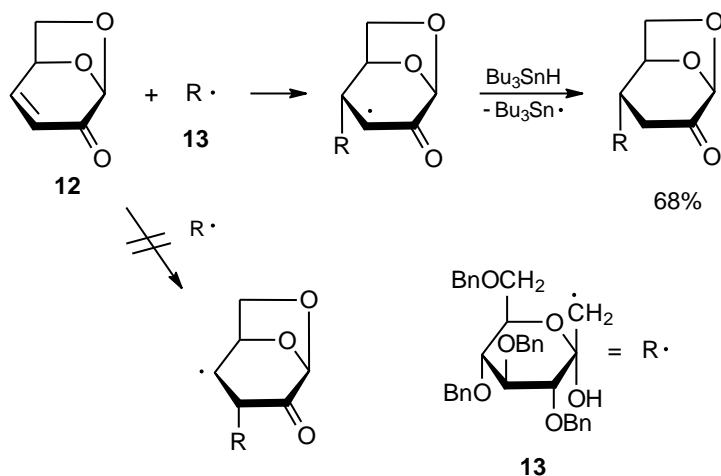


Figure 2. Resonance structures showing a shift of electron density to the carbonyl groups

The data shown in eq 7 illustrate the importance that polar effects have on radical addition reactions.<sup>7</sup> These data describe the relative rate constants for addition of the nucleophilic cyclohexyl radical ( $C_6H_{11}\cdot$ ) to substituted  $\alpha,\beta$ -unsaturated esters. The rate constant is large when a strongly electron-withdrawing substituent (e.g., CN,  $CO_2Me$ ) is attached to the  $\alpha$ -carbon atom in one of these unsaturated esters. Electron withdrawal from the double bond by either CN or  $CO_2Me$  is due primarily to delocalization that shifts electron density to one of these the  $\alpha$ -substituents. In the case where the  $\alpha$ -substituent is a methoxycarbonyl group ( $Z = CO_2Me$ ), the electron-density shift can be seen in the contributing resonance structures shown in Figure 2. Although the polar effects being described are those that exist in the reactants, the rate constants in eq 7 support the idea that these effects remain significant at the transition state.

#### Scheme 6



Polar effects not only explain the difference in rate constants for the reactions shown in eq 7, but they also rationalize the regioselectivity of these reactions. The resonance hybrid pictured in Figure 2 indicates a reduced electron density at the  $\beta$ -carbon atom in the carbon–carbon double bond of the ester; consequently, this atom represents a point of attraction for a nucleophilic radical. In such a situation regioselective,  $\beta$ -carbon-atom addition can be expected. An example of this type of addition is shown in Scheme 6 where the nucleophilic carbohydrate radical **13** adds regioselectively to the  $\beta$ -carbon atom of the  $\alpha,\beta$ -unsaturated ketone **12**.<sup>20</sup>

Addition of a nucleophilic radical to an electron-rich double bond is too slow to compete with other radical reactions, but if the radical is electrophilic, addition takes place. The dimethylmalonyl radical **11**, for example, adds to the electron-rich double bond in the D-glucal **10** (Scheme 5).<sup>17–19</sup> As the resonance hybrid pictured in Figure 3 indicates, C-2 in **10** has greater electron density than C-1; thus, the electrophilic radical **11** not only adds to the double bond in **10** but it does so regioselectivity at C-2 (Scheme 5).

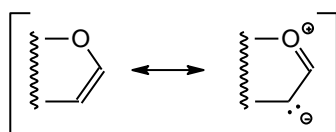
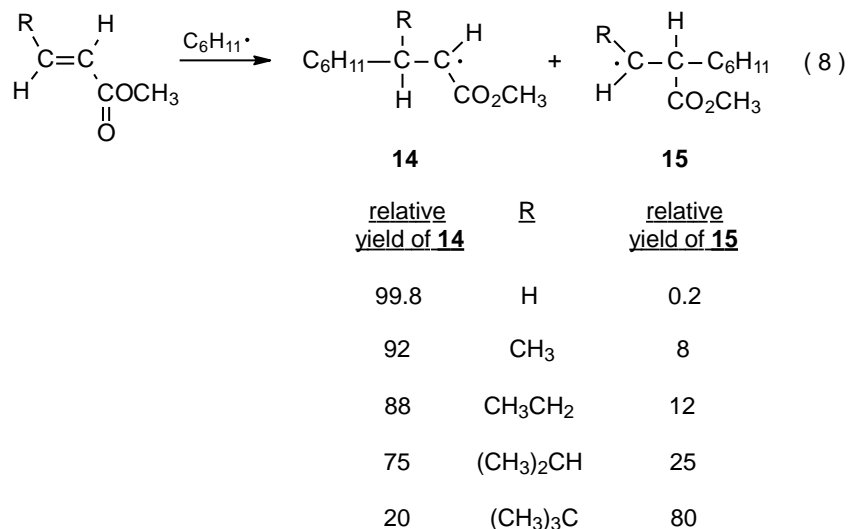


Figure 3. Resonance structures showing a shift of electron density to C-2



Since steric and polar effects often favor formation of the same product in a radical addition reaction (i.e., that from addition to the least substituted carbon atom in the double bond of the

unsaturated reactant), it is sometimes difficult to determine the relative contribution of each effect to the regioselectivity of a reaction. A series of experiments designed to test these contributions is shown in eq 8.<sup>7</sup> The first experiment involves addition of the cyclohexyl radical to methyl acrylate (eq 8, R = H). In this reaction both steric and polar effects favor addition of the nucleophilic cyclohexyl radical to the less substituted carbon atom in the carbon-carbon double bond, but as the R group becomes sterically larger, the regioselectivity of the reaction decreases. For the sterically largest R group the favored direction of addition actually changes. The message here is that steric effects can overwhelm polar effects in establishing reaction regioselectivity, but a sterically quite demanding group (e. g., a *t*-butyl group) is necessary to overcome a strong polar effect.

Another indication of the significance of polar effects in radical addition reactions can be seen by returning to the Evans-Polanyi relation (eq 4). This relation applies to radical addition reactions in which polar factors are not important. For reactions where polar factors are important, energies of activation are lower than those calculated from eq 4. In such situations a modified equation (eq 9), one including the multiplicative terms  $F_n$  and  $F_e$ , reflecting nucleophilic and electrophilic polar effects, respectively, is more accurate.<sup>8,15</sup>

$$E_a = (C + \alpha H_r) F_n F_e \quad (9)$$

$$0 < F_n, F_e < 1$$

$E_a$  = energy of activation

$H_r$  = reaction enthalpy

$F_n$  = a nucleophilic polar factor

$F_e$  = an electrophilic polar factor

C and  $\alpha$  are constants.

#### 4. Frontier-Orbital Interactions

Because radical addition reactions have early transition states,<sup>7</sup> frontier-orbital interactions are able to provide an alternative approach for explaining reaction regioselectivity. The first step in this approach is identifying the frontier orbitals in the reaction of interest; for example, in the addition of the dimethylmalonyl radical **11** to the electron-rich double bond in the D-glucal **10** (Scheme 5), the primary interaction is between the SOMO of **11** and the HOMO of **10** (Figure 10 in Chapter 7). Identifying the frontier-orbital interactions in a reaction does not, by itself, explain reaction regioselectivity, but orbital identification is a critical first step for such understanding because the atomic-orbital coefficients that form the basis for explaining regioselectivity come from frontier orbitals.

Atomic orbital coefficients are valuable in determining the regioselectivity of a reaction with an early transition state because the rate constant for the bond-forming reaction between two atoms in such a reaction depends to a large extent on the magnitude of the coefficients in their interacting frontier orbitals.<sup>17,18</sup> In the reaction pictured in Scheme 5 the most effective bonding is between the

radical **11** and C-2 in the D-glucal **10** because the atomic orbital coefficient at C-2 for the HOMO in **10** is larger than that at C-1 (Figure 4);<sup>21</sup> consequently, regioselective addition to C-2 is favored.<sup>17,18</sup>

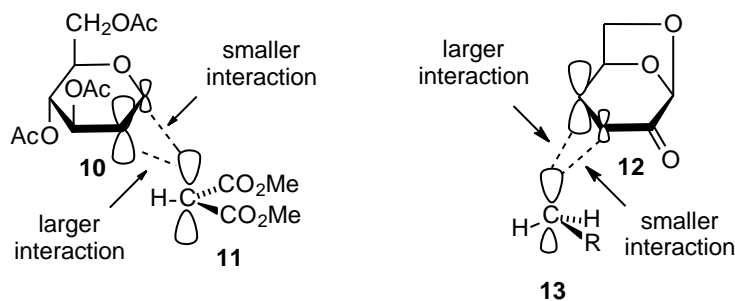
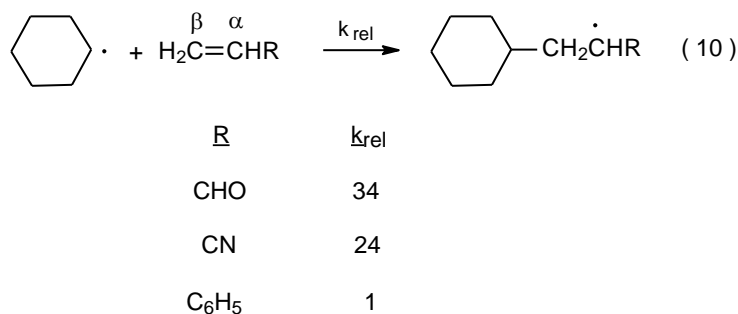


Figure 4. Frontier orbital interactions that affect reaction regioselectivity

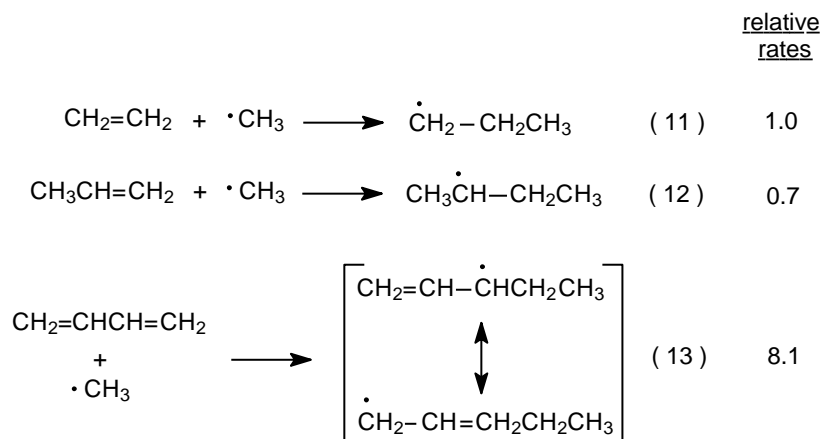
Frontier-orbital interactions also explain regioselectivity in the addition reaction shown in Scheme 6, where a nucleophilic radical (**13**) is adding to an electron-deficient double bond.<sup>20</sup> Addition of the radical **13** to C-4, rather than C-3, in the  $\alpha,\beta$ -unsaturated ketone **12** cannot be explained by steric effects, but frontier-orbital interactions do provide a basis for understanding the observed regioselectivity. The most important interaction in this case is between the SOMO of **13** and the LUMO of **12**. (A justification for this being the primary, frontier-orbital interaction is given in Section IV.B.1 of Chapter 7) For a LUMO such as that in **12** the largest atomic orbital coefficient is associated with the  $p$  orbital at C-4 (Figure 4);<sup>21</sup> consequently, regioselective addition to C-4 is favored.<sup>22</sup>



## 5. Adduct-Radical Stabilization

Adduct-radical stabilization as a possibility for explaining regioselective addition of a carbon-centered radical to a multiple bond is not highly regarded because the exothermic nature of and probable early transition state for radical addition reactions argue against significant, transi-

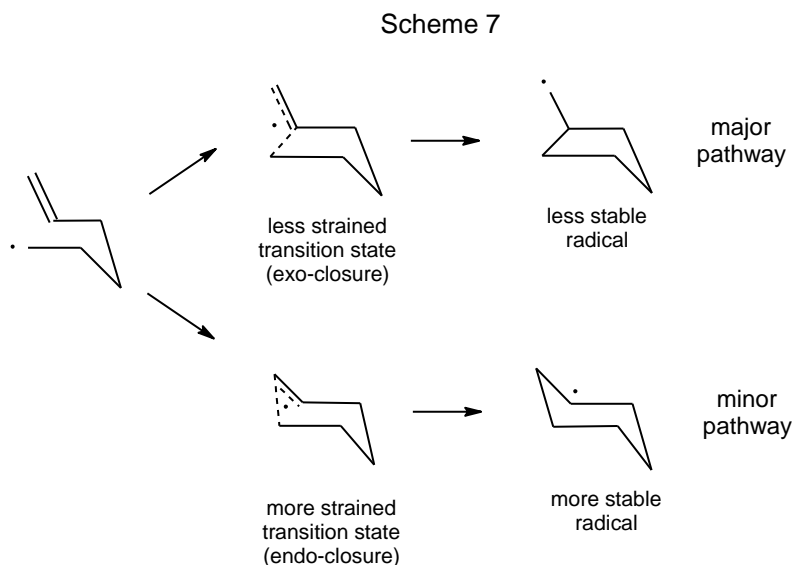
tion-state stabilization due to the developing radical. Evidence from study of model compounds that is cited in support of this point of view is that the cyclohexyl radical adds more rapidly to acrolein and acrylonitrile than to styrene (eq 10),<sup>7,23</sup> even though a phenyl group is more effective at stabilizing a radical center than is a carbonyl or cyano group.<sup>7,24</sup> This information indicates that adduct-radical stabilization is less important than polar effects at the transition state for an addition reaction; thus, polar effects are primarily responsible for the differences in reactivity of the unsaturated compounds, differences such as those shown in eq 10.<sup>7</sup> (As discussed in Section II.D.2 and seen in eq 6, steric hindrance from the  $\alpha$  substituents used in the reactions shown in eq 10 should be inconsequential.) Since reactions between electron-deficient alkenes and nucleophilic radicals are stabilized at the transition state by polar effects, these effects could mask less important, adduct-radical stabilization. A better test of the importance of adduct-radical stabilization on regioselective addition would be one in which polar effects could not be the determining factor.



The addition reactions shown in equations 11 and 12 are ones for which polar effects should be minimal.<sup>10</sup> The similarity in relative rates for the two reactions indicates that adduct-radical stabilization is inconsequential at the transition state. These reactions also underscore the difficulty in eliminating completely the influence of polar effects when comparing radical reactions. The slightly reduced rate for the reaction shown in eq 12, when compared to that in eq 11, could be due to the effect of the weakly electron-donating methyl group in propene reducing to a small extent the rate of addition of a nucleophilic radical to a slightly more electron-rich double bond. (As mentioned in Chapter 7, Sections III.C. and III.E., there is not complete agreement about the nucleophilicity of the methyl radical.)

The reaction shown in eq 13 supports the idea that the stability of the developing radical can be a factor in reducing transition-state energy.<sup>10</sup> The greater rate for this reaction, when compared to those shown in equations 11 and 12, can be explained by resonance stabilization in the developing radical contributing significantly to transition-state stabilization. The limited data in equations 11-13 are consistent with the idea that adduct-radical stability is only a factor in radical addi-

tion reactions when such stabilization is considerable. Once again, however, polar effects cloud this interpretation. 1,3-Butadiene can be viewed as a molecule in which each double bond has an ethenyl substituent attached. Such a substituent should be electron-withdrawing or, at least, less electron-donating than a methyl group; consequently, the double bonds in 1,3-butadiene should be more reactive toward the methyl radical than is the double bond in propene. This difference could explain, at least in part, the difference in relative rates for the reactions shown in eq 12 and eq 13.



### III. Intramolecular Addition (Cyclization) Reactions

#### A. Five- and Six-Membered Rings

##### 1. Factors Determining Ring Size

When a radical center and a double bond are situated so that formation of either a five- or a six-membered ring is possible, the smaller ring generally is produced.<sup>25,26</sup> The reason for forming the smaller ring is that the strain engendered in reaching the transition state for a six-membered ring is greater than that required for reaching a five-membered one (Scheme 7).<sup>27-29</sup> In the reaction shown in Scheme 2, for example, even though radical cyclization producing a six-membered ring is possible and generates a more stable intermediate radical than five-membered ring formation, the only pathway followed is the one leading to the smaller ring.

For formation of a five-membered ring the calculated angle of approach of the atom bearing the radical center to the multiple bond is  $106^\circ$ , an angle similar to the  $104^\circ$  calculated for the transition state in the strain-free addition of the methyl radical to propene (Figure 5).<sup>27</sup> For six-membered ring formation the transition state has a calculated angle of approach of  $94^\circ$  (Figure 5). This considerable angle deformation away from a strain-free situation is a major factor in raising the energy of the transition state leading to a six-membered ring.

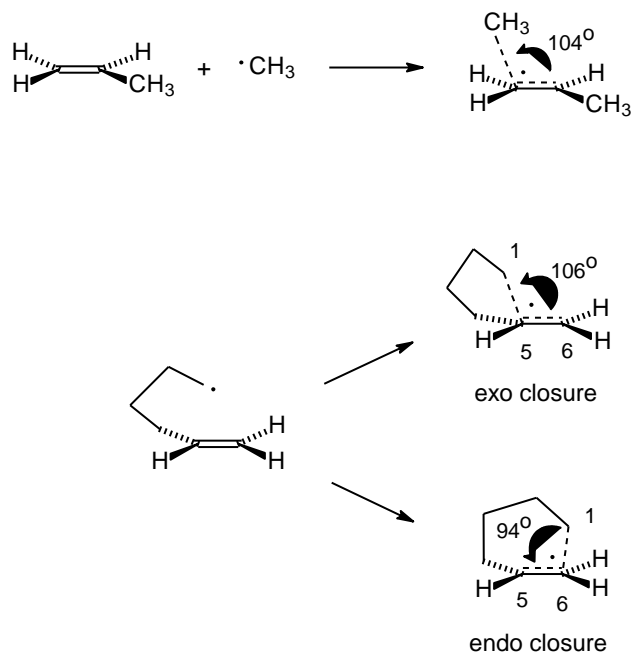
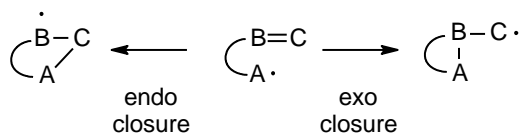


Figure 5. Transition state structures for addition of the methyl radical to propene and cyclization of the 5-hexenyl radical

In addition to describing cyclization reactions by the size of the ring produced, the terms *exo* and *endo* indicate the way in which the ring is formed. The meaning of these terms is illustrated in the reactions shown in Scheme 8. When the *exo/endo* terminology is used to describe ring formation from reaction of the 5-hexenyl radical, the five-membered ring is seen as arising from *exo* closure and the six-membered one from *endo* closure (Scheme 7).

Scheme 8



## 2. Transition-State Structure

Transition-state structures for radical addition and radical cyclization are given in Figure 6 in a general form. For cyclization reactions not only ring size but also ring conformation affect transition-state energy; thus, both chair-like<sup>25,27</sup> and boat-like<sup>27,30</sup> structures are possible during five-membered ring formation. For the unsubstituted 5-hexenyl radical the chair-like transition state leading to a five-membered ring is calculated to be lower in energy, but only slightly so, than the boat-like transition state (Scheme 9).<sup>27</sup> (The “flagpole” interactions that contribute to making the boat conformation of cyclohexane much less stable than the chair conformation are less severe

in the boat-like transition state for radical cyclization.) Both transition states (boat-like and chair-like) leading to a five-membered ring (Scheme 9) are calculated to be lower in energy than any transition states leading to a six-membered ring. These calculations match well the experimental observation that cyclization of the 5-hexenyl radical gives a five-membered ring in a highly regioselective fashion (eq 14, R = H).<sup>25,31</sup>

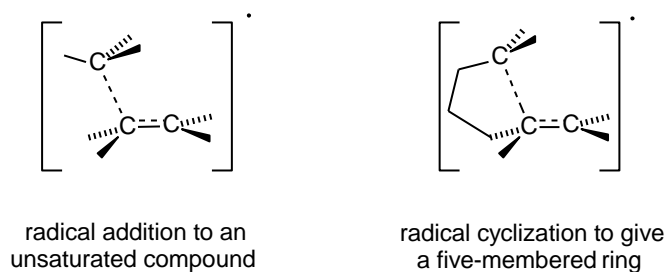
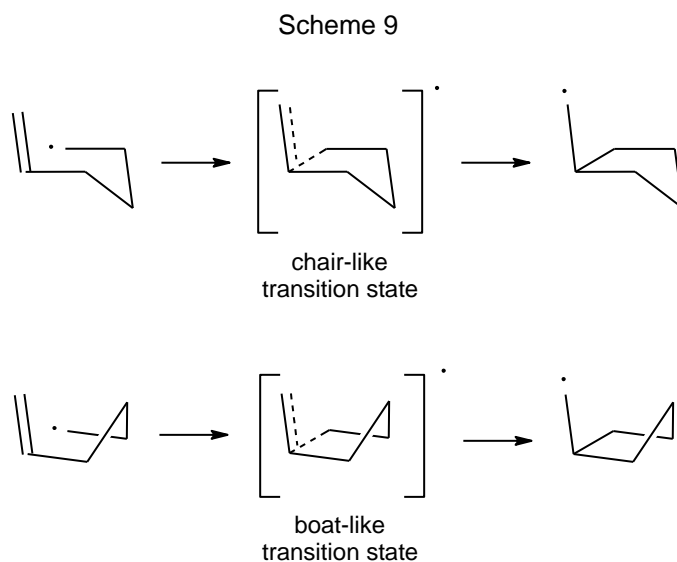


Figure 6. Favored transition states for radical addition and cyclization



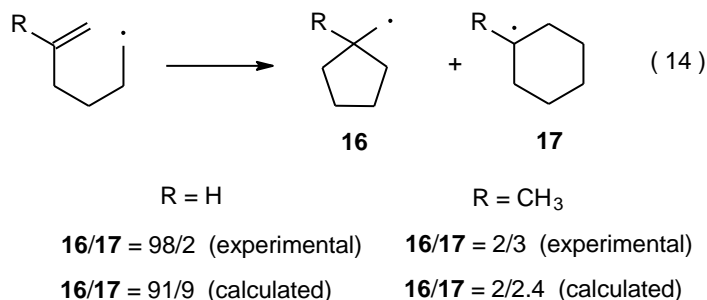
### 3. Altering Normal Regioselectivity

#### a. Steric Interactions and Adduct-Radical Stability

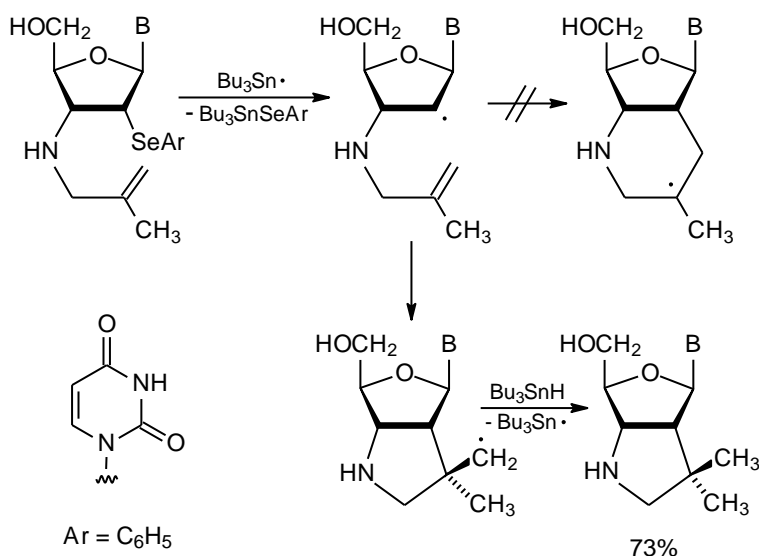
Although ring size is the primary factor affecting regioselectivity in cyclization reactions, other factors sometimes have a modifying effect; for example, in the reaction of the 5-methyl-5-hexenyl radical the presence of the methyl group increases the amount of six-membered-ring formation (eq 14, R = CH<sub>3</sub>).<sup>25,27</sup> In this reaction steric effects and adduct-radical stability both favor a six-membered ring. The transition state in this reaction presumably is reached late enough



that either steric effects or adduct-radical stability or both have a substantial impact on regioselectivity. Predicting when the transition state in this type of reaction will be early enough to cause highly regioselective, five-membered-ring formation is not easy. In the reaction shown in Scheme 10, where steric interactions and adduct-radical stability appear to favor six-membered-ring formation at least as much as they do in the reaction shown in eq 14 ( $R=CH_3$ ), only a product with a five-membered ring forms.<sup>32</sup>



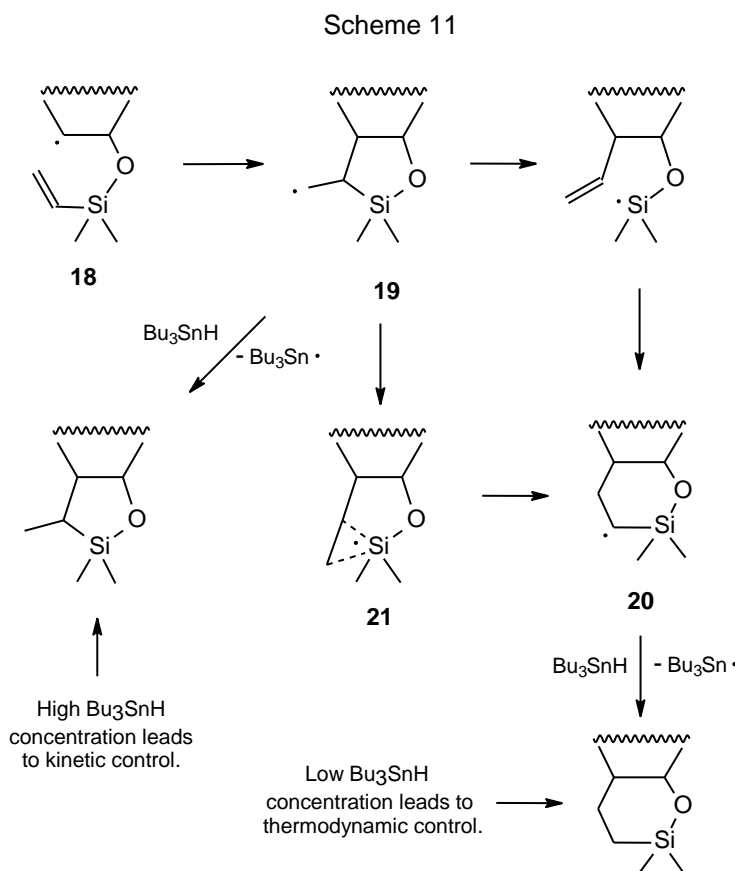
Scheme 10



#### b. Thermodynamic Control

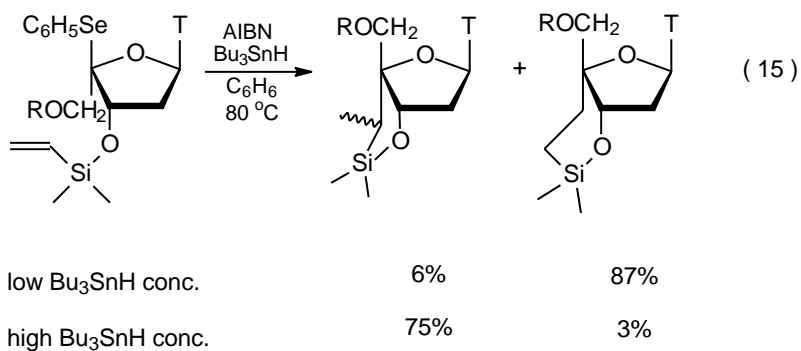
Although kinetically controlled reaction is the norm in radical cyclization, thermodynamic control is observed in the reaction shown in eq 15 where the substrate is an unsaturated silyl ether and the hydrogen-atom donor ( $Bu_3SnH$ ) is maintained at a low level.<sup>33</sup> When this reaction is conducted with a high  $Bu_3SnH$  concentration, kinetically controlled, five-membered ring formation is the major reaction pathway. An explanation for this dependence on hydrogen-atom-donor concentration begins with the radical **18** cyclizing to form **19**, a radical with a new

five-membered ring (Scheme 11). If the concentration of  $\text{Bu}_3\text{SnH}$  is high, hydrogen-atom abstraction rapidly completes the reaction, but if the donor concentration is low, rearrangement to the more stable radical **20**, via the transition state **21**, takes place before hydrogen-atom abstraction can occur.<sup>34</sup> Hydrogen-atom abstraction by **20** then gives the thermodynamically favored product. An alternative mechanism for this reaction, also shown in Scheme 11, is that ring opening of **19** produces a silicon-centered radical that undergoes ring closure to give the intermediate radical **20**.<sup>35</sup>

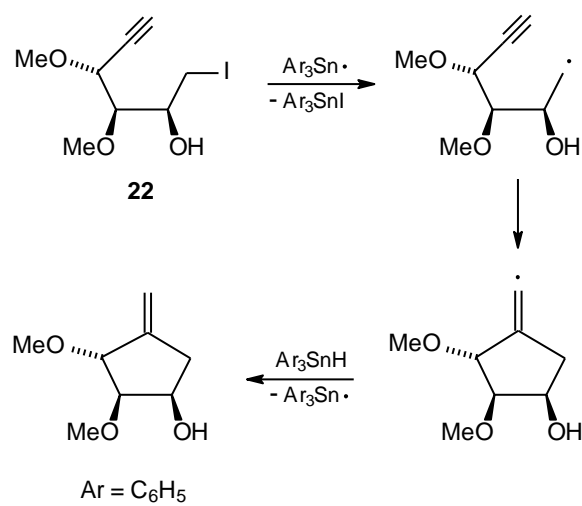


### c. Reversal Due to Stereochemistry

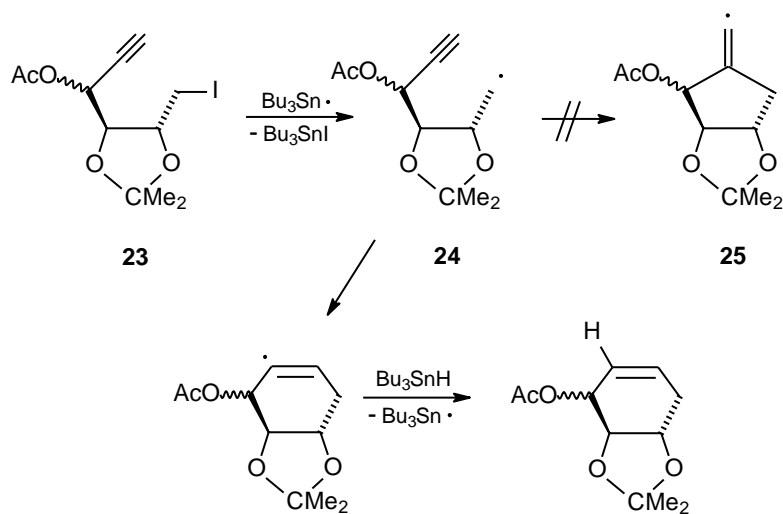
One situation where six-membered ring formation is favored consistently over reaction producing a five-membered ring is when cyclization would produce a pair of *trans*-fused, five-membered rings. Reactions of iodides **22** and **23** illustrate the effect that stereochemistry can have on radical cyclization. The acyclic iodide **22** undergoes an expected cyclization to give a five-membered ring (Scheme 12),<sup>36</sup> but reaction of the iodide **23** forms a six-membered ring (Scheme 13).<sup>37</sup> Since a *trans* fusion between two five-membered rings would produce the highly strained radical **25**, the stereochemistry of the radical **24** dictates the regioselectivity of the cyclization reaction. Six-membered-ring formation also occurs in the reaction shown in Scheme 14<sup>38</sup>, again, because the other option would force the formation of *trans*-fused, five-membered rings.



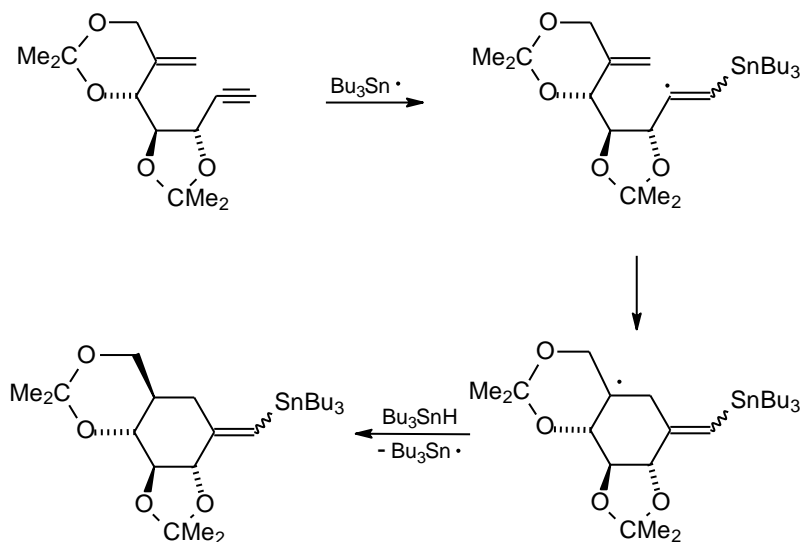
Scheme 12



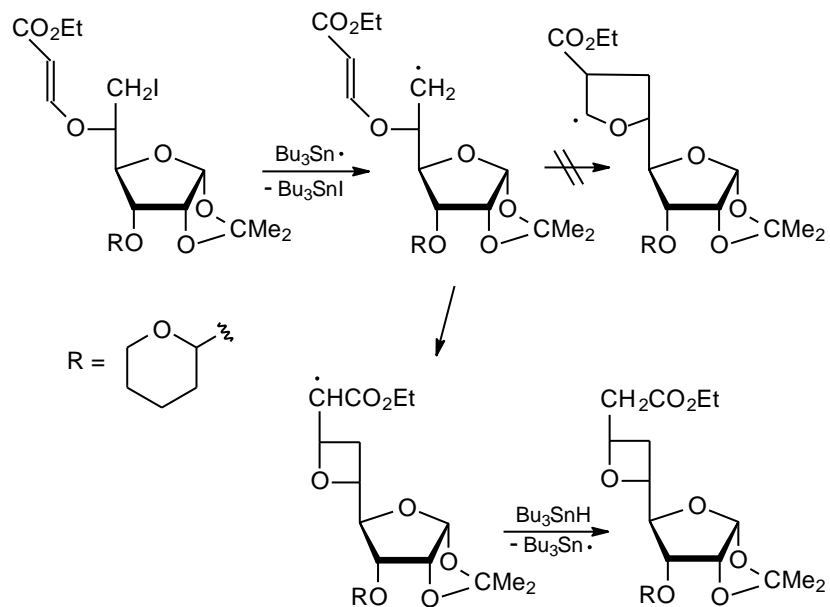
Scheme 13



Scheme 14



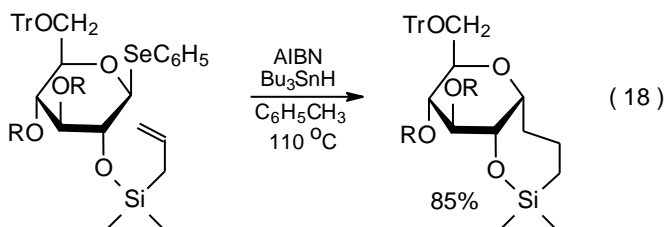
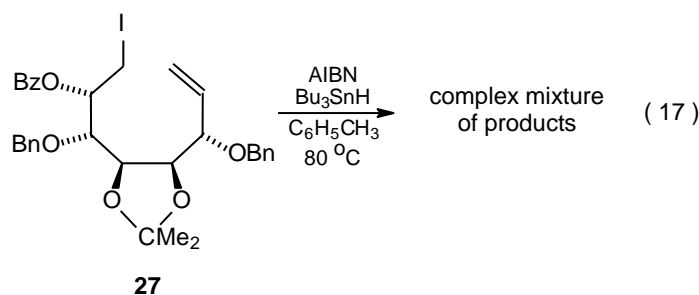
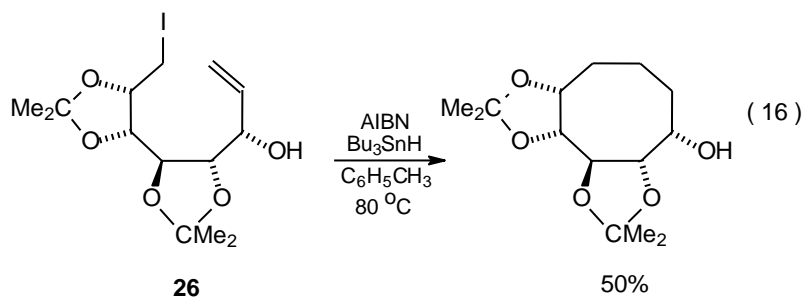
Scheme 15



## B. Three- and Four-Membered Rings

Radical cyclization to form a three-membered ring is a rare event because cyclization does not compete well with ring opening of the cyclized radical.<sup>39</sup> Although competitive ring opening remains a possibility during four-membered-ring formation, the reaction pictured in Scheme 15 shows that it is possible to obtain a cyclic product with a four-membered ring.<sup>40</sup> Even though for-

mation of a larger ring would produce a less strained radical (Scheme 15), the transition state in this reaction must be reached before ring strain becomes a significant factor. This result is not a general one. A reaction discussed later in this Chapter (Section V.A.2.b) describes forming a five-membered ring by radical cyclization even though a four-membered one is possible.

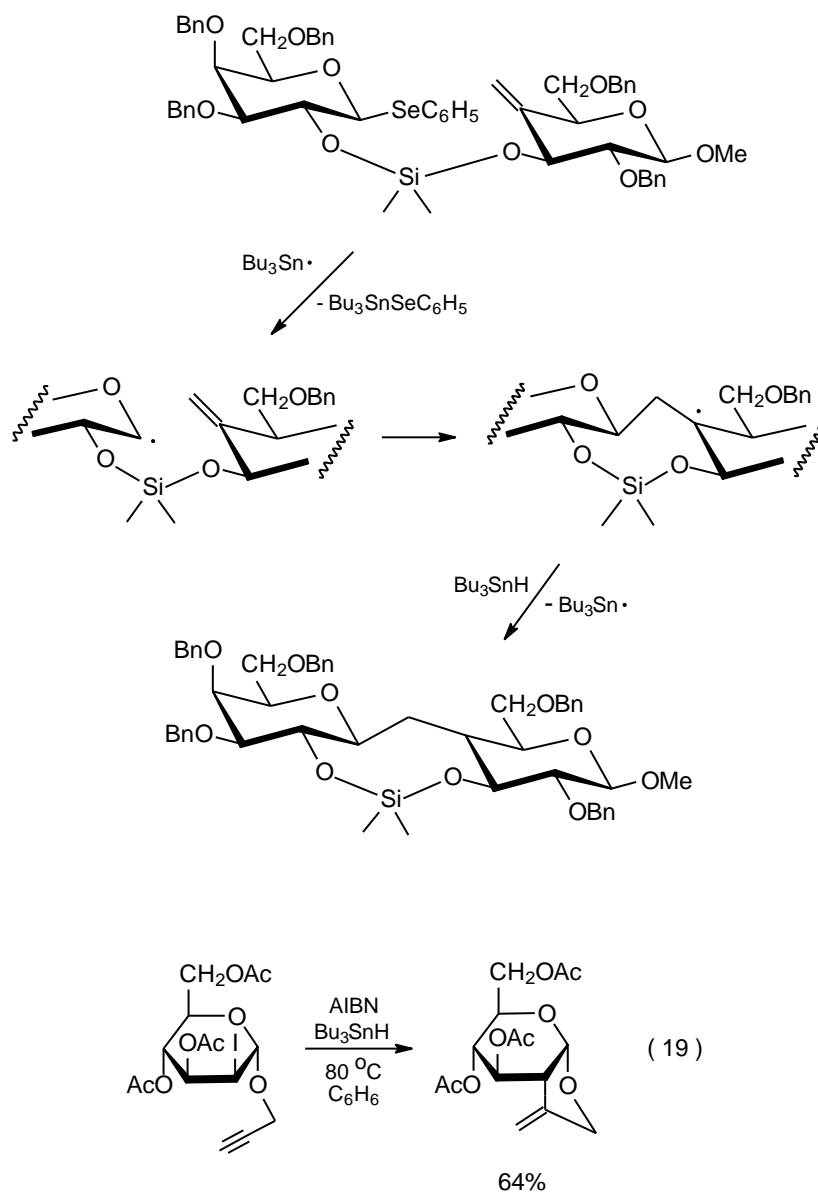


### C. Larger Rings

Radical cyclization can be effective in producing rings with more than six members. In forming a larger ring (seven or more members) not only must the radical center be able to react rapidly with the multiple bond but the reacting radical also needs to be able to adopt a conformation that brings the reactive centers within bonding distance often enough for detectable reaction to take place. The ability of the iodide **26** to form an eight-membered ring in 50% yield (eq 16) while the iodide **27** gives a complex mixture of products (eq 17) seems likely to be a matter of the rigidity and ring fusion of the radical derived from **26** causing it frequently to adopt a suitable conformation for ring formation.<sup>41</sup>

Normal formation of the smaller of the two rings when the choice is between a five-membered or six-membered ring no longer is adhered to where larger rings are involved. Examples of reactions of carbohydrates that regioselectively produce the larger of the two possible rings are found in the reactions shown in eq 16 and eq 18. Larger ring formation frequently is associated with reaction between parts of a molecule, often two monosaccharide units,<sup>42,43</sup> linked together by a silicon–oxygen tether.<sup>42–45</sup> An example of such a reaction is shown in Scheme 16, where cyclization involves formation of an eight-membered ring.<sup>45</sup>

Scheme 16



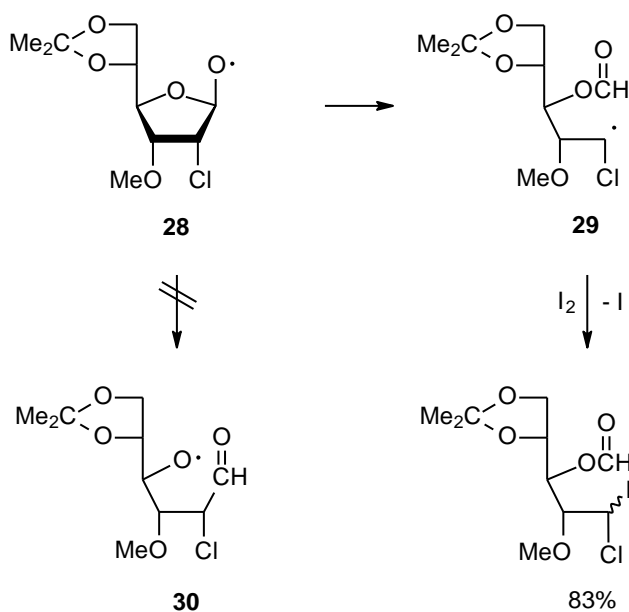
## D. A Terminology for Describing Cyclization Reactions

A terminology for categorizing cyclization reactions expands on endo-exo designations.<sup>26</sup> In this description each term consists of three parts: (a) a number identifying the size of the ring system being formed, (b) an “exo” or “endo” designation that tells whether one (exo) or both (endo) of the atoms in the multiple bond become part of the ring system, and (c) a tetra ( $sp^3$ ), trig ( $sp^2$ ), or dig ( $sp$ ) term to describe the hybridization of the atom bonding to the radical center. The reaction shown in Scheme 2, for example, is 5-exo-trig,<sup>4</sup> while that in eq 19 is 5-exo-dig.<sup>46</sup> Schemes 15<sup>40</sup> and 16<sup>45</sup> describe 4-exo-trig and 8-endo-trig cyclizations, respectively.

## IV. $\beta$ -Fragmentation Reactions

$\beta$ -Fragmentation is an elementary reaction that exhibits regioselectivity in ring opening and in radical expulsion. Regioselective ring opening occurs when a radical centered on an atom attached to a ring preferentially fragments one of the ring bonds. Regioselective radical expulsion takes place when one of the bonds to an atom  $\beta$ -related to a radical center preferentially cleaves to generate two fragments, one a new radical and the other an unsaturated compound.

Scheme 17



### A. Ring-Opening Reactions

#### 1. Oxygen-Centered Radicals

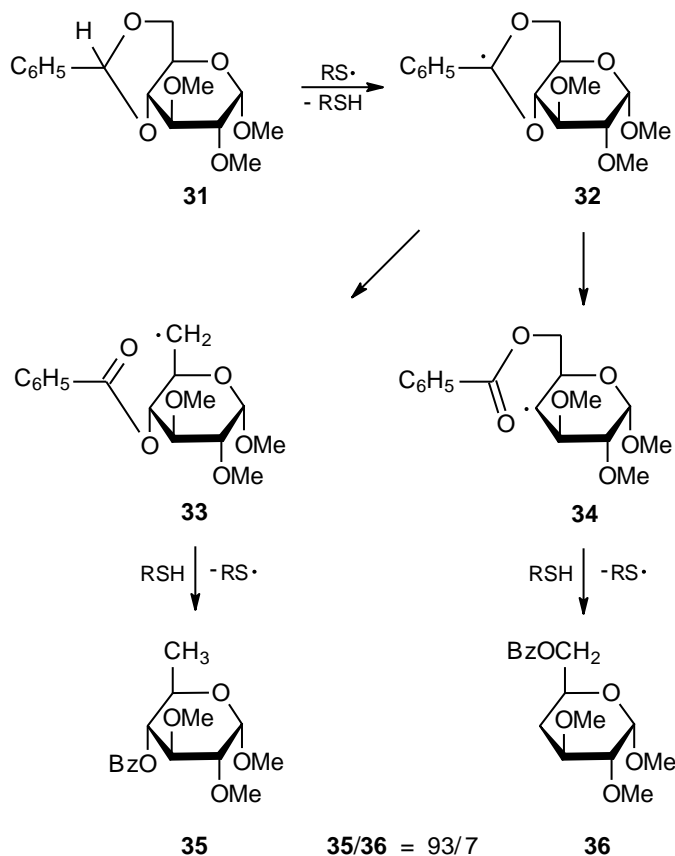
Oxygen-centered radicals derived from carbohydrates usually have the radical-bearing oxygen atom bonded to a ring carbon atom; thus,  $\beta$ -fragmentation is likely to result in opening the





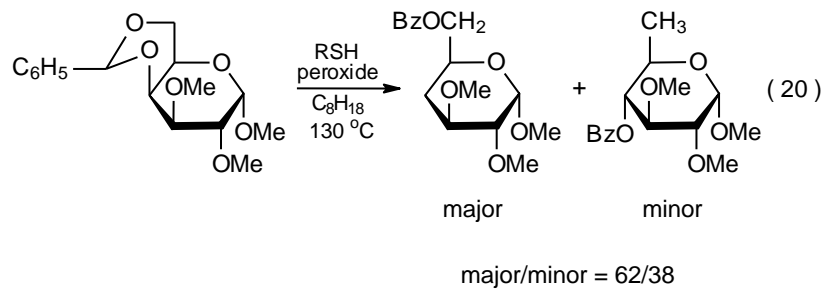
cautionary note is sounded in ref 48a about assuming that a secondary radical is necessarily more stable than an isomeric primary radical.)

Scheme 19

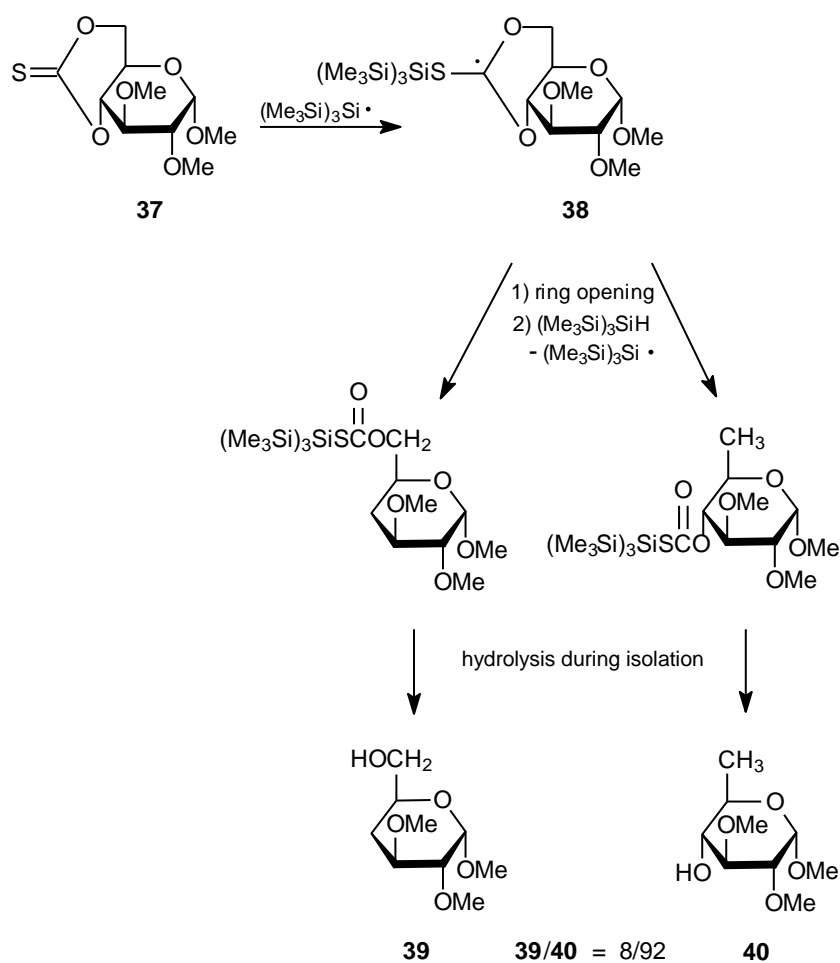


A cis-fused ring system in a benzylidene acetal is more flexible than one that is trans-fused; consequently, less angle strain develops at the transition state for ring opening of a radical derived from a cis-fused benzylidene acetal. This reduction in strain is enough to make thermodynamic stability a more important factor in ring opening; thus, the major product in the reaction shown in eq 20 arises from formation of a secondary, rather than a primary, radical.<sup>48,49</sup>

Reaction of a cyclic thionocarbonate represents a different approach to generating a carbon-centered radical that has ring-opening options similar to those available to a radical produced by hydrogen-atom abstraction from a benzylidene acetal. Addition of the tris(trimethylsilyl)silyl radical to the cyclic thionocarbonate **37** produces the radical **38**, which undergoes ring opening with a contra-thermodynamic regioselectivity (Scheme 20) similar to that observed from the radical **32**.<sup>49</sup>



Scheme 20

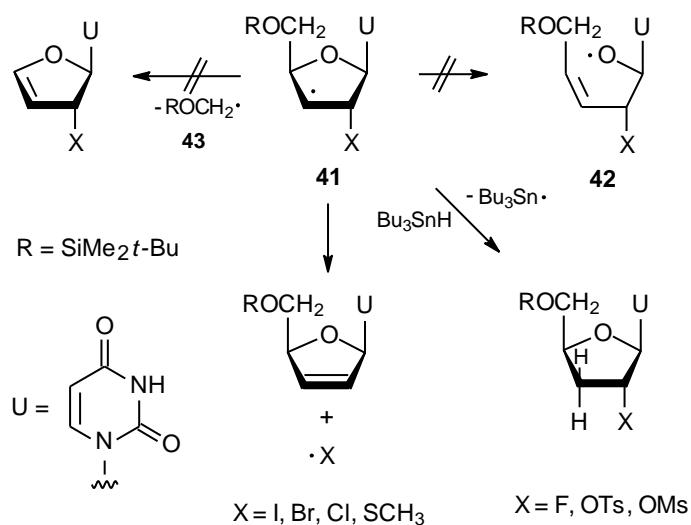


## B. Radical Expulsion

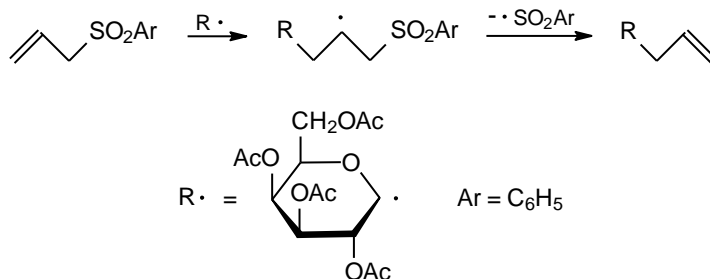
In the reaction pictured in Scheme 21 ring-opening of the radical **41** to produce the highly energetic, oxygen-centered radical **42** cannot compete with radical expulsion.<sup>50</sup> Even fragmentation that keeps the ring intact and gives the carbon-centered radical **43** is unable to match reactions

that cause C–I, C–Br, C–Cl, and C–SR bonds to break and to produce I·, Br·, Cl·, and RS·, respectively. When loss of a radical from **41** would require breaking a stronger bond and producing a less stable radical (i.e., X = F, OTs, or OMs),  $\beta$ -fragmentation is too slow to compete with hydrogen-atom abstraction.

Scheme 21

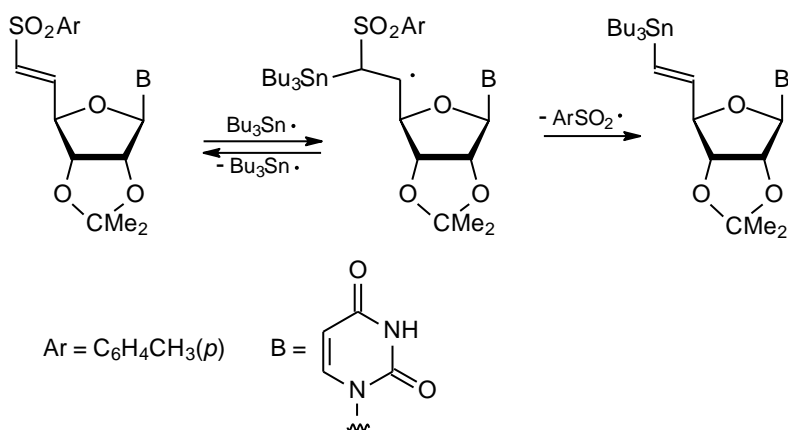


Scheme 22



Some reactions combine regioselective addition with regioselective  $\beta$ -fragmentation. This combination can cause the double bond in a molecule to relocate to a new position, as it does in the reaction shown in Scheme 22,<sup>51</sup> or it can lead to the multiple bond remaining between the original two carbon atoms, as happens in the reaction shown in Scheme 23.<sup>52</sup>

Scheme 23



## V. Site-Selective Reactions

The regioselectivity discussed thus far has involved reactions in which a compound with a single functional group generates products that include two or more structural isomers. The term regioselectivity also can be used to describe the preference for reaction of a particular atom or group in a molecule that contains at least one other atom or group of the same type. Regioselectivity of this sort is sometimes referred to as site selectivity. An example of a site-selective reaction is shown in Scheme 4, where H-5 is abstracted even though there are other hydrogen atoms present in the molecule that potentially could have been abstracted.<sup>6</sup>

Although there are a large number of radical reactions in carbohydrate chemistry that involve group and atom replacement, only for hydrogen-atom abstraction is regioselectivity a common consideration. Nearly all carbohydrates have the hydrogen atoms necessary to make site-selective abstraction conceivable, but few carbohydrates have the two or more other groups or atoms required to make selective reaction of one of these groups (or atoms) a possibility. Hydrogen-atom abstraction, therefore, provides the pool from which most site-selective reactions are drawn.

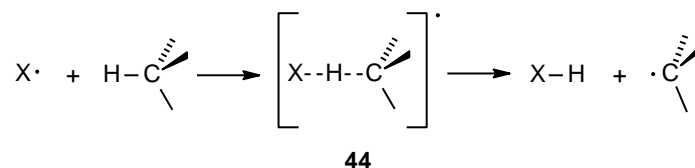
### A. Atom Replacement Reactions

#### 1. Intermolecular Hydrogen-Atom Abstraction

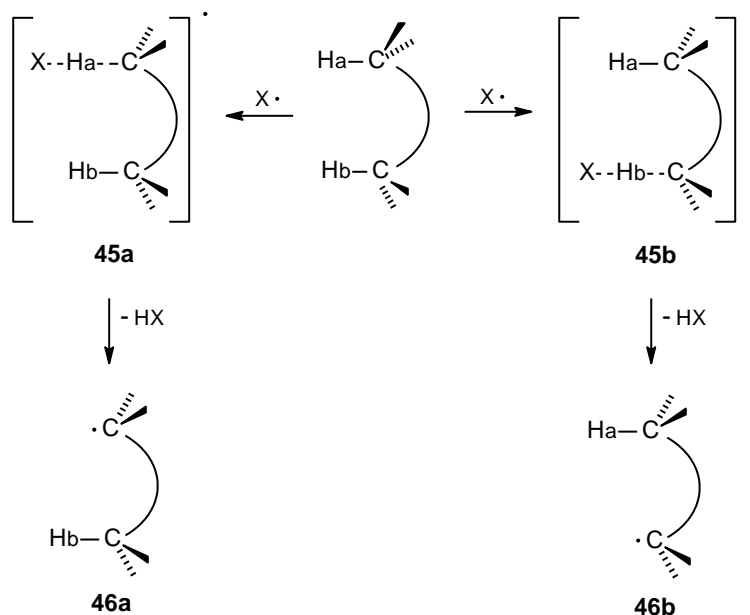
##### a. Transition-State Structure

A proposed structure (**44**) for the transition state in a hydrogen-atom abstraction reaction is shown in Scheme 24.<sup>53</sup> Based on this structure, one can conclude that the abstracting radical usually will have a largely unobstructed approach to the hydrogen-atom donor. Although some molecules have hydrogen atoms buried in the interior of their structure where such atoms are difficult to reach, access to most hydrogen atoms, even in complicated molecules, is largely unhindered.

Scheme 24



Scheme 25



To assist in analyzing regioselectivity in hydrogen-atom abstraction reactions the mechanism shown in Scheme 24 is recast in Scheme 25 with a substrate that has two, nonequivalent, abstractable hydrogen atoms ( $\text{H}_a$  and  $\text{H}_b$ ). Regioselectivity depends on the difference in energies required to reach the transition states **45a** and **45b**. If these transition states occur late in the two reactions and the difference in stabilities of the developing radicals **46a** and **46b** is considerable, hydrogen-atom abstraction will be highly regioselective (Figure 7). If the transition states are reached early, they will be similar in energy and the regioselectivity of the reaction will be modest. The position of the transition state on the reaction pathway depends upon a variety of factors that include the reactivity of the abstracting radical, the stability of the developing radical, relief of strain in the substrate, and polarity matching. All of these must be taken into account in analyzing regioselectivity in a hydrogen-atom abstraction reaction.

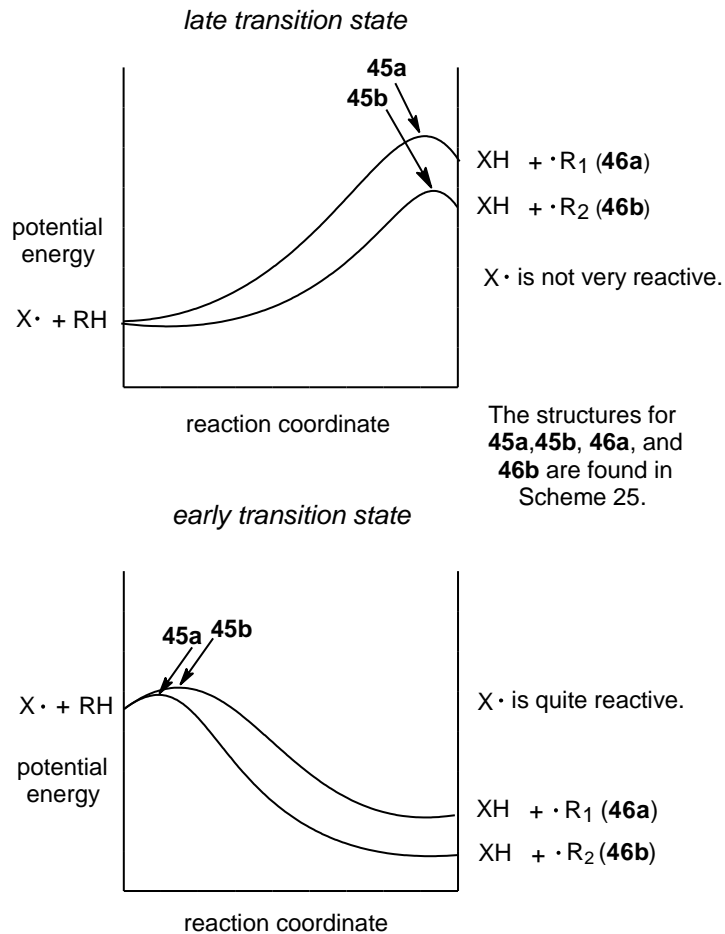
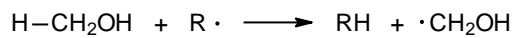


Figure 7. Energy diagrams for hydrogen-abstraction reactions



R·	$\Delta\text{H}$ (kcal/mole) <sup>a</sup>
HO·	-26 [-109]
CH <sub>3</sub> O·	-9 [-37]
Br·	+6 [25]

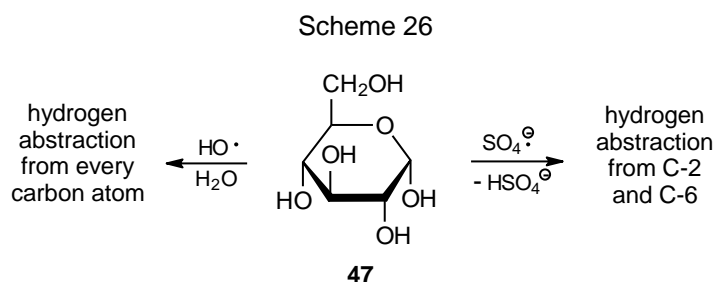
<sup>a</sup>Numbers in brackets are in  $\text{kJ mol}^{-1}$

Table 1. Enthalpies of reaction for hydrogen abstraction from methanol

## b. Reactivity of the Abstracting Radical and Stability of the Developing Radical

## (1.) Abstraction by a Hydroxyl Radical

Abstraction of a hydrogen atom by a hydroxyl radical from a C–H bond in a carbohydrate is an exothermic reaction. [The reaction enthalpy for hydrogen-atom abstraction by the hydroxyl radical from methanol gives an approximate idea of the exothermicity of such a reaction (Table 1)<sup>54</sup>.] According to Hammond's postulate,<sup>55</sup> this abstraction should have an early transition state. Since most hydrogen atoms in carbohydrates have similar immediate environments (i.e., they are attached to carbon atoms that are bonded to at least one oxygen atom), similar reactivity leading to low regioselectivity should be expected. In line with this expectation is the observation that the ESR spectrum of the reaction mixture produced by treatment of  $\alpha$ -D-glucopyranose (**47**) with hydroxyl radicals contains signals from radicals produced by hydrogen-atom abstraction from each of the six carbon atoms (Scheme 26).<sup>56</sup>



## (2.) Abstraction by a Sulfate Radical Anion

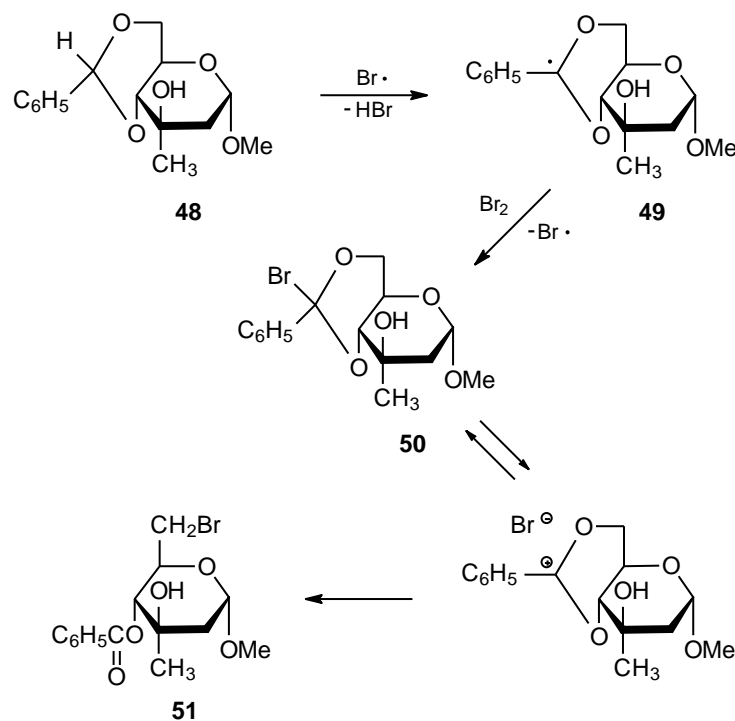
As the reactivity of an abstracting radical decreases, the transition state for a reaction moves to a position later on the reaction pathway. When this occurs, the stability of the developing radical becomes a more important factor in transition-state stabilization. For the sulfate radical anion, which is less reactive than the hydroxyl radical, the transition state for hydrogen-atom abstraction occurs late enough in the reaction that differences in stability of the developing radicals become significant and only hydrogen atoms attached to C-2 and C-6 are abstracted from  $\alpha$ -D-glucopyranose (**47**) (Scheme 26).<sup>57</sup> The reason for the regioselective abstraction of hydrogen atoms attached to C-2 and C-6 in **47** is explained in Section III.B.2 of Chapter 7 in Volume II. [Explanation is delayed until this later chapter because Chapter 7 (Volume II) contains a broad discussion of hydrogen-atom abstraction from unprotected sugars.]

## (3.) Abstraction by a Bromine Atom

When a radical far less reactive than the hydroxyl radical or the sulfate radical anion abstracts a hydrogen atom, the transition state will occur much later in the reaction. In this situation the stability of the developing radical will be far more important in determining reaction regioselectivity. Free-radical reaction of the benzylidene acetal **48** (Scheme 27) with a bromine atom

provides an example of such a situation.<sup>58</sup> Hydrogen-atom abstraction from the benzylidene group gives the resonance-stabilized radical **49**, which then reacts with molecular bromine to produce the bromide **50**. The stability of the radical **49**, when compared to any other radical produced by hydrogen-atom abstraction from **48**, is the primary factor in determining which hydrogen atom in **48** will be abstracted and, ultimately, where a bromine atom will be introduced into the product (Scheme 27). (The bromide **50**, which is not stable under the reaction conditions, undergoes ionization and subsequent nucleophilic displacement that causes ring opening to produce the bromodeoxy sugar **51** as the final product.)

Scheme 27

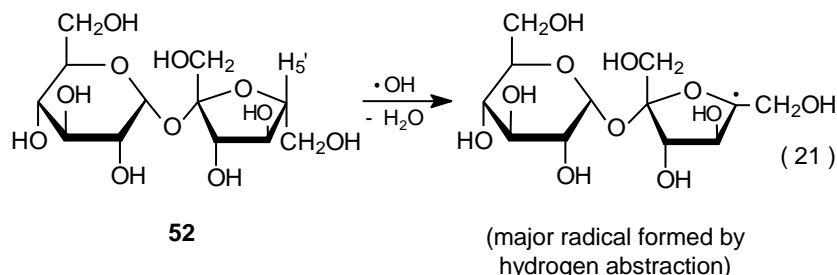


#### (4.) Transition-State Location Using the Evans-Polanyi Relation

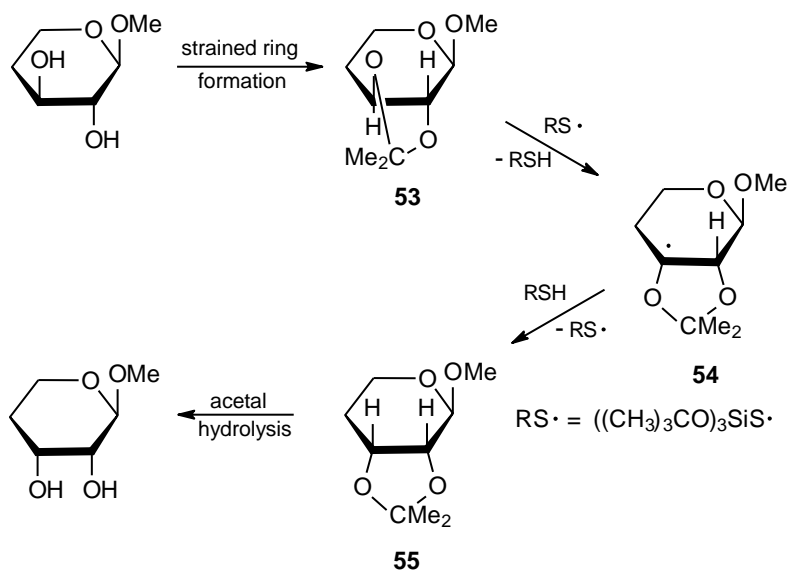
As mentioned earlier in this chapter (Section II.D.1.), for many reactions the energy of activation and the reaction enthalpy are related by the Evans-Polanyi relation (eq 4). The value of the constant  $\alpha$  in eq 4 provides an indication of the extent to which the enthalpy change during a reaction is reflected in its energy of activation. For reaction with a late transition state the value of  $\alpha$  should be close to unity. In line with this expectation the  $\alpha$  value for free-radical hydrogen-atom abstraction by a bromine atom from simple organic compounds is 0.86,<sup>59</sup> a number consistent with the proposed, late transition state in this type of reaction (Figure 7). (By way of comparison, the  $\alpha$



value noted Section II.D.1 for radical addition to a C–C double bond by a carbon-centered radical is 0.25, a number characteristic of a reaction with an early transition state.<sup>8)</sup>



Scheme 28



### c. Reduction in Substrate Strain

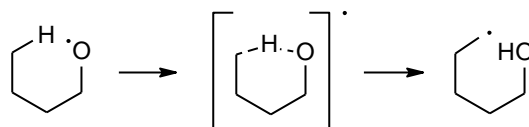
Torsional strain refers to the rise in total energy of a system that occurs when the bonds attached to groups on any two neighboring atoms move closer together as a result of rotation about the bond connecting these atoms.<sup>60</sup> This rise in energy causes staggered conformations to be preferred over eclipsed ones in order to maximize separation between bonds to substituent atoms or groups. In comparing two otherwise similar, hydrogen-abstraction reactions the favored reaction will be the one that most effectively reduces torsional strain at the transition state.

Since the hydroxyl radical exhibits little, if any, regioselectivity in hydrogen-atom abstraction from  $\alpha$ -D-glucopyranose (**47**, Scheme 26), it is initially surprising that this radical selectively abstract H-5' from sucrose (**52**, eq 21).<sup>57,61</sup> Preferential abstraction from the furanoid

ring in **52** can be explained in part by a reduction in torsional strain. Torsional strain is greater in five-member rings than it is in six-membered ones because substituent groups attached to the carbon atoms in five-membered rings are partially or completely eclipsed, but in six-membered rings these groups have a staggered arrangement.<sup>59</sup> Reduction in torsional strain thus favors hydrogen-atom abstraction from the furanoid ring in sucrose (**52**). The small dihedral angle between H-5' and the *p*-type orbital on the oxygen atom in the furanoid ring allows radical stabilization to develop early during abstraction of this hydrogen atom; in addition, because the CH<sub>2</sub>OH group is sterically larger than other substituents attached to the furanoid ring, abstraction of H-5' is more effective than abstraction of other hydrogen atoms in relieving steric strain.<sup>57</sup>

Relief of ring strain also can contribute to regioselective hydrogen-atom abstraction. In the reaction shown in Scheme 28 site-selective abstraction of H-3 by the electrophilic radical RS· allows ring strain due to the trans fusion of the two rings in the acetal **53** to be relieved.<sup>62</sup> Hydrogen-atom abstraction from RSH by the intermediate radical **54** produces the less strained acetal **55**.

Scheme 29



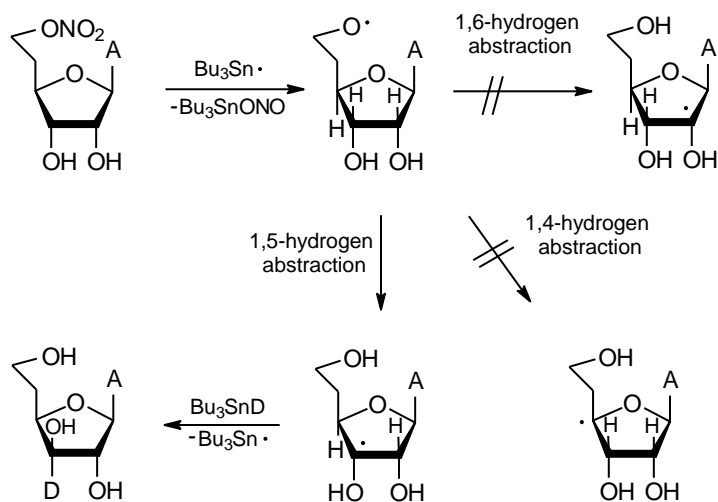
## 2. Intramolecular Hydrogen Atom Abstraction

### a. Oxygen-Centered Radicals

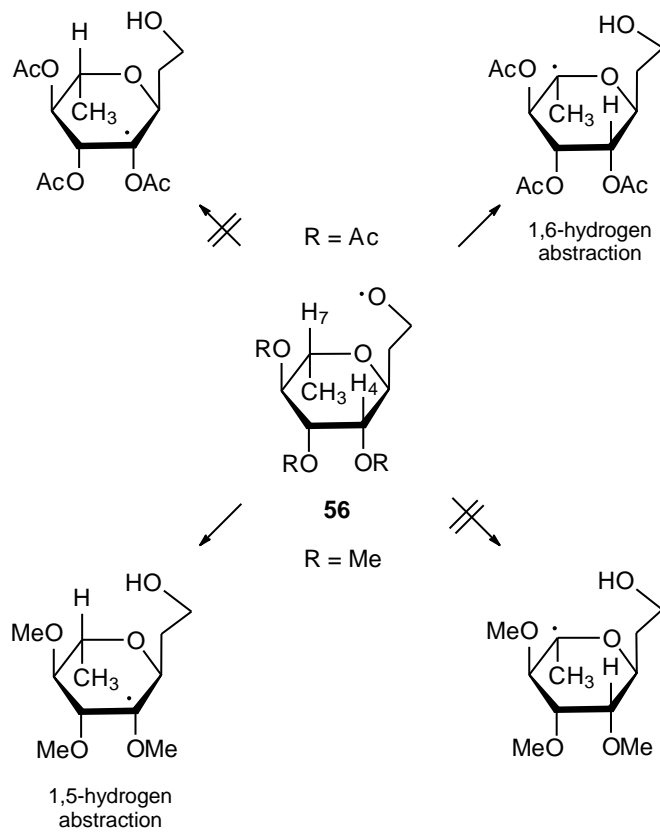
#### (1.) The Effect of Ring Size on Radical Translocation

Where carbohydrates are concerned, intramolecular hydrogen-atom abstraction often involves reaction of a radical centered on an oxygen atom. Since internal hydrogen-atom abstraction passes through a cyclic transition state, the ring size that minimizes transition-state energy determines which hydrogen atom will be abstracted. Energetically favored transition states, such as that involved in 1,5-hydrogen-atom abstraction (Scheme 29), contain six-membered rings and lead to 1,5-radical translocation. In the reaction shown in Scheme 30, for example, only 1,5-hydrogen-atom transfer takes place even though 1,4- and 1,6-transfers are possible.<sup>63</sup> For the transition state in a hydrogen-atom abstraction reaction that involves a three- or four-membered ring, the atoms participating in the abstraction process are unable to attain the approximate colinearity that is preferred energetically for hydrogen-atom abstraction (Scheme 29).<sup>64</sup> Compounds with larger rings also have higher transition state energies due to entropy requirements associated with the reduced probability for attaining the proper conformation for reaction; in addition, in larger rings enthalpy increases at the transition state can be caused by increased, nonbonded interactions.<sup>65</sup>

Scheme 30



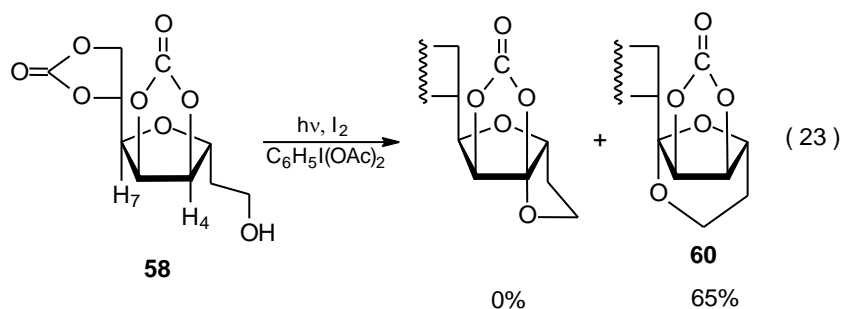
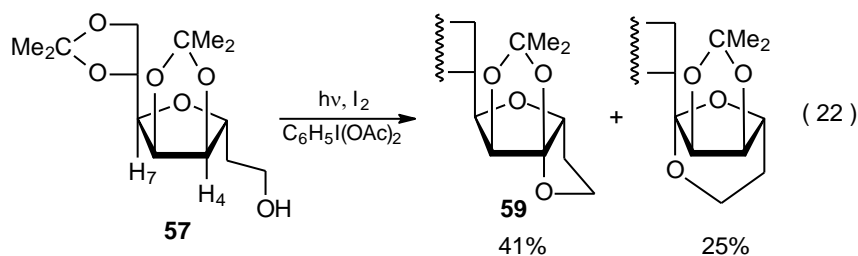
Scheme 31



## (2.) Radical Philicity

Radical philicity can play a significant role in site-selective reactions; thus, the oxygen-centered, electrophilic radical **56** (Scheme 31, R = Ac) abstracts the electron-rich H-7 via a transition state with a seven-membered ring rather than the less electron-rich H-4 by the usually favored six-membered-ring transition state.<sup>66</sup> When electron densities on H-4 and H-7 are made more equal by replacing electron-withdrawing acetyl groups with methyl groups (Scheme 31, R = Me), the major reaction pathway shifts to one involving a six-membered-ring transition state.

Radical philicity also determines whether H-4 or H-7 will be abstracted in the reactions of compounds **57** (eq 22) and **58** (eq 23).<sup>67</sup> Abstraction of H-4 by the electrophilic radical centered on O-1 is part of the process leading to regioselective formation of a product (**59**) with a new five-membered ring (eq 22). When the hydroxyl protection at C-4 becomes more electron-withdrawing, as is the case in compound **58**, the less electron-rich H-4 is not abstracted at all; regio-specific abstraction of H-7 leads to **60**, the only product formed (eq 23).



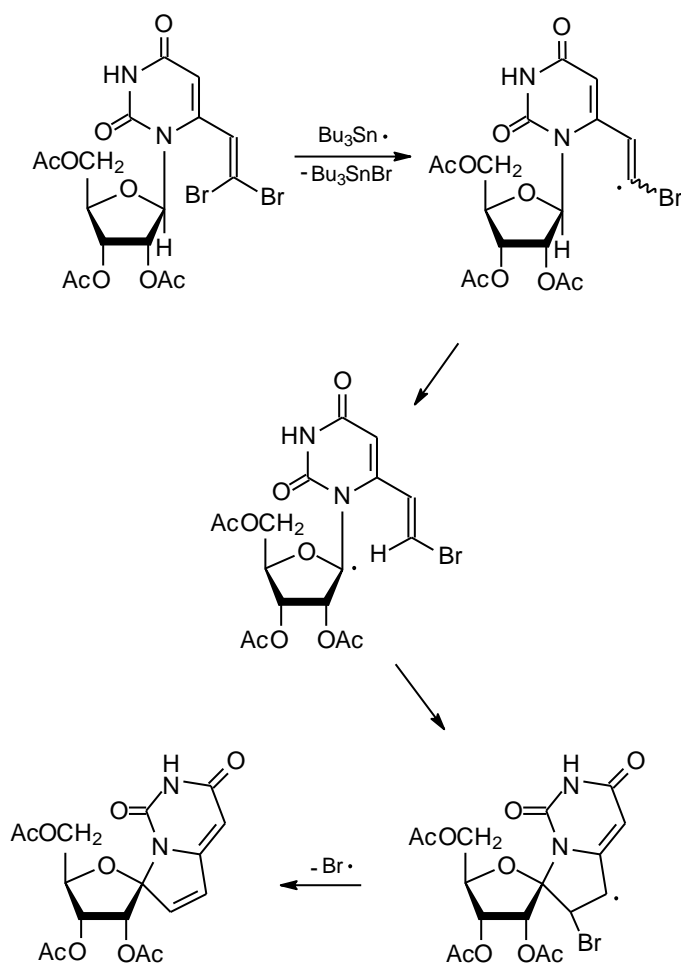
## b. Carbon-Centered Radicals

Since internal hydrogen-atom abstraction by a carbon-centered radical in a typical carbohydrate involves replacing one carbon–hydrogen bond with another, it is a reaction that does not take place easily unless the radical doing the abstracting is a very reactive one. Vinylic radicals are one of the few types of carbon-centered radicals that are sufficiently reactive routinely to abstract hydrogen atoms from carbon–hydrogen bonds. Most of the reported examples of abstraction by vinylic radicals are sequential reactions and are similar to that shown in Scheme 32 in that

hydrogen-atom abstraction is intramolecular and regioselective. This abstraction is followed by a regioselective, radical cyclization.<sup>68</sup>

Primary radicals also are able to abstract hydrogen atoms from carbon-hydrogen bonds. When this occurs, as it does in the reaction shown in Scheme 33, it usually is intramolecular and involves regioselective abstraction that produces a considerably more stable radical. Evidence from deuterium incorporation in this reaction (Scheme 33) indicates that internal, site-selective abstraction of H-5 by the primary radical **61** to produce the oxygen-stabilized, tertiary radical **62** competes effectively with direct deuterium abstraction by **61** from Bu<sub>3</sub>SnD.<sup>69</sup>

Scheme 32

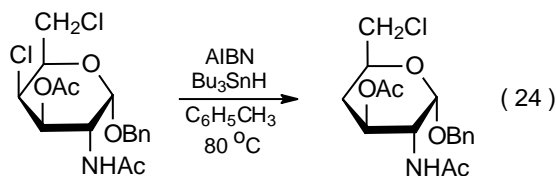
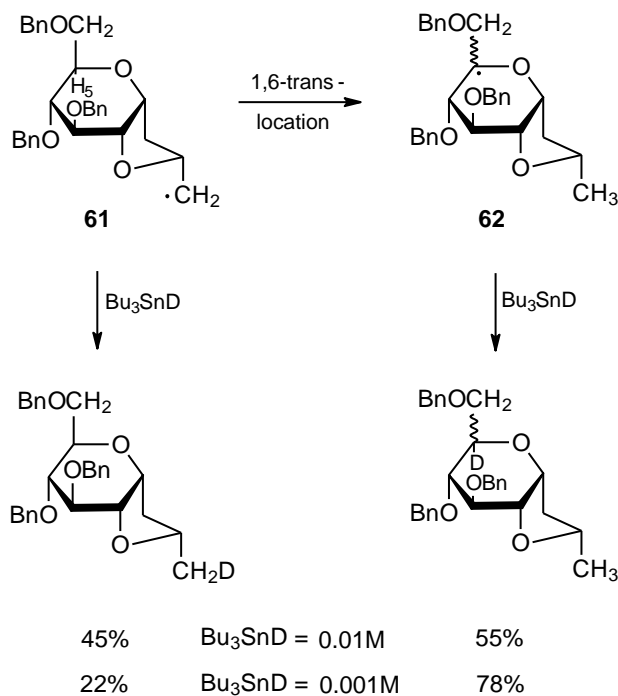


### 3. Halogen-Atom Abstraction Reactions

Although almost all regioselective, atom-abstraction reactions involve hydrogen-atom abstraction, site-selective reaction can take place in molecules that have two or more halogen atoms. Halogenated carbohydrates are common, but few of these contain more than a single halogen

atom. One that has two such atoms and undergoes regiospecific chlorine-atom abstraction is shown in eq 24.<sup>70</sup>

Scheme 33



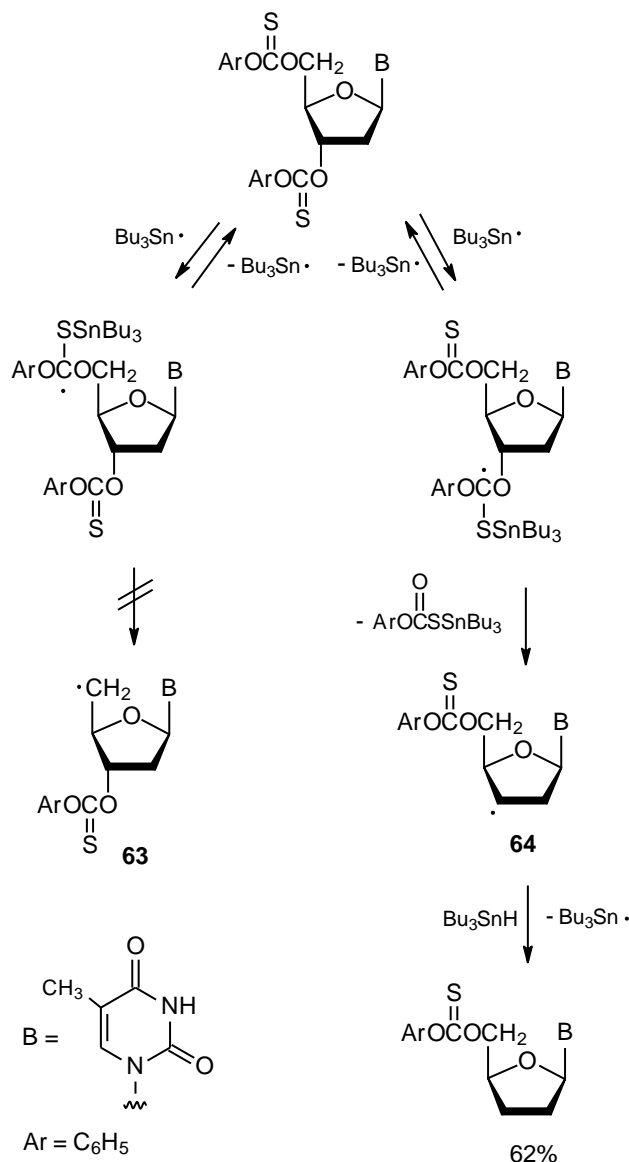
## B. Group Replacement Reactions

### 1. *O*-Thiocarbonyl Compounds

Regioselective reaction can take place when two (or more) of the same *O*-thiocarbonyl groups are present in a molecule. An example is provided by the reaction shown in Scheme 34, where only one of the two *O*-phenoxythiocarbonyl groups is replaced by a hydrogen atom.<sup>71</sup> To understand the site-selectivity of this reaction it is useful to recall from the discussion in Chapter 7 (Section III.B.) that the addition of  $\text{Bu}_3\text{Sn}\cdot$  to a carbon–sulfur double bond is reversible, and reaction moves forward only when this reversibility is interrupted by adduct radical fragmenting to give a carbon-centered radical (Scheme 34). The transition state for formation of the primary

radical **63** is enough higher in energy than that for formation of the secondary radical **64** that the only reaction observed involves **64** as an intermediate. Site selectivity in this reaction, therefore, depends on the reversibility of the  $\text{Bu}_3\text{Sn}\cdot$  addition and the typically lower transition state energy for forming a secondary radical as opposed to a primary one.

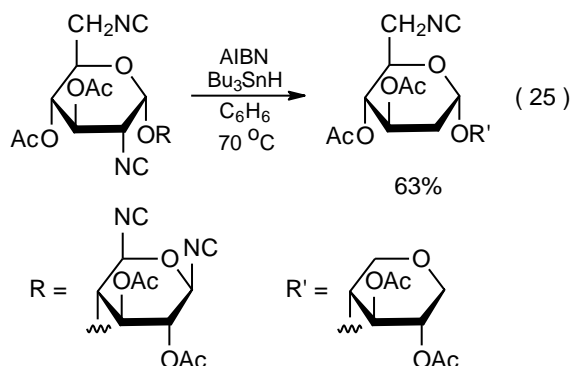
Scheme 34



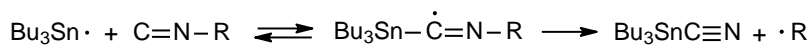
## 2. Isonitriles

Site-selective reaction can take place when compounds containing two or more isocyanato groups react with tri-*n*-butyltin hydride (eq 25).<sup>72</sup> This selectivity is determined by the stability of

each carbon-centered radical produced by loss of an isocyano group. This loss, which follows reversible addition of  $\text{Bu}_3\text{Sn}\cdot$  to an isocyano group (Scheme 35), is more rapid if a secondary, rather than a primary, radical is being formed as an intermediate.



Scheme 35



## VI. Summary

Regioselectivity is a term that describes reactions in which one structural isomer is generated in preference to other possible structural isomers. It refers to reactions that involve a single functional group (e.g., a multiple bond in an unsaturated compound) and to those in which abstraction of a particular atom or group takes place in compounds that contain at least one other atom or group of the same type.

Most addition reactions are regioselective because a radical adds to the less-substituted carbon atom in a carbon–carbon multiple bond. Steric effects are the primary factor controlling most such reactions, but in those where steric effects are minimal, polar effects often become the determining factor.

Internal addition of a radical to a multiple bond often has the choice of generating either a five- or a six-membered ring or either a six- or seven-membered ring. Regioselectivity in most of these reactions favors formation of the smaller ring even though cyclization to give the larger ring often produces the thermodynamically more stable radical.

The reverse of radical addition to a double bond is  $\beta$ -fragmentation. Where carbohydrates are concerned, oxygen-centered radicals generally undergo a  $\beta$ -fragmentation that involves ring opening. Carbon-centered radicals also undergo  $\beta$ -fragmentation that can cause ring opening, and can lead to unsaturated compounds by radical expulsion.

Regioselectivity in hydrogen-atom abstraction depends on the abstracting agent and can vary considerably. The extremely reactive hydroxyl radical can abstract a hydrogen atom from any of



the six carbon–hydrogen bonds in  $\alpha$ -D-glucopyranose. This type of reaction is exothermic and exhibits little, if any, site selectivity. Hydrogen-atom abstraction by a bromine atom, on the other hand, is an endothermic process that is highly regioselective.

Intramolecular hydrogen abstraction often involves reaction of an oxygen-centered radical. Since the most stable transition state for internal hydrogen-atom transfer nearly always has a six-membered ring, the 1,5-hydrogen-atom migration (1,5-radical translocation) that occurs is a highly regioselective reaction. Only the most reactive carbon-centered radicals (e.g., vinylic and primary) consistently are able to abstract hydrogen atoms from carbon–hydrogen bonds. Such abstraction usually is an intramolecular reaction.

Site selectivity occurs in reactions of compounds with groups and atoms other than hydrogen, but such reactions are rare because few carbohydrates contain two or more of the same reactive groups (or atoms). Compounds with two of the same *O*-thiocarbonyl groups or two isocyanato groups are known to react selectively with the tri-*n*-butyltin radical. In such reactions significant selectivity exists if there is a choice between forming a primary or a secondary radical.

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