

Chapter 9

Chemoselectivity

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I. Introduction

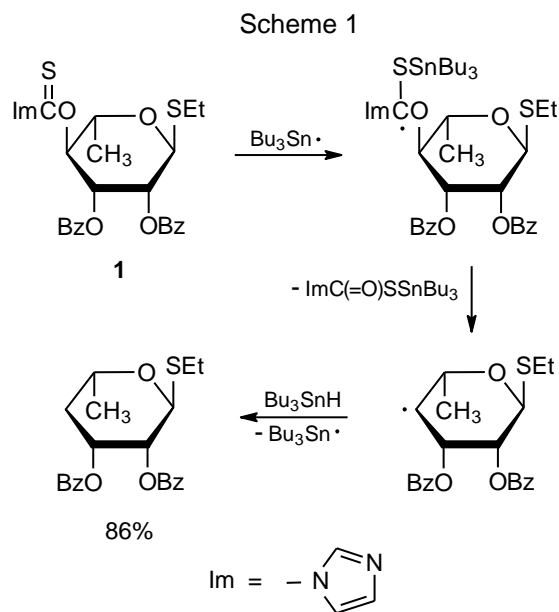
Chemoselectivity is a term that describes the ability of a reagent or intermediate to react with one group or atom in a molecule in preference to another group or atom present in the same molecule. Since most carbohydrate radicals trace their beginnings to reactions involving either a tin-centered [usually $\text{Bu}_3\text{Sn}\cdot$] or a silicon-centered [usually $(\text{Me}_3\text{Si})_3\text{Si}\cdot$] radical, the chemoselectivity in reactions of these radicals plays a central role in carbohydrate radical formation. An example of a chemoselective reaction is found in Scheme 1, where the tri-*n*-butyltin radical abstracts the *O*-thiocarbonyl group from the thioglycoside **1** while the potentially reactive ethylthio group remains in place.¹

Chemoselective reaction also can occur when a carbohydrate radical reacts with another molecule present in the reaction mixture. Such a process is shown in Scheme 2, where the pyranos-1-yl radical **2** adds to the C–C double bond in **3** rather than reacting with the chlorine atom or phenylseleno group also present in this molecule (**3**).²

II. Formation of Carbon-Centered Radicals

The best method for determining the chemoselectivity of two groups in a particular reaction is to compare their reactivity in a substrate containing both. Since this type of testing rarely has taken place, another approach is needed if chemoselectivity in a particular reaction is to be estab-

blished from existing data. One alternative is to construct an order of reactivity based on rates of reaction of compounds that each contains a single substituent. Such an order can be established from information that exists about rates of reaction of $\text{Bu}_3\text{Sn}\cdot$ and $(\text{Me}_3\text{Si})_3\text{Si}\cdot$ with compounds that have a single reactive substituent.



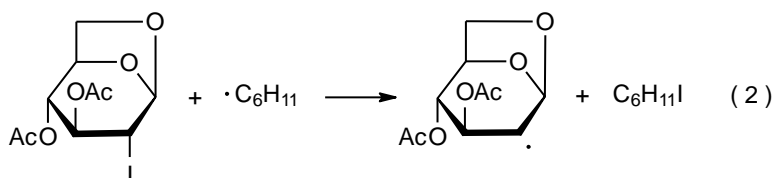
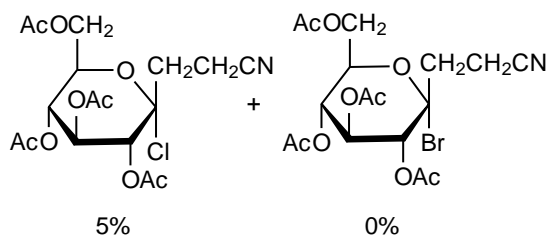
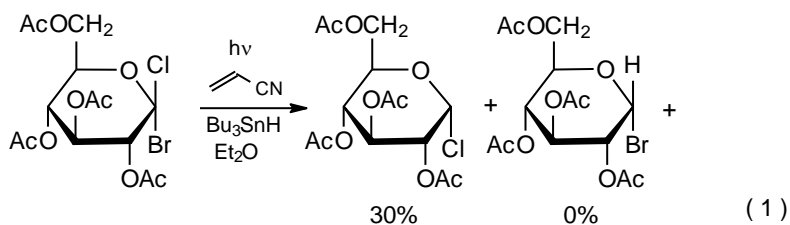
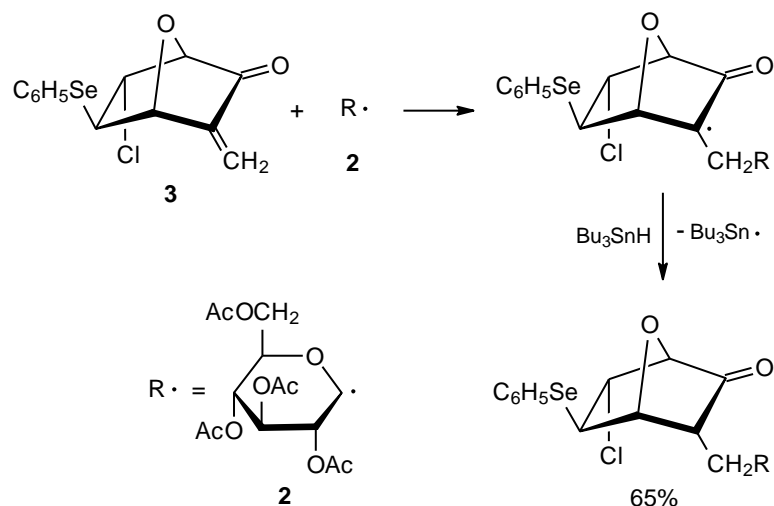
A. Atom Abstraction

1. Halogen Atoms

Relative reactivity of halogenated compounds with the tri-*n*-butyltin radical has been determined by allowing pairs of alkyl halides to compete for a limited amount of Bu_3SnH . Emerging from such study is the order of reactivity $\text{RI} > \text{RBr} > \text{RCl} \gg \text{RF}$.³⁻⁷ A similar reactivity order exists for reaction of halogenated compounds with $(\text{Me}_3\text{Si})_3\text{SiH}$.^{8,9} In the reaction shown in eq 1, the replacement of a bromine atom in the substrate, in preference to a chlorine atom, is “in line” with the chemoselectivity determined from competition experiments.¹⁰ Absolute rate constants for reaction of alkyl halides with the tri-*n*-butyltin radical (Table 1 in Chapter 8) confirm this order of reactivity (i.e., iodides most reactive, fluorides^{6,11} effectively unreactive).

Carbohydrate radical formation also can take place when a simple, carbon-centered radical reacts with a halogenated carbohydrate. An example of this type of reaction is found in the iodine-atom abstraction by the cyclohexyl radical shown in eq 2.¹² Absolute rate constants for halogen-atom abstraction by alkyl radicals (Table 5, Chapter 8) show the order of reactivity to be $\text{RI} \gg \text{RBr} > \text{RCl}$. The data in this table indicate that unlike iodides, the rate constants for reaction of some bromides and most chlorides with alkyl radicals are small enough that a chain reaction involving these compounds is likely to collapse. (Chain collapse is discussed in Section V of Chapter 8.)

Scheme 2



2. Hydrogen Atoms

Carbon-centered, carbohydrate radicals also form from hydrogen-atom abstraction by oxygen- and sulfur-centered radicals as well as by bromine and chlorine atoms. Differences in reactivity of hydrogen atoms in the same molecule do exist, but since such abstraction would

involve two atoms of the same type, any selectivity observed would be regioselectivity, which is discussed in Chapter 10.

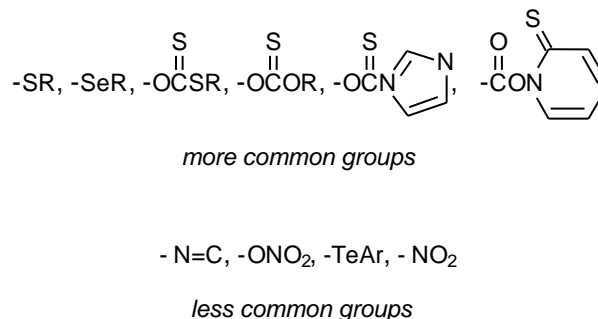


Figure 1. Groups abstracted from carbohydrates to form carbon-centered radicals

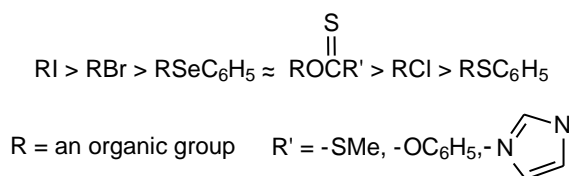


Figure 2. Relative reactivity of compounds with $\text{Bu}_3\text{Sn}\cdot$

B. Group Abstraction

Groups that have been abstracted from carbohydrate derivatives by tin- and silicon-centered radicals are listed in Figure 1. The relative reactivity of $\text{Bu}_3\text{Sn}\cdot$ with simple organic compounds containing the more common of these groups is integrated into the reactivity order of this radical with halogenated compounds to provide the listing shown in Figure 2. These relative reactivities, which are based on the absolute rate constants given in Table 1 of Chapter 8, provide a means for predicting chemoselectivity in the reactions of $\text{Bu}_3\text{Sn}\cdot$ with compounds containing two or more of these substituents.

1. The Effect on Chemoselectivity of a Reversible First Step

Many group-abstraction reactions, such as the ones shown in Schemes 1 and 3, are two-step processes in which the first step is reversible. Due to this reversibility the rate constant for this first step is larger than the rate constant for carbon-centered radical formation. (The effect of a reversible first step on the rates for carbon-centered radical formation from reaction of $(\text{Me}_3\text{Si})_3\text{Si}\cdot$ with an isonitrile, a phenyl selenide, and a xanthate are discussed in Section III.B. of Chapter 8.) Reversible addition is responsible for the existence of two reactivity orders. The first (Figure 3) is based

on the absolute rate constants for group- and atom-abstraction reactions given in Table 2 of Chapter 8 and the second (Figure 4) on rate constants for carbon-centered radical formation after modification, when necessary, for the effect of a reversible first step.

Scheme 3

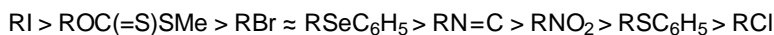
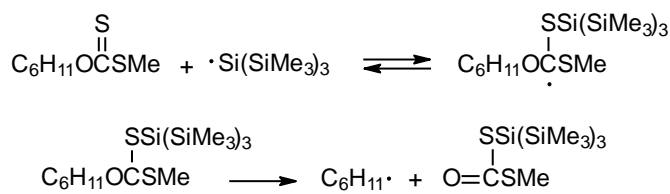


Figure 3. Relative reactivity of compounds with $(\text{Me}_3\text{Si})_3\text{Si}\cdot$
(based on absolute rate constants)

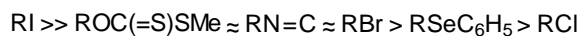


Figure 4. Relative reactivity of compounds with $(\text{Me}_3\text{Si})_3\text{Si}\cdot$
(based on carbon-centered radical formation)

Group abstraction also takes place from carbohydrates by radicals centered on phosphorous,^{13–15} boron,¹⁶ and carbon¹⁷ atoms. Little is known about the chemoselectivity of these reactions, but there is indication that selective reaction will take place. Carbohydrate xanthates undergo group abstraction in the presence of either phosphine-boranes¹⁶ or trialkylborane/air/water.¹⁸ In each case when alkyl bromides or chlorides are present in the reaction mixture, these halides do not react. (Alkyl iodides, however, are reactive under these conditions.) These results suggest that chemoselective reaction will take place in carbohydrates that contain an *O*-thiocarbonyl group along with either a chlorine or bromine atom.

2. *O*-Thiocarbonyl Compounds

Among the *O*-thiocarbonyl compounds that produce carbon-centered radicals by reaction with $\text{Bu}_3\text{Sn}\cdot$, differences in rate constants are small (Figure 5);¹⁹ consequently, chemoselectivity also can be expected to be small. In compounds as structurally complicated as carbohydrates, it is reasonable to expect that characteristics of individual structures are more important to chemoselectivity than small differences in inherent reactivity of *O*-thiocarbonyl groups.

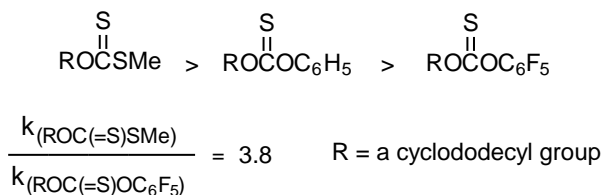


Figure 5. Relative reactivity of thiocarbonyl-containing compounds with the tri-*n*-butyltin radical

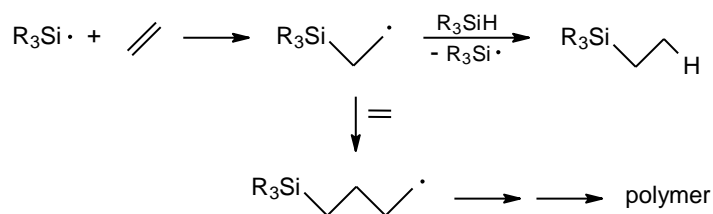
C. Radical Addition

1. Reversible Reaction

Addition of the tri-*n*-butyltin radical to a carbon–carbon multiple bond usually is reversible.^{20–22} This reversibility is attributed to the weakness of the carbon–tin bond [BDE = 278 kJ mol⁻¹ (66 kcal mol⁻¹)]^{23,24} and the stability of Bu₃Sn·.²⁵ Reversing the addition process eliminates opportunity for chemoselective reaction other than possible (*E*)-(*Z*) isomerization. If, however, this reversal can be prevented, chemoselective reaction becomes possible.

Bond dissociation energies are greater for carbon–silicon bonds than for carbon–tin bonds;^{20,23,24} consequently, reversing the addition of a silyl radical to a multiple bond is more difficult than the comparable reversal of a tin-centered radical. Greater Si–C bond strength means that some silyl radicals add irreversibly to carbon–carbon double bonds. (The addition of Et₃Si· to 1-hexene is irreversible even at 140 °C.²⁶) Irreversibility is a “two-edged sword” because although it makes chemoselective addition possible, it also “opens the door” for radical polymerization; consequently, in order to observe a nonpolymerizing, chemoselective reaction from the addition of a silicon-centered radical to a carbon–carbon multiple bond, it is necessary to prevent both reversible addition and radical polymerization.

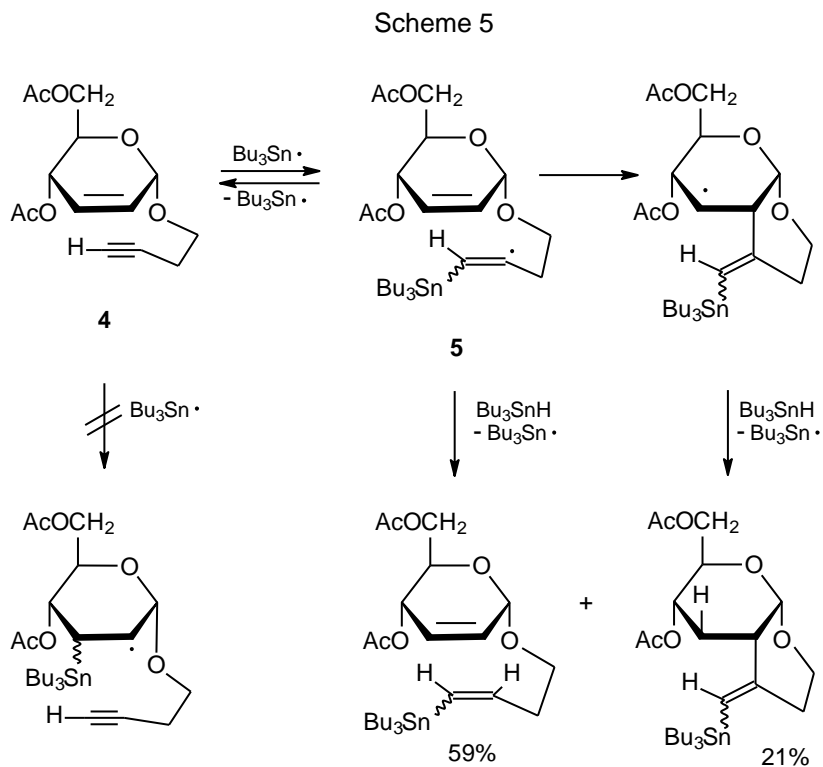
Scheme 4



2. Preventing Reversible Addition and Polymerization

Since neither addition of Bu₃Sn· nor (Me₃Si)₃Si· to a carbon–carbon multiple bond produces a chemoselective reaction unless a second reaction prevents both reversal of radical addition and

polymerization, chemoselectivity depends on the existence of this second reaction. Because Bu_3SnH and $(\text{Me}_3\text{Si})_3\text{SiH}$ both are effective hydrogen-atom donors, hydrogen-atom abstraction by an adduct radical is one reaction that stops both polymerization and reverse addition (Scheme 4).²⁷ Other reactions that have this effect are internal addition of the adduct radical to a second multiple bond (cyclization) and bond fragmentation that expels a radical different from the one that added to the multiple bond.

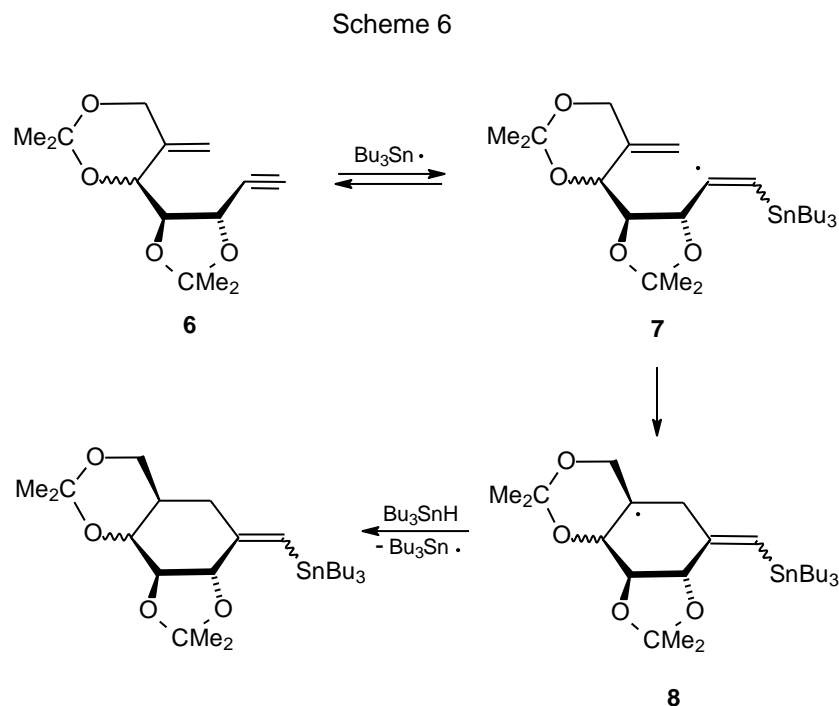


a. Hydrogen-Atom Abstraction

When the adduct radical **5** abstracts a hydrogen atom from Bu_3SnH , reversal of the radical addition shown in Scheme 5 stops. Hydrogen-atom abstraction then is the critical second step in the chemoselective reaction of **4**, a compound with several, potentially reactive functional groups.²⁸ Hydrogen-atom abstraction that prevents reversal of an addition reaction occurs easily in compounds that contain a triple bond^{28,29} because the vinyl radicals produced by the addition process readily abstract hydrogen atoms.²¹

Tris(trimethylsilyl)silane is a sufficiently effective hydrogen-atom donor that hydrogen-atom abstraction is favored over polymerization when this silane is used; in fact, polymerization can be avoided altogether by conducting reactions with a slight excess of $(\text{Me}_3\text{Si})_3\text{SiH}$.²⁷ Another characteristic of tris(trimethylsilyl)silane that separates it from most other silanes is that

the addition of $(\text{Me}_3\text{Si})_3\text{Si}\cdot$ to a carbon–carbon multiple bond is reversible.^{27,30,31} (Evidence for this reversibility is that $(\text{Me}_3\text{Si})_3\text{Si}\cdot$ is able to isomerize double bonds.^{30,31})

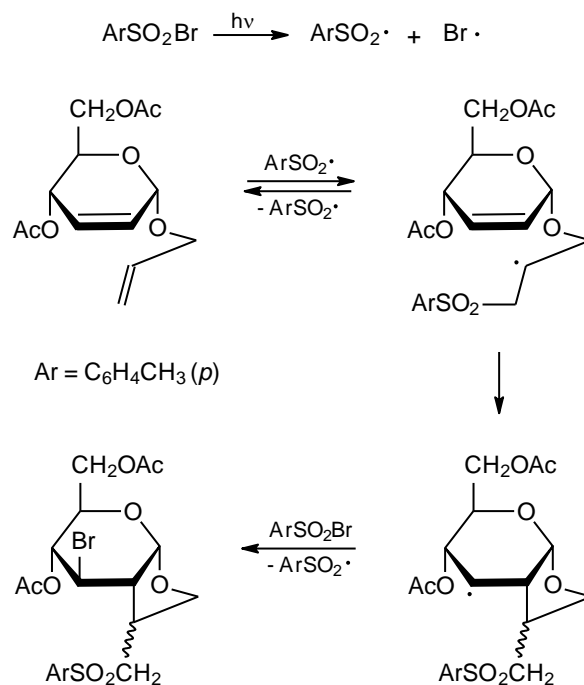


b. Cyclization

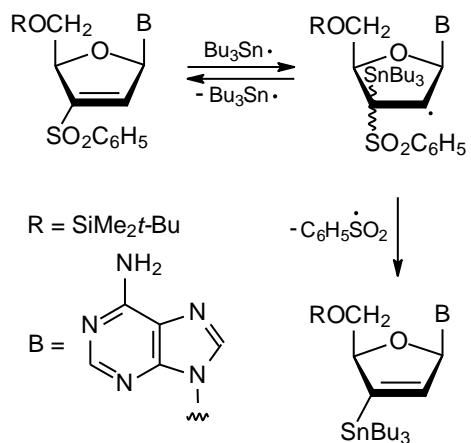
Another reaction that prevents an adduct radical from reversing the addition process is radical cyclization; thus, the vinyl radical **7** avoids eliminating $\text{Bu}_3\text{Sn}\cdot$ by cyclizing to produce the tertiary radical **8** (Scheme 6).³² Although the product from the reaction pictured in Scheme 6 arises from $\text{Bu}_3\text{Sn}\cdot$ addition to the triple bond in the starting material **6**, the reversibility of $\text{Bu}_3\text{Sn}\cdot$ addition to carbon–carbon multiple bonds raises some question as to which multiple bond in **6** is more reactive. When results from reactions of less structurally complicated molecules are considered,^{22,25} it is likely that addition to the double bond in **6** also is occurring but is not observed because such a reaction reverses before cyclization can take place. Even though reaction reversibility leads to some uncertainty about whether the addition of $\text{Bu}_3\text{Sn}\cdot$ is more rapid to the double or triple bond in **6**, the chemoselectivity of the reaction is not in question because the only product formed comes from addition of $\text{Bu}_3\text{Sn}\cdot$ to the triple bond.

The reaction shown in Scheme 7 describes a chemoselective addition of $\text{ArSO}_2\cdot$ to a compound that contains two double bonds.³³ In this case the addition is preferentially to the less substituted double bond in the starting material. Once again radical cyclization stops reversal of the addition process.

Scheme 7



Scheme 8

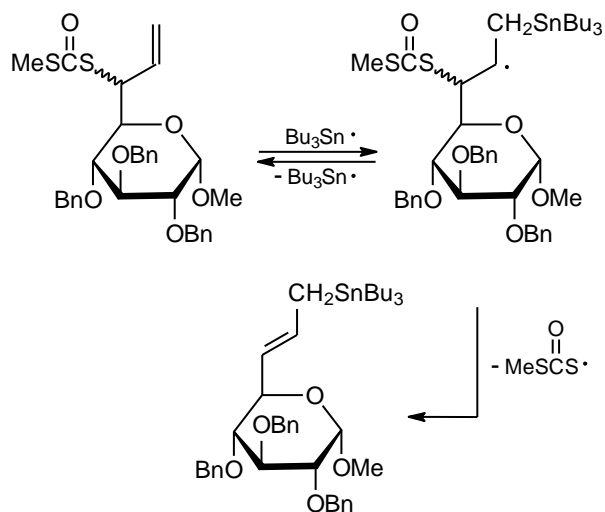


c. Bond Fragmentation

Sometimes reversal of the addition process is prevented when the adduct radical fragments by expelling a radical different from the one that added to the multiple bond. This type of reaction occurs when a tri-*n*-butyltin radical adds to a compound that has a double bond with a substituent,

such as $\text{SO}_2\text{C}_6\text{H}_5$, that can depart from the adduct radical by bond fragmentation (Scheme 8).³⁴ A similar reaction, but one involving expulsion of a different, sulfur-centered radical, is shown in Scheme 9.³⁵

Scheme 9



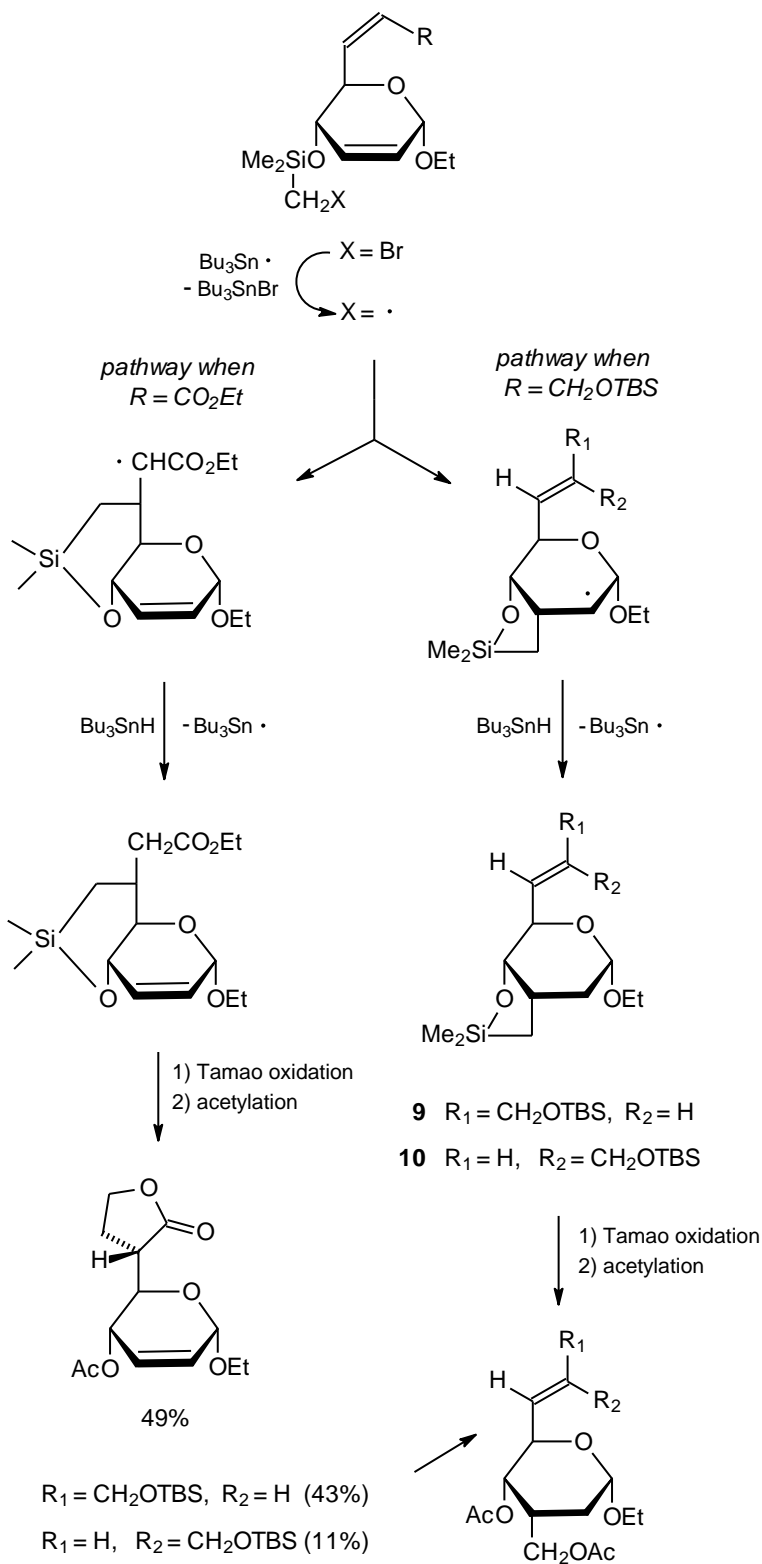
D. Unreactive Groups and Atoms

Although the discussion thus far naturally has focused on reactive groups, equally important, as far as chemoselectivity is concerned, are groups that are unreactive. One of the reasons that tin- and silicon-centered radicals are such useful intermediates in synthetic reactions is that many of the groups (acyloxy, acetal, acetamido, amino, cyano, hydroxy, silyloxy, tosyloxy, and trityloxy) and atoms (fluorine and hydrogen) often present in carbohydrates belong in the “unreactive” category. When reactive and unreactive substituents are viewed together, a picture emerges of tin- and silicon-centered radicals being able to react chemoselectively with a wide variety of carbohydrates to produce specific, carbon-centered radicals but, at the same time, avoid reaction with most common protecting groups.

III. Carbon-Centered Radicals

Although the primary reason for reacting carbohydrates with $(\text{Me}_3\text{Si})_3\text{Si}\cdot$ or $\text{Bu}_3\text{Sn}\cdot$ is to generate carbon-centered radicals, the chemoselectivity of the reactions of carbohydrate radicals formed in this way also is a matter of importance. Nearly all carbon-centered radicals derived from carbohydrates are nucleophilic and, consequently, add more readily to carbon–carbon multiple bonds that are electron deficient than to ones that are electron rich. (The rationale behind this selectivity is discussed in Sections IV.A.1. and IV.B.1. of Chapter 7.) The cyclization reactions shown in Scheme 10 illustrate the influence of an electronegative substituent on the chemoselec-

Scheme 10



tivity of addition of a nucleophilic radical to a compound with two double bonds.^{36,37} Reaction occurs at the double bond external to the ring when an electron-withdrawing substituent ($R = \text{CO}_2\text{Et}$) is present, but if the substituent is not electron-withdrawing ($R = \text{CH}_2\text{OTBS}$), addition is exclusively at the endocyclic double bond. (The *cis-trans* isomerization that takes place during formation of **9** and **10** results from reversible addition of $\text{Bu}_3\text{Sn}\cdot$ to the double bond external to the ring.)

A variety of groups (e.g., acetal, acetoxy, carbonyl, cyano, hydroxy, and silyloxy groups) can be present in a reactant molecule but remain unchanged during carbon-centered radical addition to a carbon-carbon multiple bond. Carbon-centered radicals also participate less readily in substitution reactions with normally reactive substituents than do tin- and silicon-centered radicals; for example, Tables 1, 2, and 5 in Chapter 8 show the absolute rate constants for reaction of *tert*-butyl bromide with $\text{Bu}_3\text{Sn}\cdot$, $(\text{Me}_3\text{Si})_3\text{Si}\cdot$, and $\text{CH}_3(\text{CH}_2)_6\text{CH}_2\cdot$ are $1.4 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$, $1.2 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$, $4.6 \times 10^3 \text{ M}^{-1}\text{s}^{-1}$, respectively. This reluctance to become involved in substitution reactions is illustrated in Scheme 2 where the radical **2** does not react with the chlorine atom or phenylseleno group in **3** but rather adds to the C-C double bond in this molecule.²

IV. Summary

Chemoselectivity refers to ability of a reagent or intermediate (e.g., a radical) to react with one group in a molecule in preference to a different, but potentially reactive, group present in the same molecule. Since most carbohydrate radicals trace their beginnings to reactions involving either the tri-*n*-butyltin [$\text{Bu}_3\text{Sn}\cdot$] or tris(trimethylsilyl)silyl [$(\text{Me}_3\text{Si})_3\text{Si}\cdot$] radical, chemoselectivity in the reactions of these radicals plays a central role in carbohydrate radical formation. In many reactions a second opportunity for chemoselectivity arises when an initially formed, carbon-centered radical reacts selectively with another molecule present in solution.

The tri-*n*-butyltin radical adds to carbon-carbon, carbon-oxygen, and carbon-sulfur multiple bonds in a reversible fashion; consequently, for chemoselective reaction to occur, the reverse reaction must be blocked in some manner. Preventing reversal of radical addition usually is achieved by hydrogen-atom abstraction, addition to a multiple bond, or fragmentation of the adduct radical. Silicon-carbon bonds tend to be stronger than tin-carbon bonds so addition of some silyl radicals to unsaturated compounds is not reversible at normal reaction temperatures. The tris(trimethylsilyl)silyl radical, however, does add reversibly to unsaturated compounds.

Carbon-centered radicals tend to be quite chemoselective intermediates. They add readily to electron-deficient, carbon-carbon, multiple bonds but are less reactive in group and atom replacement reactions than are $(\text{Me}_3\text{Si})_3\text{Si}\cdot$ and $\text{Bu}_3\text{Sn}\cdot$.

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