Appendix I

Hydrogen-Atom Donors

I. Introduction ........................................................................................................................................532
II. Organotin Hydrides .........................................................................................................................532
   A. Tri-\textit{n}-butyltin Hydride ...........................................................................................................533
      1. Advantages of Tri-\textit{n}-butyltin Hydride ..................................................................................533
      2. Problems Associated with the use of Tri-\textit{n}-butyltin Hydride .................................................533
      3. Reducing the Negative Impact of Tri-\textit{n}-butyltin Hydride .......................................................533
   B. Polymer-Supported Reagents .......................................................................................................537
   C. Fluorous Tin Hydrides ................................................................................................................537
III. Organosilanes ...................................................................................................................................538
   A. Tris(tri-methylsilyl)silane ...........................................................................................................538
   B. Phenyl-Substituted and Related Silanes .......................................................................................539
   C. Triethylsilane ..................................................................................................................................540
IV. Compounds with Phosphorous–Hydrogen Bonds ........................................................................542
V. Compounds with Boron–Hydrogen Bonds .....................................................................................543
VI. Compounds with Carbon–Hydrogen Bonds ....................................................................................544
   A. 2-Propanol .......................................................................................................................................544
   B. Cyclohexane .....................................................................................................................................545
   C. Silylated Cyclohexadienes ............................................................................................................546
VII. Compounds with Sulfur–Hydrogen or Selenium–Hydrogen Bonds ............................................547
VIII. Summary .........................................................................................................................................547
IX. References .........................................................................................................................................547

I. Introduction

Hydrogen-atom donors are widely used in radical reactions because hydrogen abstraction is the final step in most radical chain processes. Donors can have a hydrogen atom bonded to a tin, silicon, sulfur, selenium, boron, phosphorous, or carbon atom. Most reactions involve organotin compounds, usually tri-\textit{n}-butyltin hydride (Bu\textsubscript{3}SnH). Some organosilanes, in particular tris(tri-methylsilyl) silane [(Me\textsubscript{3}Si)\textsubscript{3}SiH], are effective enough as hydrogen donors to serve as replacements for organotin hydrides. Most other hydrogen donors are either so reactive or so unreactive that they typically are used only in special situations.

II. Organotin Hydrides

Organotin hydrides are the most frequently employed hydrogen-atom donors in radical reactions of carbohydrates. Clearly, the compound of choice is tri-\textit{n}-butyltin hydride (Section
II.A. Phenyl-substituted compounds, such as triphenyltin hydride, can serve in the same role, but they offer no advantage and are rarely used. Polymer-supported (Section II.B) and fluorous (Section II.C) tin hydrides have been used as replacements that avoid some of the difficulties inherent in the use of tri-\textit{n}-butyltin hydride.

A. Tri-\textit{n}-butyltin Hydride

1. Advantages of Tri-\textit{n}-butyltin Hydride

In some ways \textit{Bu}_3\text{SnH} is an ideal hydrogen donor. It reacts rapidly with a carbon-centered radical to produce a carbon–hydrogen bond and, at the same time, generates the chain-transfer agent (\textit{Bu}_3\text{Sn·}) required for successful reaction. An important characteristic of \textit{Bu}_3\text{Sn·} is that it does not cause side reactions by abstracting hydrogen atoms from carbon–hydrogen bonds.

2. Problems Associated With the Use of Tri-\textit{n}-butyltin Hydride

Even with its extensive, successful applications and significant advantages, tri-\textit{n}-butyltin hydride suffers from several substantial drawbacks. One of these is that complete separation of tin-containing compounds from deoxygenated products is often difficult.\textsuperscript{1–11} Another problem is that the toxicity of \textit{Bu}_3\text{SnH}\textsuperscript{12,13} and the tin-containing substances it produces are a danger to those handling these materials and a complication for waste disposal.\textsuperscript{1–11} This combination of problems places a severe limitation on the use of \textit{Bu}_3\text{SnH} in the synthesis of therapeutic agents and other compounds destined for biological applications.\textsuperscript{14} Another concern about tri-\textit{n}-butyltin hydride is that although it is not too costly for small-scale laboratory use, large-scale reactions with this compound are expensive.\textsuperscript{1,2,11}

\[
\begin{align*}
2 \textit{Bu}_3\text{SnX} &+ 2\text{NaBH}_4 & \rightarrow & 2\textit{Bu}_3\text{SnH} &+ 2\text{NaX} &+ \text{B}_2\text{H}_6 & (1) \\
X &= \text{I, Br, Cl}
\end{align*}
\]

3. Reducing the Negative Impact of Tri-\textit{n}-butyltin Hydride

The modifications to the use of tri-\textit{n}-butyltin hydride that are described in the next three sections reduce its negative impact. One approach is to use \textit{Bu}_3\text{SnH} in catalytic amounts and to regenerate this tin hydride during reaction. Sodium borohydride and polymethylhydrosiloxane are two reagents that can regenerate \textit{Bu}_3\text{SnH} in a reaction mixture quickly after it is consumed. Recycling using these reagents allows complete reaction to take place when only a small amount of tin-containing material is present. Product purification is easier for reactions run under these conditions. A different approach to product purification calls for potassium fluoride to be added to a reaction mixture after reaction is complete. This addition precipitates insoluble tin fluorides and permits them to be removed by filtration.
Appendix I

Reagents That Regenerate Tri-\(n\)-butyltin Hydride During a Reaction

(1). Sodium Borohydride

The tin-containing product from reaction of a halogenated carbohydrate with tri-\(n\)-butyltin hydride is a tri-\(n\)-butyltin halide. Sodium borohydride regenerates hydride from halide (eq 1) rapidly enough that \(\text{Bu}_3\text{SnH}\) can be used in far less than stoichiometric amounts.\(^{15}\) Using sodium borohydride naturally is limited to situations in which undesired side reactions with this reagent [or the diborane it produces (eq 1)] do not take place. Equation 2 describes a reaction in which tin-containing compounds are used in only catalytic amounts due to the presence of sodium borohydride.\(^{16}\)

\[
\text{Bu}_3\text{SnX} + (\text{MeSiHO})_n \xrightarrow{\text{KF}} \text{Me}_3\text{Si} \xrightarrow{\text{Et}_2 \text{O}} (\text{MeSiHO})_n
\]

polymethylhydrosiloxane \(X = \text{I, Br, Cl}\)

\[
\text{Me}_2\text{C}<\ \text{S} \xrightarrow{\text{AIBN}} \text{Me}_2\text{C}<\ \text{O}\text{COC}_6\text{H}_5
\]

\[\text{C}_6\text{H}_5\text{CH}_3 \xrightarrow{\text{110 °C}} \text{Me}_2\text{C}<\ \text{O}\text{COC}_6\text{H}_5\]

\(63\%\)
(2). Polymethylhydrosiloxane

Polymethylhydrosiloxane [PMHS, (MeSiHO)\textsubscript{n}] in the presence of potassium fluoride reacts with tri-\textit{n}-butyltin halides to produce Bu\textsubscript{3}SnH (eq 3).\textsuperscript{17} Since this reaction can generate Bu\textsubscript{3}SnH \textit{in situ}, only 10 mol\% of a tri-\textit{n}-butyltin iodide, bromide, or chloride in the presence of excess KF and PMHS is sufficient for complete hydrogen-for-halogen substitution. Tri-\textit{n}-butyltin hydride formation depends on fluoride ion converting PMHS into a powerful reducing agent,\textsuperscript{18} one which is thought to contain hypervalent silicon atoms.\textsuperscript{17,19}

Another way in which the inexpensive, nontoxic PMHS generates tri-\textit{n}-butyltin hydride is when it reacts with bis(tri-\textit{n}-butyltin) oxide (Scheme 1).\textsuperscript{20–24} Not only is the Barton-McCombie reaction shown in eq 4 successful when Bu\textsubscript{3}SnH is generated in this way, but recycling is rapid enough that only a catalytic amount (7.5 mol\%) of (Bu\textsubscript{3}Sn)\textsubscript{2}O is necessary for complete reaction.\textsuperscript{20} The reactions that describe the cycle for using and continuously refreshing the Bu\textsubscript{3}SnH supply are
given in equations 5 and 6. (For the reaction shown in eq 5 including BuOH as a cosolvent substantially increases the yield of Bu$_3$SnH.)

\[
\begin{align*}
\text{Bu}_3\text{SnOC}_6\text{H}_5 + \text{C}_6\text{H}_5\text{CH}_3 & \rightarrow \text{Bu}_3\text{SnH} + \text{C}_6\text{H}_5\text{CHOH} & (5) \\
\text{S} \quad \text{CARB-OOC}_6\text{H}_5 + \text{Bu}_3\text{SnH} & \rightarrow \text{CARB-H} + \text{COS} + \text{Bu}_3\text{SnOC}_6\text{H}_5 & (6)
\end{align*}
\]

\[
\begin{align*}
\text{Bu}_3\text{SnX} + F^- & \rightarrow \text{Bu}_3\text{SnF}^- + X^- & (7)
\end{align*}
\]

b. Reagents That Assist in Removing Tin-Containing Residues

(1) Potassium Fluoride

The difficulty in purification of a reaction mixture after organotin hydride reduction stems from the release of organotin compounds by slow hydrolysis of tin-containing byproducts during the chromatography that typically is part of product isolation. These tin-containing byproducts can be precipitated by addition of potassium fluoride to the reaction mixture after reaction is complete. The insoluble “polymeric” tin fluorides that form can be removed by filtration (eq 7).

(2) Sodium Borohydride

Tin-containing residues also can be removed by treating a crude reaction mixture with sodium borohydride prior to chromatography. This treatment converts organotin compounds into tri-$n$-butyltin hydride and, thereby, eliminates their slow release from the chromatography column. Deoxygenated products then can be isolated in much purer form, and the regenerated Bu$_3$SnH can be recovered in high yield.
B. Polymer-Supported Tin Hydrides

A different approach to solving problems created by tin-containing byproducts in radical reactions is to replace the tri-\(n\)-butyltin hydride with a polymer-supported, organotin hydride.\(^{29,30}\) Polymer-based reagents, such as 1, make purification of reaction mixtures much simpler because tin-containing materials can be removed by filtration; as a result, risks associated with exposure to organotin compounds are greatly reduced. Also, polymer-supported reagents such as 1 can be regenerated and used again.

Using polymer-supported reagents in catalytic amounts further reduces exposure to and contamination from tin-containing materials.\(^{31,32}\) In such reactions trimethoxysilane can serve as a source of hydrogen atoms to regenerate the spent polymer. When the level of tin residue in these reactions is compared to that in typical, organotin hydride reductions, the difference is striking. Dehalogenation of 1-bromoadamantane by the catalytic, polymer-based procedure yields a tin residue in the product of less than 26 ppm (the detection level), while reduction of the same compound with tri-\(n\)-butyltin hydride gives a product which, after chromatography, has a tin-residue level of 152,000 ppm. The product yields with the polymer-supported reagent are comparable to those from tri-\(n\)-butyltin hydride reactions.

Although the insolubility of polymer-supported reagents allows their simple removal from a reaction mixture, this insolubility creates other problems. The two-phase nature of reactions involving insoluble reagents can require long reaction times and large excesses of reagents and initiators.\(^{33}\) One way to overcome these problems is by using an organotin hydride that is part of a noncross-linked, polystyrene polymer. This polymer is soluble in many organic solvents, does not require long reaction times, or need to be used in excess. Flash chromatography removes the polymer from the reaction mixture and reduces the tin-containing materials in the products to "minute" levels.\(^{33}\)

C. Fluorous Tin Hydrides

Highly fluorinated organotin hydrides, such as compound 2, provide a different approach to solving the problems created by the use of tri-\(n\)-butyltin hydride.\(^{34}\) This new approach depends upon the solubility characteristics of highly fluorinated compounds in relation to typical organic and inorganic ones. Fluorocarbon liquids are extremely poor solvents for most organic and inorganic compounds but are excellent solvents for highly fluorinated compounds such as the tin...
Appendix I

 Compound 2 is comparable in reactivity to tri-\textit{n}-butyltin hydride, and its reaction products can be separated completely from nonfluorous compounds by partitioning the components of the reaction mixture between a fluorocarbon solvent (e.g., perfluoromethylcyclohexane) and a nonfluorocarbon solvent such as dichloromethane. (If water soluble compounds are present, the reaction mixture can be partitioned among three phases: water, dichloromethane, and perfluoromethylcyclohexane.) Following such partitioning, fluororous compounds (and only fluororous compounds) are dissolved in the fluororous phase and nonfluorous, organic compounds in the organic phase. Partitioning thus provides a simple procedure for separating various reaction products; in particular, it places 2 and tin-containing byproducts in the fluororous phase.

$$\text{Bu}_3\text{SnH} > (\text{Me}_3\text{Si})_3\text{SiH} > 3$$

$$\begin{align*}
4 & \equiv \text{H} \quad \text{H} \\
5 & \equiv \text{Me} \\
6 & < \text{H} \quad \text{H} \\
7 & \equiv (\text{C}_6\text{H}_5)_2\text{Si} \text{Si}(\text{C}_6\text{H}_5)_2 > \text{C}_6\text{H}_5\text{SiH}_3 \\
8 & \equiv (\text{C}_6\text{H}_5)_2\text{SiH}_2 \\
9 & \equiv (\text{C}_6\text{H}_5)_3\text{SiH} > \text{Et}_3\text{SiH}
\end{align*}$$

\[\text{Figure 1. Relative hydrogen-atom donating abilities of various organosilanes compared to tri-\textit{n}-butyltin hydride}\]

III. Organosilanes

Difficulties associated with use of tri-\textit{n}-butyltin hydride have prompted chemists to search for alternative, hydrogen-atom sources, ones that avoid the problems associated with organotin compounds. Most attention has focused on organosilanes, compounds that do not have the toxicity associated with organotin reagents. Initially, the outlook was not promising because simple organosilanes are poor hydrogen donors when reacting with alkyl radicals and do not support chain reactions under normal conditions. Innovative ideas, however, have overcome these problems.

A. Tris(trimethylsilyl)silane (3)

One approach to converting organosilanes into useful hydrogen donors begins with determining which structural features in a typical silane might be changed to make it a more effective hydrogen donor. Since the bond dissociation energy (BDE) for the silicon–hydrogen bond in triethylsilane [90 kcal mol\(^{-1}\) (377 kJ mol\(^{-1}\))]\(^{36}\) is 16 kcal mol\(^{-1}\) (67 kJ mol\(^{-1}\)) greater that the BDE for the tin–hydrogen bond in tri-\textit{n}-butyltin hydride [74 kcal mol\(^{-1}\) (310 kJ mol\(^{-1}\))]\(^{4}\) lowering the BDE
of the silicon–hydrogen bond by changing the organosilane structure has the potential for improving its hydrogen donating ability.\textsuperscript{36} Replacing the ethyl groups in triethylsilane with trimethylsilyl groups gives tris(trimethylsilyl)silane (3, Figure 1), a compound with an Si–H bond dissociation energy of only 79 kcal mol\textsuperscript{−1} (331 kJ mol\textsuperscript{−1}).\textsuperscript{5,6,36}

When tris(trimethylsilyl)silane (3) was tested as a substitute for tri-\textit{n}-butyltin hydride, this silane was found to be an excellent, although less reactive, hydrogen donor.\textsuperscript{4,5} In some instances, notably the reaction of primary thionocarbonates, 3 was superior to Bu\textsubscript{3}SnH because reaction occurred at lower temperature and produced "cleaner" reaction mixtures.\textsuperscript{37} In these reactions tri-\textit{n}-butyltin hydride was less effective due to greater reversibility of Bu\textsubscript{3}Sn· addition to the thiocarbonyl group (Scheme 2). Because the S–Si bond [90 kcal mol\textsuperscript{−1} (377 kJ mol\textsuperscript{−1})]\textsuperscript{38} is stronger than the S–Sn bond [65 kcal mol\textsuperscript{−1} (272 kJ mol\textsuperscript{−1})],\textsuperscript{38} reversal of addition of (Me\textsubscript{3}Si)\textsubscript{3}Si· is less likely to occur. Reduced reversibility appears to be the factor responsible for better product yields.\textsuperscript{39,40} Once a silyl radical has added to an \textit{O}-thiocarbonyl group, a difficult forward reaction (i.e., one producing a primary radical) can compete more effectively with reverse reaction to the starting materials. Limiting reversibility is even more effective when reaction is conducted under the low temperature conditions made possible by Et\textsubscript{3}B–O\textsubscript{2} initiation.\textsuperscript{41} Although, as described in the following sections, other silanes can be used in radical reactions, none is as widely so as tris(trimethylsilyl)silane (3).

\begin{center}
\textbf{Scheme 2}
\end{center}

\begin{center}
more reversible addition
\begin{align*}
\text{CH}_3\text{SCOR} + \cdot \text{SnBu}_3 & \rightleftharpoons \text{CH}_3\text{SCOR} + \text{CH}_3\text{SC} = \text{O} + \cdot \text{RSnBu}_3 \\
\text{weaker bond} & \quad \text{SSnBu}_3
\end{align*}
\end{center}

less reversible addition
\begin{center}
\begin{align*}
\text{CH}_3\text{SCOR} + \cdot \text{Si(SiMe}_3)_3 & \rightleftharpoons \text{CH}_3\text{SCOR} + \text{CH}_3\text{SC} = \text{O} + \cdot \text{Si(SiMe}_3)_3 \\
\text{stronger bond} & \quad \text{SS(SiMe}_3)_3
\end{align*}
\end{center}

R· = a carbohydrate radical

B. Phenyl-Substituted and Related Silanes

9,10-Dimethyl-9,10-dihydro-9,10-disilaanthracene (4)\textsuperscript{42} and 9,10-dihydro-9,10-disilaanthracene (5)\textsuperscript{43} are silanes that can serve as hydrogen donors in radical reactions of carbohydrates (Figure 1). Although as indicated in Figure 1 these compounds are among the more effective,
hydrogen-donating silanes; examples of their use are limited. One indication that they may not be generally useful is an investigation that found phenylthionocarboxylate to be the only O-thiocarbonyl compounds for which 5 is an effective donor.\(^{43}\)

\[
\begin{align*}
\begin{array}{c}
\text{C}_{6}\text{H}_{5}\text{OCO} \quad \text{OCOC}_{6}\text{H}_{5} \\
\text{S} \quad \text{S} \quad \text{S} \quad \text{S}
\end{array}
\end{align*}
\]

Tetraphenylsilane (6)\(^{44-46}\) and mono-, di-, and triphenylsilanes (7-9, respectively)\(^{47,48}\) all have been tested as hydrogen donors in radical reactions (Figure 1). Although conditions exist under which each of these compounds functions effectively, each has a significant drawback or special requirement or both. Reactions with the phenylsilanes 7-9 all require nearly an equal molar amount (sometimes more) of initiator added in portions until reaction is complete.\(^{47,48}\) A complication with diphenylsilane (8) is that it can react with free hydroxyl groups to form silyl ethers (eq 8).\(^{47}\) Although tetraphenylsilane (6) has the attractive characteristics of being a crystalline, air-stable compound, its use requires a full equivalent of 6 be added to a reaction mixture for complete conversion to take place because only one of the two hydrogen atoms attached to silicon is available for abstraction.\(^{44-46}\)

\[
\begin{align*}
\begin{array}{c}
\text{C}_{6}\text{H}_{5}\text{OCO} \quad \text{OCOC}_{6}\text{H}_{5} \\
\text{S} \quad \text{S} \quad \text{S} \quad \text{S}
\end{array}
\end{align*}
\]

C. Triethylsilane

1. An Inefficient Hydrogen Donor

Radical reactions with triethylsilane (10) as the hydrogen donor are similar to those in which phenyl-substituted silanes fill this role in that repeated addition of substantial amounts initiator is necessary. The low reactivity of 10 as a hydrogen donor for carbon-centered radicals can be partially compensated for by using triethylsilane (10) as the reaction solvent (eq 9).\(^{48}\) Another indication of the inability of the silicon–hydrogen bond in triethylsilane (10) to function
Effectively as a hydrogen donor is that a significant portion of hydrogen-atom transfer to a carbon-centered radical comes from the ethyl groups attached to silicon.\textsuperscript{49,50} When this information is combined with the rate constant for hydrogen abstraction from triethylsilane by a carbon-centered radical (\(k_H = 3 \times 10^3 \text{M}^{-1}\text{s}^{-1}\) at 50 °C),\textsuperscript{51} it points to 10 not being able to support a chain reaction under normal conditions because hydrogen abstraction is too slow.\textsuperscript{52}

Another disadvantage to reactions with triethylsilane (10) is that 2,2′-azobis(isobutyronitrile) is not an effective initiator. Its failure apparently is due to the azo compound trapping the silyl radical to produce a hydroazyl radical that itself acts as a radical scavenger (Scheme 3).\textsuperscript{53} Peroxides are more efficient initiators in such reactions even though benzoyl peroxide also can trap triethyldisilyl radicals.\textsuperscript{48} A final cautionary note in the use of triethylsilane (10) is that aromatic reaction solvents need to be avoided because triethyldisilyl radicals react with aromatic compounds.\textsuperscript{2,53}

\begin{equation}
\text{Me}_2C\text{OMe} + \text{Et}_3\text{SiH} \rightarrow \text{Me}_2C\text{OEt}_3 \quad (10)
\end{equation}

2. Effect of Polarity-Reversal Catalysis

Triethylsilane (10) becomes a more effective hydrogen donor when reaction is conducted in the presence of a compound that functions as a polarity-reversal catalyst; \(t\)-dodecanethiol is one
such compound.\textsuperscript{2} (Polarity-reversal catalysis is discussed more thoroughly in Chapter 7 of Volume I.) Briefly, this thiol acts as a catalyst by causing a polarity “mismatched” reaction to be replaced with a pair of polarity “matched” reactions (Scheme 4).\textsuperscript{2,54} When this occurs, chain reactions involving hydrogen abstraction from triethylsilane (10) can take place.

Polarity-reversal catalysis has been proposed as an explanation for triethylsilane (10) being able to participate in the Barton-McCombie reaction even though it is a poor hydrogen donor (eq 10).\textsuperscript{2} According to this proposal, reduction of xanthates (and, presumably, other O-thiocarbonyl compounds) by silanes produces COS (eq 11), a compound that then reacts with the silane to give the corresponding silanethiol (eq 12).\textsuperscript{55,56} This thiol then functions as a polarity-reversal catalyst in the deoxygenation process.

### IV. Compounds with Phosphorous–Hydrogen Bonds

The search for less problematic hydrogen donors for use in the Barton-McCombie reaction has led to compounds with phosphorus–hydrogen bonds. These include dialkylphosphine oxides (11), alkyl phosphites (12), hypophosphorous acid (13), and salts of hypophosphorous acid (14) (Figure 2). All of these compounds can function as inexpensive, nontoxic hydrogen donors that
form the chain-carrying radicals needed for reaction and do not produce byproducts difficult to remove.\textsuperscript{3,10,57} An example of a reaction in which hydrogen donation is from a P–H bond is shown in eq 13.\textsuperscript{58}

\[
\begin{array}{cccccc}
O & R & P & R \\
H & R & P & O & H \\
R & P & \text{Ph} & \text{O} & \text{H} \\
11 & 12 & 13 & 14 & 15 \\
R = \text{an alkyl group}
\end{array}
\]

Figure 2. Hydrogen donors with P-H or B-H bonds.

Alkyl phosphites (12) are excellent hydrogen donors, but reactions involving these compounds have the disadvantage of not being able to be initiated by 2,2'-azobis(isobutyronitrile); benzoyl peroxide usually is the initiator.\textsuperscript{3,10} Reactions in which the hydrogen donor is a dialkylphosphine oxide (11), hypophosphorous acid (13), or a salt of hypophosphorous acid (14) can be initiated by AIBN.\textsuperscript{9,57} Because it is difficult to completely remove water from hypophosphorous acid and its salts, these donors are less attractive choices when moisture sensitive compounds are reacting.\textsuperscript{9}

V. Compounds with Boron–Hydrogen Bonds

Phosphine-boranes (15) (Figure 2) are a group of compounds that have the ability to react selectively with xanthates in the presence of compounds containing bromine or chlorine (but not iodine).\textsuperscript{11} For example, cyclohexyl bromide is recovered without change when it is added to the
reaction shown in eq 14; in contrast, tri-\(n\)-butyltin hydride and most other hydrogen donors used in radical reactions readily dehalogenate bromides. If this lack of reactivity between alkyl bromides and phosphine-boranes extends to halogenated carbohydrates, it will make possible their chemoselective deoxygenation without dehalogenation.

\[
\begin{align*}
\text{Scheme 5} \\
\text{RH} & \rightarrow (\text{CH}_3)_2\text{CHOH} \\
& \rightarrow (\text{CH}_3)_2\text{COH} \\
\text{R}^\cdot + (\text{CH}_3)_2\text{COH} & \rightarrow \text{MeS}^\cdot \text{OR} \\
& \rightarrow \text{MeSCSR} \\
17 & \rightarrow \text{18}
\end{align*}
\]

VI. Compounds with Carbon–Hydrogen Bonds

A. 2-Propanol

Few compounds in which a carbon–hydrogen bond must serve as the hydrogen-atom source are reactive enough to function as hydrogen donors in radical reactions of carbohydrates. The reason for this is that when less reactive donors are used, other reactions become competitive. Even compounds with quite reactive C–H bonds are poor hydrogen donors when compared to tri-\(n\)-butyltin hydride or tris(trimethylsilyl)silane. One compound that does have the necessary reactivity, but just barely, is 2-propanol. When reaction of the xanthate 16 is conducted with 2-propanol as the solvent, hydrogen abstraction is in spirited competition with xanthate-dithiocarbonate rearrangement (eq 15). This competition exists because hydrogen abstraction by the carbohydrate radical \(R^\cdot\) is slow enough that addition of \(R^\cdot\) to another molecule of the xanthate 16
has a comparable rate (Scheme 5). The adduct radical formed by this addition fragments to give the dithiocarbonate 18 and a carbohydrate radical (R·).

\[
\text{Me}_3\text{CCH}_2\text{OCS} \quad \text{OBz} \quad \text{OMe} \quad \overset{\text{O}}{\text{R}} \quad \text{C}_6\text{H}_{12} \quad \overset{\text{O}}{\text{OBz}} \quad \text{OBz} \quad (16)
\]

85%

\[\text{R} = (\text{CH}_2)_{10}\text{CH}_3\]

Scheme 6

B. Cyclohexane

The xanthate 19 reacts to form the corresponding deoxy sugar in 85% yield (eq 16). In this reaction cyclohexane functions as the hydrogen donor. Since cyclohexane is not a noticeably better hydrogen donor than 2-propanol, it is initially surprising that no dithiocarbonate is formed from 19 even though (as described in the previous section) dithiocarbonate formation is significant in reaction of the xanthate 16 (eq 15). The structural difference between the starting materials (16 and 19) in these two reactions accounts for their difference in reactivity. Unlike 16, the xanthate 19 has a sulfur atom directly attached to the carbohydrate portion of the molecule. This means that when the carbohydrate radical R· adds to 19, the options available to the adduct radical 20 are either regenerating the starting materials or expelling an unstabilized, primary radical (Scheme 6). Not surprisingly, no dithiocarbonate from primary radical expulsion is observed; therefore, the only operative pathway for the radical 20 is reforming of R· and the xanthate 19. Each regeneration of R· creates a new opportunity for it to abstract a hydrogen atom. With these multiple opportunities even a marginally effective hydrogen donor eventually is able to react with R· to produce the hydrogen-abstraction product RH.

Even though the yield is good, the reaction shown in eq 16 is not an attractive option for deoxy sugar synthesis because it requires reaction of the carbohydrate to replace a C–O bond with
a C–S bond before conducting the Barton-McCombie reaction. The additional steps necessary for this conversion add to the effort required for deoxygenation.

\[
\text{R} + \text{MeO} \quad \text{CMe}_2 \quad \text{MeO} \quad \text{R} = \quad \text{a carbohydrate radical} 
\]

\[
\text{Scheme 7}
\]

C. Silylated Cyclohexadienes

Silylated cyclohexadienes, such as 21, are effective hydrogen donors in Barton-McCombie reactions (eq 17).\(^{61}\) Compound 21 has the advantage of being a solid material that can be easily
stored and handled. Although this compound (21) is an order of magnitude less reactive than (Me₃Si)₃SiH (3), it is able to support chain reactions. The propagation steps in a proposed mechanism for replacement of an O-phenoxythiocarbonyl group with a hydrogen atom supplied by 21 are given in Scheme 7.

VII. Compounds with Sulfur–Hydrogen or Selenium–Hydrogen Bonds

The rate constants for hydrogen abstraction from sulfur–hydrogen and selenium–hydrogen bonds are so rapid \[ k_{\text{SH}} = 1.5 \times 10^8 \text{ M}^{-1}s^{-1} \text{ (from C}_6\text{H}_5\text{SH}) \text{ and } k_{\text{SeH}} = 2.1 \times 10^9 \text{ M}^{-1}s^{-1} \text{ (from C}_6\text{H}_5\text{SeH}) \] that abstraction typically will take place before other radical reactions (e.g., addition, cyclization, and rearrangement) can occur. (Rate constants for hydrogen abstraction from various, hydrogen-atom donors, as well as rate constants for other radical reactions are given in Chapter 8 of Volume I.)

VIII. Summary

Since some tin-containing compounds are toxic and can cause purification problems, procedures have been developed both to minimize the amount of these materials needed for successful reaction and to make their removal easier and more complete. Another solution to toxicity and purification problems created by tin-containing compounds is to replace them with less offensive reagents. An effective replacement is tris(trimethylsilyl)silane. For reactive carbohydrate iodides cyclohexane also can be used.

IX. References

Appendix I