Organosilanes as Radical-Based Reducing Agents in Synthesis

## Chryssostomos Chatgilialoglu

ICoCEA, Consiglio Nazionale delle Ricerche, I-40064 Ozzano Emilia, Bologna, Italy

Free radicals are of considerable importance in the development of organic chemistry, as has been shown in recent years in the synthesis of complicated polyfunctional molecules.[1] The majority of radical reactions of interest to synthetic chemists are chain processes in which radicals are generated by some initiation process, then undergo a series of propagation steps generating fresh radicals, and finally disappear, usually by mutual coupling or disproportionation. While pioneers like D. H. R. Barton[2] have employed them for a long time, most chemists have avoided radical reactions as messy, unpredictable, unpromising, and essentially mysterious. The overall yields of free-radical chain reactions are determined by the efficiency of various propagation steps, and their principles need to be understood if they are to be carried out successfully. Therefore, for the design of new radical reactions, one is faced with the difficult task of considering kinetic and thermodynamic knowledge of each individual step when possible or, alternatively, following the fundamental concepts of free-radical chemistry.

In fine chemical synthesis, the majority of free-radical applications deal with tri-*n*-butyltin hydride. Thus, the most useful types of free-radical reactions, i.e., the reductions of a variety of functional groups[3] (eq 1 and Scheme I) and the formation of carbon–carbon bonds either inter- or intramolecularly[1] (eq 2), have been carried out using Bu$_3$SnH. These general procedures are straightforward and involve at least two- and three-step free-radical chain processes, respectively.

$$RZ + Bu_3SnH \rightarrow RH + Bu_3SnZ \quad (1)$$

$$RZ + H_2C=CHY + Bu_3SnH \rightarrow$$
$$RCH_2CH_2Y + Bu_3SnZ \quad (2)$$
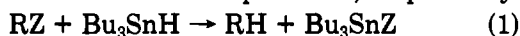
However, there are several problems associated with triorganotin compounds. For example, (i) organotin compounds are toxic and create a disposal problem;[4] (ii) the formation of organotin compounds often makes workup and product isolation difficult;[5,6] (iii) the desired products are frequently contaminated by traces of organotin compounds;[6] (iv) the experimental procedure often requires several hours in order to keep the tri-*n*-butyltin hydride concentration low;[1] (v) GC analyses of mixtures containing organotin compounds show complications; (vi) the purity of commercially available Bu$_3$SnH varies widely; and (vii) the available related kinetic and thermodynamic data, although numerous, are still insufficient relative to the importance of this compound in fine chemical synthesis.[7] In the last

Scheme I
Propagation Steps for the Reduction Reaction[a]
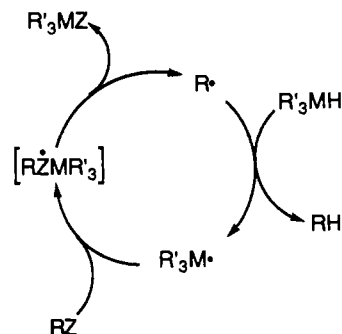
[a] [RŻMR′$_3$] represents a transition state or a reactive intermediate.

decade, other organometallic hydrides such as Bu$_3$GeH[8] and RHgH[9] have been applied as alternatives or complements to tri-*n*-butyltin hydride. However, there is a tendency to avoid the use of these compounds due mainly to the high cost of germanium hydrides and the high toxicity of mercurial derivatives.

It seemed to me a few years ago that an alternative approach based on organosilanes would be more suitable. Trialkylsilanes are poor reducing agents in free-radical chain processes. That is, although trialkylsilyl radicals are among the most reactive species toward various organic functional groups,[10] the corresponding silanes are rather poor H-atom donors toward alkyl radicals[11] and therefore do not support chain reactions under normal conditions. I was persuaded from our own work and the work of others that the incorporation

Chryssostomos Chatgilialoglu was born in 1952 at Nikea, Greece, and studied at the University of Bologna, Italy. He was a postdoctoral fellow at the University of York, England, from 1977 to 1979, and from 1979 until 1982 he worked with K. U. Ingold at the National Research Council of Canada. Since 1983 he has worked for the Consiglio Nazionale delle Richerche, Bologna, where he is currently Principal Research Officer. His research has focused on reactive intermediates in solution, with an emphasis on organosulfur- and organosilicon-centered radicals.

(1) For example, see: (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Pergamon Press: Oxford, 1986. (b) Curran, D. P. *Synthesis* 1988, 417–439, 489–513. (c) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* 1991, 91, 1237–1286. (d) Curran, D. P. In *Comprehensive Organic Synthesis*; Vol. 4; Semmelhack, M. F., Ed.; Pergamon Press: Oxford, 1991; pp 715–831.

(2) Prof. D. H. R. Barton recently gave a series of lessons on "Half a Century of Radicals: The Discovery and Invention of Chemical Reactions" at the Accademia Nazionale dei Lincei (17–20 June 1991, Milan, Italy). The content of these lessons will be published by Cambridge University Press in due course.

(3) For a recent review, see: Neumann, W. P. *Synthesis* 1987, 665–683.

(4) Evans, C. J.; Karpel, S. *Organic Compounds in Modern Technology*; Elsevier: New York, 1985; Chapter 10.

(5) For example, see: (a) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* 1989, 54, 3140–3157. (b) Baldwin, J. E.; Adlington, R. M.; Mitchell, M. B.; Robertson, J. *J. Chem. Soc., Chem. Commun.* 1990, 1574–1575.

(6) Gerigk, U.; Gerlach, M.; Neumann, W. P.; Vieler, R.; Weintritt, V. *Synthesis* 1990, 448–452 and references cited therein.

(7) *Radical Reaction Rates in Liquids*; Landolt-Börnstein, New Series, Group II, Vol. 13; Fisher, H., Ed.; Springer-Verlag: Berlin, 1984.
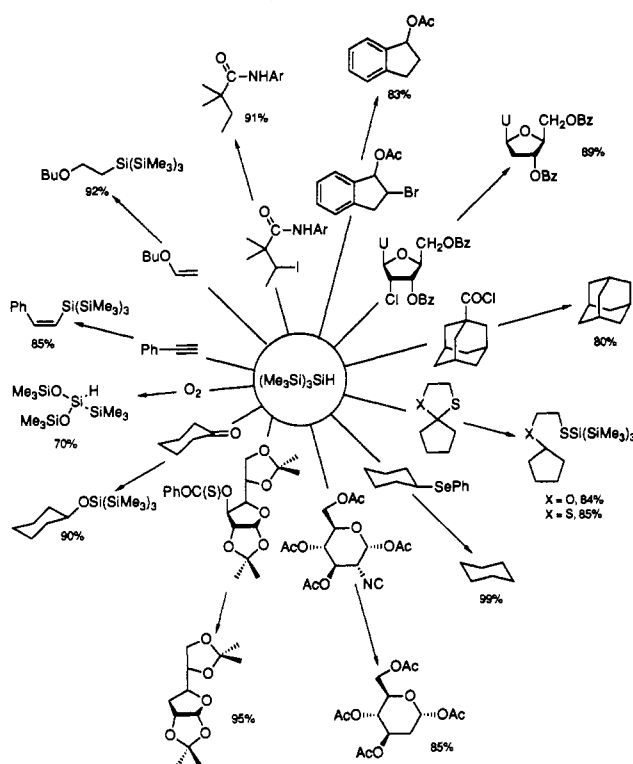
(8) Clark, K. B.; Griller, D. *Organometallics* 1991, 10, 746–750 and references cited therein.

(9) Giese, B. *Angew. Chem., Int. Ed. Engl.* 1985, 24, 553–565 and referenced cited therein.

(10) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* 1982, 104, 5119–5123; 5123–5127; 1983, 105, 3292–3296; *J. Org. Chem.* 1987, 52, 938–940.

(11) Newcomb, M.; Park, S. U. *J. Am. Chem. Soc.* 1986, 108, 4132–4134.

Scheme II

Table I
Absolute Rate Constants at 25 °C for Hydrogen Abstraction by Some Radicals

| | k, M^{-1} s^{-1} | |
radical[a]	(Me$_3$Si)$_3$SiH	Bu$_3$SnH
RCH$_2$•	3.8×10^{5} [b]	2.3×10^{6} [d]
RR'CH•	1.4×10^{5} [b]	1.5×10^{6} [d]
R$_2$R'C•	2.6×10^{5} [b]	1.9×10^{6} [d]
t-BuO•	1.1×10^{8} [c]	2.2×10^{8} [e]

[a] R,R' = alkyl. [b] From ref 29. [c] From ref 30. [d] From ref 31.
[e] From ref 32.

Table II
Absolute Rate Constants at 20 °C for the Reaction of (Me$_3$Si)$_3$Si• Radicals with Some Organic Substrates

substrate	k, M^{-1} s^{-1}
c-C$_6$H$_{11}$I[a]	$>4 \times 10^{9}$
c-C$_6$H$_{11}$OC(S)SMe[b]	1.1×10^{9}
(CH$_3$)$_3$CBr[a]	1.2×10^{8}
C$_{10}$H$_{21}$SePh[b]	9.6×10^{7}
c-C$_6$H$_{11}$NC[b]	4.7×10^{7}
(CH$_3$)$_3$CNO$_2$[b]	1.2×10^{7}
CH$_3$(CH$_2$)$_4$C(CH$_3$)$_2$Cl[a]	4.0×10^{5}

[a] From ref 33. [b] From ref 18.

of suitable thermodynamic driving forces could change significantly the hydrogen donor ability of organosilanes.[12,13] This turned out to be the case. For example, silicon–hydrogen bonds can be weakened dramatically by successive substitution of silyl groups at the Si–H function.[14] The purpose of this Account is to report mainly our recent data concerning organosilanes as radical-based reducing agents. This Account has been divided into two sections. The first will deal with tris(trimethylsilyl)silane and the second with other organosilanes.

Tris(trimethylsilyl)silane (TTMSS)[15]

(Me$_3$Si)$_3$SiH, TTMSS, was first reported by Gilman et al.[16] in 1965 and then was almost totally ignored for the next 20 years. The rationalization of chemical physical data of the silane/silyl radical systems allowed the characterization of the reducing ability of TTMSS.[12] Thus, it was suggested that tris(trimethylsilyl)silane might be a good hydrogen donor and capable of sustaining a radical chain reduction of organic substrates analogous to reaction 1. Scheme II shows that the reduction of a variety of organic functional groups by TTMSS are very efficient. Yields are good for most of the precursors, i.e., iodides,[17–19] bromides,[17–19] chlo-

rides,[18,19] secondary selenides[18,19] and thiono esters,[18–21] isocyanides,[18,19] acid chlorides,[22] and sulfides having a heteroatom in a β-position.[23]   The procedures are straightforward, i.e., reaction of each derivative with TTMSS at ca. 80 °C in toluene or benzene in the presence of AIBN (azobisisobutyronitrile) as radical initiator gives the desired products after a short time (0.5–2 h). TTMSS is preferable to Bu$_3$SnH, since its use avoids the need for a special workup procedure; the reaction mixtures are simply concentrated and directly flash chromatographed.[19] Furthermore, evidence shows that TTMSS and its silicon-containing byproducts are less toxic than the corresponding tin compounds.[21]

The reduction of isocyanides and acid chlorides warrants further comments. The reduction yields of tertiary, secondary, and primary isocyanides by Bu$_3$SnH are dependent on the temperature,[24] i.e., the yields are good in boiling toluene or benzene for secondary and tertiary isocyanides, but primary isocyanides can be reduced in acceptable yields only in refluxing xylene. When Bu$_3$SnH is replaced by TTMSS, the reduction of isocyanides becomes more facile; the reactivity is less dependent on the nature of the alkyl substituent at 75 °C.[18] Bu$_3$SnH reacts spontaneously at ambient temperature with acid chlorides, RC(O)Cl, to form Bu$_3$SnCl, RCHO, RC(O)OCH$_2$R, and a number of minor products.[25] Ingold and co-workers[26] have shown, in contrast

(12) (a) Chatgilialoglu, C. In *Paramagnetic Organometallic Species in Activation/Selectivity, Catalysis*; Chanon, M., Julliard, M., Poite, J. C., Eds.; Kluwer: Dordrecht, 1989; pp 119–129. (b) Chatgilialoglu, C. In *Free Radicals in Synthesis and Biology*; Minisci, F., Ed.; Kluwer: Dordrecht, 1989; pp 115–123.

(13) Walsh, R. *Acc. Chem. Res.* 1981, *14*, 246–252.

(14) Kanabus-Kaminska, J. M.; Hawari, J. A.; Griller, D.; Chatgilialoglu, C. *J. Am. Chem. Soc.* 1987, *109*, 5267–5268.

(15) (a) Reagent of the Year 1990 (Fluka prize). (b) Tris(trimethylsilyl)silane is commercially available (Fluka or Aldrich).

(16) Gilman, H.; Atwell, W. H.; Sen, P. K.; Smith, C. L. *J. Organomet. Chem.* 1965, *4*, 163–167.

(17) Chatgilialoglu, C.; Griller, D.; Lesage, M. *J. Org. Chem.* 1988, *53*, 3641–3642. Chatgilialoglu, C.; Griller, D. In *Organic Free Radicals*; Fischer, H., Heimgartned, H., Eds.; Springer-Verlag: Berlin, 1988; pp 25–26 (Proceedings of the Fifth International Symposium on Organic Free Radicals).

(18) Ballestri, M.; Chatgilialoglu, C.; Clark, K. B.; Griller, D.; Giese, B.; Kopping, B. *J. Org. Chem.* 1991, *56*, 678–683.

(19) Barbaro, G.; Ballestri, M.; Battaglia, A.; Giorgianni, P.; Chatgilialoglu, C. *Tetrahedron*, submitted.

(20) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. Cs. *Tetrahedron Lett.* 1990, *31*, 4681–4684.

(21) Schummer, D.; Höfle, G. *Synlett* 1990, 705–706.

(22) Ballestri, M.; Chatgilialoglu, C.; Cardi, N.; Sommazzi, A. *Tetrahedron Lett.*, in press.

(23) (a) For 1,3-dithiolane and 1,3-dithiane derivatives, see: Arya, P.; Samson, C.; Lesage, M.; Griller, D. *J. Org. Chem.* 1990, *55*, 6248–6250. (b) For 1,3-oxothiolane and 1,3-thiazolidine derivatives, see: Arya, P.; Lesage, M; Wayner, D. D. M. *Tetrahedron Lett.* 1991, *32*, 2853–2856.

(24) Barton, D. H. R.; Bringmann, G.; Lamotte, G.; Hay Motherwell, R. S.; Motherwell, W. B.; *Tetrahedron Lett.* 1979, 2291–2294. Barton, D. H. R.; Bringmann, G.; Lamotte, G.; Motherwell, W. B.; Hay Motherwell, R. S.; Porter, A. E. A. *J. Chem. Soc., Perkin Trans. 1* 1980, 2657–2664. Barton, D. H. R.; Bringmann, G.; Motherwell, W. B. *Synthesis* 1980, 68–70.

Scheme III
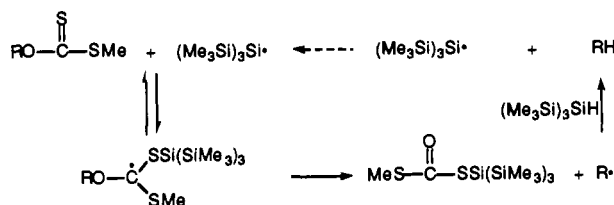
to early conclusions,[25] that free radicals are not involved in those spontaneous reactions.[27] TTMSS does not react spontaneously with acid chlorides at ordinary temperatures.[22] However, free-radical-initiated reaction of TTMSS with tertiary and secondary acid chlorides at 80 °C gives the corresponding decarbonylation product in good yield[22] (i.e., C(O)Cl is replaced by H). This procedure could be an alternative to the Barton reaction for the free-radical decarboxylation of carboxylic acids via the acyl derivatives of *N*-hydroxy-2-thiopyridone.[28]

The above reductions consist of chain processes with either two or three steps (see Scheme I). The key step in these reactions is H-atom abstraction from silane by the carbon-centered radicals. Rate constants (at 25 °C) for the reaction of primary, secondary, and tertiary alkyl radicals as well as *tert*-butoxyl radical with tris(trimethylsilyl)silane are reported in Table I together with the analogous parameters for tri-*n*-butyltin hydride. Activation parameters are available for both substrates.[29,31] The silane is a slightly less reactive hydrogen donor than the stannane, presumably because the Si–H bond is 5 kcal mol^{-1} stronger than the Sn–H bond: TTMSS has a Si–H bond strength of 79 kcal mol^{-1}, Bu$_3$SnH a Sn–H bond strength of 74 kcal mol^{-1}.[14]

The second propagation step is the reaction of (Me$_3$Si)$_3$Si· radicals with the organic substrates. The efficiency of these reactions is further supported by the available kinetic data (see Table II for some representative rate constants). The reactivities decrease in the order iodide > xanthate > bromide ≈ selenide > isocyanide ≈ nitro > sulfide ≈ chloride ≈ acyl chloride. The rate constants with halides also depend to a limited extent on the kind of substituent, i.e., the rates decrease along the series R = benzyl > tertiary alkyl > secondary alkyl > primary alkyl > phenyl.[33] Furthermore, Table II reveals that there is an enormous spread in the reactivities (rate constants varied by at least 4 orders of magnitude) and, consequently, the chemoselectivity in

Table III
Absolute Rate Constants at 20 °C for the Reaction of (Me$_3$Si)$_3$Si· Radicals with Some Ketones and Alkenes

substrate	k, M^{-1} s^{-1}
duroquinone[a]	1.0 × 10^8
fluorenone[a]	3.8 × 10^7
acetone[a]	8.0 × 10^4
styrene[b]	5.9 × 10^7
acrylonitrile[b]	6.3 × 10^7
ethyl acrylate[b]	9.7 × 10^7

[a] From ref 39. [b] From ref 18.

Scheme IV
Propagation Steps for the Hydrosilylation Reaction[a]
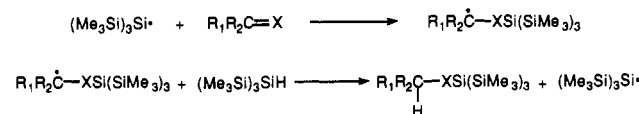
[a] X is an O atom or CR$_3$R$_4$.

polyfunctional molecules can be predicted. It is worth mentioning that the group removal for some of these substrates, i.e., xanthates, isocyanides, and selenides, passes through an intermediate (see Scheme I). Evidence that the addition of (Me$_3$Si)$_3$Si· radicals to xanthates and selenides is reversible has also been obtained.[18] For example, the mechanism for the reduction of xanthates is outlined in Scheme III.[34]

TTMSS is not able to reduce tertiary nitroalkanes to the corresponding hydrocarbons, a transformation that can be achieved with tin hydride.[3] Electron spin resonance experiments and product studies have shown that this "anomalous" behavior is due to the fact that the nitroxide adducts formed by addition of tris(trimethylsilyl)silyl radical to the nitro compounds, i.e., RN(O·)OSi(SiMe$_3$)$_3$, fragment preferentially at the nitrogen–oxygen bond rather than at the carbon–nitrogen bond as in the analogous tin adducts.[37]

TTMSS can be also used as a reagent for driving reactions through a radical mechanism with sodium borohydride, the reductant that is consumed.[38] That is, the bromide or iodide is treated with an excess of NaBH$_4$ and a small amount of TTMSS or its corresponding halide, under photochemical initiation conditions. The cycle is given in eqs 3 and 4.

$$(Me_3Si)_3SiX \xrightarrow{NaBH_4} (Me_3Si)_3SiH \qquad (3)$$

$$RX + (Me_3Si)_3SiH \rightarrow RH + (Me_3Si)_3SiX \qquad (4)$$

Tris(trimethylsilyl)silyl deuteride has been employed similarly to the hydride with a variety of substrates.[19] For example, treatment of the nucleoside 1 with

(25) For reviews, see: Kupchik, E. J. In *Organotin Compounds*; Sawyer, A. K., Ed.; Marcel Dekker: New York, 1971; Vol. 1, pp 28–33. Kuivila, H. G. *Synthesis* 1970, 499–509.

(26) Lusztyk, J.; Lusztyk, E.; Maillard, B.; Lunazzi, L.; Ingold, K. U. *J. Am. Chem. Soc.* 1983, *105*, 4475–4477. Lusztyk, J.; Lusztyk, E.; Maillard, B.; Ingold, K. U. *J. Am. Chem. Soc.* 1984, *106*, 2923–2931.

(27) When free radicals are deliberately generated in the system, the nature of the products may be changed. In fact, the reproducibility of the product distribution for the radical-initiated reactions has been relatively poor, the reason probably being that the free-radical process and the spontaneous reaction occur together.[26]

(28) Barton, D. H. R. *Aldrichimia Acta* 1990, *23*, 3–10 and references cited therein.

(29) Chatgilialoglu, C.; Dickhaut, J.; Giese, B. *J. Org. Chem.* 1991, *56*, 6399–6403.

(30) Chatgilialoglu, C.; Rossini, S. *Bull. Soc. Chim. Fr.* 1988, 298–300.

(31) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* 1981, *103*, 7739–7742.

(32) Chatgilialoglu, C.; Ingold, K. U.; Lusztyk, J.; Nazran, A. S.; Scaiano, J. C. *Organometallics* 1983, *2*, 1332–1335.
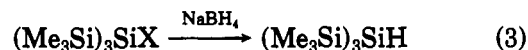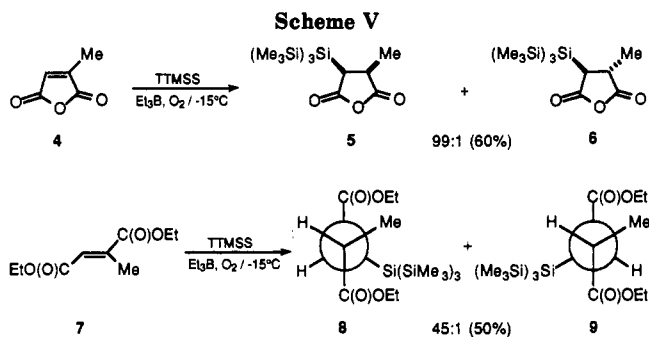
(33) Chatgilialoglu, C.; Griller, D.; Lesage, M. *J. Org. Chem.* 1989, *54*, 2492–2494.

(34) The radical deoxygenation of alcohols (Barton and McCombie reaction[35]) has been used widely in natural product synthesis. The reaction consists of transforming secondary alcohols into suitable thiocarbonyl derivatives followed by reaction with Bu$_3$SnH using AIBN as initiator. The mechanism of this reaction has been studied intensively,[36a] and only the recent ^{119}Sn NMR work would seem to settle the mechanism once and for all.[36b]

(35) For reviews, see: Barton, D. H. R.; Motherwell, W. B. *Pure Appl. Chem.* 1981, *53*, 15–31. Hartwig, W. *Tetrahedron* 1983, *39*, 2609–2645.

(36) (a) For example, see: Minisci, F. In *Sulfur-Centered Reactive Intermediates in Chemistry and Biology*; Chatgilialoglu, C., Asmus, K.-D., Eds.; Plenum: New York, 1990; pp 303–317. (b) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron Lett.* 1990, *31*, 3991–3994.

(37) Ballestri, M.; Chatgilialoglu, C.; Lucarini, M.; Pedulli, G. F. *J. Org. Chem.* 1992, *57*, 948–952.

(38) Lesage, M.; Chatgilialoglu, C.; Griller, D. *Tetrahedron Lett.* 1989, *30*, 2733–2734.

Scheme V

Scheme VI

Scheme VII
Propagation Steps for the C–C Bond Formation

$(Me_3Si)_3SiD$ under normal conditions gave a ratio of ribo/arabino (2/3) deuterium substitution of 80:20, providing evidence that the bulky silane approaches the nucleoside radical from the less hindered face (eq 5). Therefore, it is expected that $(Me_3Si)_3SiD$ will find uses in synthetic strategy when deuterium incorporation is needed and in mechanistic studies involving free radicals.

$$(5)$$
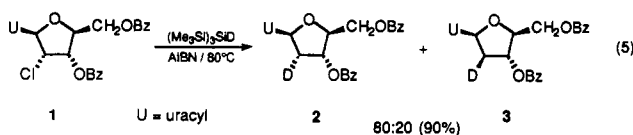
The trends in reactivity for addition of $(Me_3Si)_3Si^•$ radical to the carbonyl function are those expected on thermodynamic grounds, the rate constants decreasing in the series quinones > diaryl ketones > dialkyl ketones (see Table III).[39] However, the most striking feature of these results is the relatively high rate constant of addition of $(Me_3Si)_3Si^•$ radical to dialkyl ketones, $\sim10^5$ M^{-1} s^{-1}. Thus, TTMSS is found to be an effective hydrosilylating agent for dialkyl ketones,[39,40] operating through a free-radical mechanism as shown in Scheme IV. The reduction of ketones can also be highly stereoselective, depending upon the choice of substrate. For example, the reaction of TTMSS with 4-*tert*-butylcyclohexanone yielded the expected hydrosilylation products in a trans:cis ratio of 98:2 at 20 °C.[40] The reduction of ketones by the tin method is reported to be a rather sluggish process.[3]
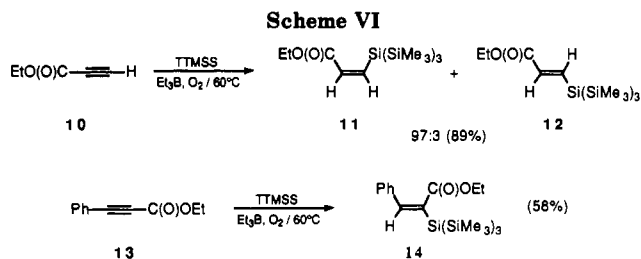
Tris(trimethylsilyl)silane adds across the double bond of a variety of mono-, di- and trisubstituted olefins under free-radical conditions in good yields.[41] The reaction, which proceeds via the mechanism shown in Scheme IV, is highly regioselective (anti-Markovnikov). Rate constants for the addition of $(Me_3Si)_3Si^•$ radicals to some activated alkenes are reported in Table III. The factors controlling stereoselectivity in radical reactions are of current interest.[42] The bulky TTMSS is an attractive substrate for such studies. Two examples show the potentialities of TTMSS in stereoselective synthesis. The hydrosilylations of citraconic anhydride (4) and diethyl mesaconate (7) are shown in Scheme V.[41] In the former, the silyl radical adds regiospecif-

ically to 4 at the less crowded end of the double bond to form a carbon-centered radical, which abstracts a H atom from the less hindered face to give ultimately the thermodynamically less stable cis product 5. In the latter, the addition of TTMSS to prochiral alkene 7 gave both diastereoisomers with preferential formation of the threo isomer 8. This suggests that the intermediate carbon-centered radical adopts a preferred conformation due to the allylic strain effect,[42c] in which the tris(trimethylsilyl)silyl moiety shields one face of the prochiral radical center, favoring hydrogen transfer to the opposite face, and therefore the threo product is predominantly formed.

TTMSS also adds across the triple bond of a variety of mono- and disubstituted acetylenes to give olefins in good yields[41] via a radical-chain mechanism similar to the one described for the hydrosilylation of alkenes (see Scheme IV). The reaction, which is highly regioselective (anti-Markovnikov), can also show high cis or trans stereoselectivity, depending on the nature of the substituent at the acetylenic moiety. For example, the hydrosilylation of ethyl propiolate and ethyl phenylpropiolate are shown in Scheme VI.[41] In both cases the silyl radical adds regiospecifically to form vinyl type radicals which abstract a hydrogen either syn or anti (or both) to the silyl group.[43]

It is worth mentioning that addition of the $(Me_3Si)_3Si^•$ radical to alkenes and alkynes is not reversible at ordinary temperatures,[44] whereas $Bu_3Sn^•$ radical adds in a reversible manner to these substrates. This different behavior could be of great importance in synthetic strategy as the two reagents can complement each other (see below).

It has been mentioned briefly in the introduction that the free-radical construction of C–C bonds either inter- or intramolecularly using Bu_3SnH as mediator (eq 2) is of great importance in the chemical synthesis.[1] The propagation steps for these reactions are shown in Scheme VII. For a successful outcome, it is important

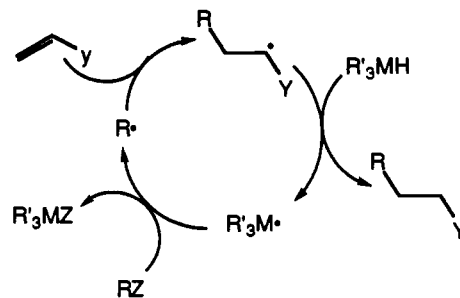(39) Alberti, A.; Chatgilialoglu, C. *Tetrahedron* **1990**, *46*, 3963–3972.

(40) Kulicke, K. J.; Giese, B. *Synlett* **1990**, 91–92.

(41) Kopping, B.; Chatgilialoglu, C.; Zehnder, M.; Giese, B. *J. Org. Chem.*, in press.

(42) (a) For a review on the stereoselectivity of intermolecular free-radical reactions, see: Giese, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 969–980. (b) For an Account on the stereochemistry of intramolecular free-radical cyclization reactions, see: RajanBabu, T. V. *Acc. Chem. Res.* **1991**, *24*, 139–145. (c) For an Account on acyclic stereochemical control in free-radical reactions, see: Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296–304.
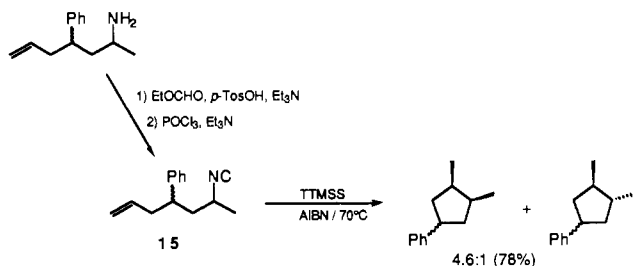
(43) It is worth mentioning that the factors which control the stereochemistry of vinyl type radicals are far from understood.[42a]

(44) Based on competitive kinetic studies: Chatgilialoglu, C. Unpublished observations.

Scheme VIII

$(Me_3Si)_3SiH$	93%	2.0%	4.1%
Bu_3SnH	83%	1.2%	15.0%

Scheme IX

4.6:1 (78%)
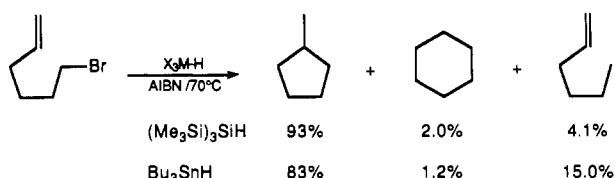
(i) that the $R'_3M^{\bullet}$ radical react faster with RZ (the precursor of radical $R^{\bullet}$) than with the alkene and (ii) that the alkyl radical react faster with alkene (to form the adduct radical) than with the hydrogen donor. For a detailed analysis of these reactions and the associated problems, the reader is referred to Giese's book.[1a] The facts that TTMSS is ca. 10 times less reactive than Bu_3SnH toward alkyl radicals (cf. Table I) and that a number of absolute rate constants for the reaction of $(Me_3Si)_3Si^{\bullet}$ radical with organic substrates are known (cf. Tables II and III) imply that the silane is a better mediator than tin hydride for C–C bond formation, although in some instances the two reagents could complement each other. A few simple examples which show the potentialities of TTMSS as mediator for the construction of C–C bonds are shown herein. The reduction of 5-hexenyl bromide is reported in Scheme VIII for both TTMSS and Bu_3SnH under the same conditions. The data indicate that the ratios of cyclized/uncyclized products are 24:1 and 6:1 for silane and stannane, respectively.[45]
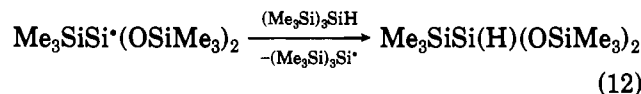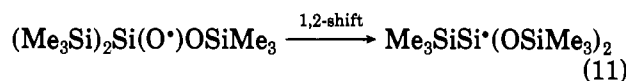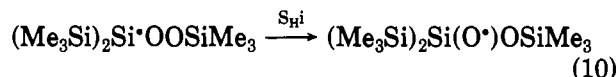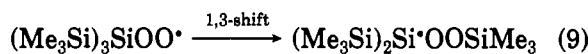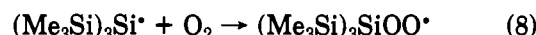
The reaction of cyclohexyl iodide, TTMSS, and methyl acrylate afforded the desired product in 85% yield, which is comparable with the yield obtained in the tin method[45] (eq 6). Similarly the reaction of cyclohexyl isocyanide, TTMSS, and acrylonitrile afforded the expected adduct in 54% yield[18,46] (eq 7). The C–C

85% (6)

54% (7)
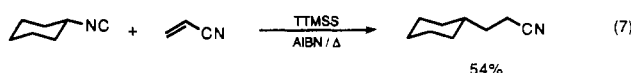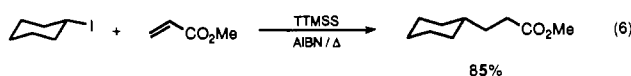
bond formation does not take place when alkyl isocyanides are used together with Bu_3SnH in the presence of alkenes.[1] We should also emphasize that up to now no method has existed in which primary alkylamines could be used as alkyl radical precursors in the formation of C–C bonds.[1] When this procedure was used for the reaction of secondary isocyanide **15**, the desired cyclization products were isolated after workup in 78%

yield as a 4.6:1 mixture of cis and trans isomers (Scheme IX).[46] TTMSS has also been used as mediator for free-radical macrocyclization. Hitchcock and Pattenden[47] have shown that TTMSS mediated a novel 14-*endo-trig* macrocyclization as a key step feature in a concise synthesis of optically acitve (–)-zearalenone. These authors pointed out that the tin method gave a comparable yield although it was not always possible to remove small traces of tin residues from the final product.

The autoxidation of TTMSS deserves comment. This silane reacts spontaneously with molecular oxygen, affording a 70% yield of a 1:1 adduct of the two reagents (see Scheme II).[48] For reduction processes of long chain length, traces of molecular oxygen serve to initiate reactions, and therefore no additional radical initiator is needed. Mechanistic studies based on labeling experiments indicate that the unexpected "intramolecular" free-radical chain process shown in eqs 8–12 is probably responsible for such behavior.[48] Steps 9–11 were unknown reactions. These steps are strongly exothermic, and it is believed that the strength of the silicon–oxygen bond is the driving force in these novel rearrangements.

$$(Me_3Si)_3Si^{\bullet} + O_2 \rightarrow (Me_3Si)_3SiOO^{\bullet} \quad (8)$$

$$(Me_3Si)_3SiOO^{\bullet} \xrightarrow{1,3\text{-shift}} (Me_3Si)_2Si^{\bullet}OOSiMe_3 \quad (9)$$

$$(Me_3Si)_2Si^{\bullet}OOSiMe_3 \xrightarrow{S_Hi} (Me_3Si)_2Si(O^{\bullet})OSiMe_3 \quad (10)$$

$$(Me_3Si)_2Si(O^{\bullet})OSiMe_3 \xrightarrow{1,2\text{-shift}} Me_3SiSi^{\bullet}(OSiMe_3)_2 \quad (11)$$

$$Me_3SiSi^{\bullet}(OSiMe_3)_2 \xrightarrow[-(Me_3Si)_3Si^{\bullet}]{(Me_3Si)_3SiH} Me_3SiSi(H)(OSiMe_3)_2 \quad (12)$$

Other Organosilanes

One of the most important considerations in selecting the conditions for radical-based chain processes similar to those mentioned above concerns the relative hydrogen-donor abilities of the hydrides. From the above discussion, the reader should by now have realized that rapidity of hydrogen transfer is not necessarily a virtue. If the synthetic strategy requires that another radical reaction take place prior to the H-transfer step, then "slowness" may be a desirable characteristic, given the limitation that the reactions must proceed with reasonable chain length to give decent yields. Because organotin hydrides were for many years the only radical-based reducing agents, a few practical methodologies have been developed to compensate for the lack of compounds with different hydrogen-donor abilities. For example, the syringe-pump method or $Bu_3SnX/NaBH_4$ systems have been used to keep tin hydride at low concentration during the reaction time.[1] However, all these methods have their weaknesses. Following the success of TTMSS, it was thought that other organo-

(45) Giese, B.; Kopping, B.; Chatgilialoglu, C. *Tetrahedron Lett.* **1989**, *30*, 681–684.

(46) Chatgilialoglu, C.; Giese, B.; Kopping, B. *Tetrahedron Lett.* **1990**, *31*, 6013–6016.

(47) Hitchcock, S. A.; Pattenden, G. *Tetrahedron Lett.* **1990**, *31*, 3641–3644.

(48) (a) Chatgilialoglu, C.; Guarini, A.; Guerrini, A.; Seconi, G. *J. Org. Chem.*, in press. (b) Chatgilialoglu, C.; Seconi, G. In *Organic Free Radicals*; Fischer, H., Heimgartned, H., Eds.; Springer-Verlag: Berlin, 1988; p 27 (Proceedings of the Fifth International Symposium on Organic Free Radicals).

Organosilanes as Radical-Based Reducing Agents

Acc. Chem. Res., Vol. 25, No. 4, 1992 **193**

**Table IV.
Reduction of Some Organic Compounds by Organosilanes
with Low Hydrogen-Donating Abilities**

compd	yield,[a] %	
	$(Me_3Si)_2Si(H)Me$[b]	$(MeS)_3SiH$[c]
$CH_3(CH_2)_{15}I$	95	97
$CH_3(CH_2)_{15}Br$	93	94
(structure: bicyclic ketone with Cl)	94	65
(structure) NC	90	96
(structure) OC(S)SMe	96	97
(structure) SePh	98	98

[a] By GC analysis. [b] From ref 49. [c] From refs 52 and 53.

silanes might be capable of sustaining analogous radical chain reactions. The expectation has turned out to be correct.

As the main scope is to modulate the strength of the Si–H bond, the rationalization of chemical physical data of the silane/silyl radical system can provide further new ideas on the reducing abilities of organosilanes. On the basis of a proposed correlation[49] between bond dissociation energies of Me_3SiH, $Me_3SiSi(H)Me_2$,[50] and $(Me_3Si)_3SiH$ and their corresponding Si–H stretching frequencies, a bond strength of 83 kcal mol^{-1} is predicted for the trisilane $(Me_3Si)_2Si(H)Me$. This compound appears to offer an alternative to other hydrides in radical chain reaction in which formation of the desired product is aided by a *slower* hydrogen transfer. In fact, as a hydrogen donor to primary alkyl radicals, $(Me_3Si)_2Si(H)Me$ shows ca. 8–16% of the reactivity of $(Me_3Si)_3SiH$ in the temperature range 25–120 °C.[49] This trisilane reduces a variety of organic functionalities at ordinary temperatures and in the presence of small amounts of radical initiators.[51] Some representative examples are reported in Table IV. Yields are comparable with those obtained in the TTMSS method. The major advantage of this method is that it is easier to purify and isolate the products.

Tris(alkylthio)silanes, $(RS)_3SiH$, are another class of new radical-based reducing agents.[52,53] The choice of an alkylthio group as the substituent on silicon was guided not only by the low electronegativity of sulfur but also by the possibility that some combination of 3p–3p overlap, (d–3p)π-type bonding, and hyperconjugation could be effective in the corresponding silyl radical.[12] The bond dissociation energy of the Si–H bond in $(MeS)_3SiH$ is found to be 82.5 kcal mol^{-1}, i.e., 3.5 kcal mol^{-1} higher than in TTMSS. $(MeS)_3SiH$ and $(i\text{-}PrS)_3SiH$ are effective reducing agents for a variety of organic functionalities,[53] in general, bromides, iodides, secondary selenides and thiono esters, isocyanides, and

chlorides with stabilizing substituents in an α-position (Table IV). These silanes can also be used as hydrosilylating agents for alkenes having electron-donating substituents.[53] The corresponding silyl radicals are believed to be electrophilic in character, and consequently, a different chemoselectivity is expected with respect to the other organometallic group 14 centered radicals.

The Ph_3SiH has been used sporadically as a reducing agent.[54] Si–H bond weakening by phenyl substitution is about 2 kcal mol^{-1}, in contrast to the 10 kcal mol^{-1} observed for a phenyl-substituted C–H bond.[13] The silicon–hydrogen bond in Ph_3SiH is ca. 84 kcal mol^{-1} and is 7 kcal mol^{-1} less than that in Et_3SiH.[55] Kinetic data on the reaction of alkyl radicals with phenyl-substituted silanes, i.e., $PhMe_2SiH$,[55] Ph_2MeSiH,[55] and Ph_3SiH,[11,55] indicated that these compounds are impractical agents (under *normal* conditions) because reaction chain lengths would be unacceptably small. It has recently been found that the deoxygenation of secondary alcohols via thiono esters (cf. Scheme III) can be accomplished using Ph_2SiH_2[20,56] or $PhSiH_3$[56] as reducing agents.[57] The fact that large quantities of initiator (1–2 equiv) are needed confirms that these reactions have very short chain lengths. A further handicap is that all of the phenyl-substituted silyl radicals add readily to aromatic rings (i.e., their precursors), and to aromatic rings in solvents (benzene or toluene are the most commonly used in synthesis via radicals) with rate constants of ca. 10^6 M^{-1} s^{-1}.[32] Consequently, only substrates that react with silyl radicals in the proximity of diffusion control can be employed.

It is well-known that thiols are rather good hydrogen donors toward carbon-centered radicals even though the S–H bond strength in alkanethiols is about 89 kcal mol^{-1}.[58,59] It is believed that polar effects in the transition state play an important role in these reactions. It has recently been demonstrated that trialkylsilanes can reduce alkyl halides and xanthates to the corresponding hydrocarbons in the presence of alkanethiols, which act as polarity reversal catalysts for hydrogen transfer from the silane to the alkyl radical (eqs 13 and 14).[60] This approach has also been applied for the hydrosilylation of chiral alkenes by Ph_2SiH_2.[61] How-

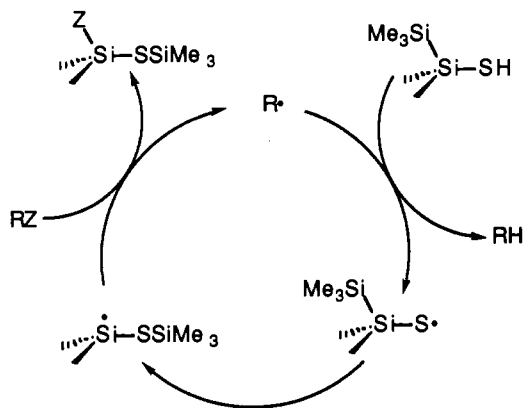(49) Chatgilialoglu, C.; Guerrini, A.; Lucarini, M. *J. Org. Chem.*, in press.

(50) As a hydrogen donor to primary alkyl radicals, the pentamethyldisilane has ca. 2% of TTMSS reactivity at ambient temperatures. See: Lusztyk, J.; Maillard, B.; Ingold, K. U. *J. Org. Chem.* **1986**, *51*, 2457–2460.

(51) Chatgilialoglu, C.; Guerrini, A.; Seconi, G. Manuscript in preparation.

(52) Chatgilialoglu, C.; Guerrini, A.; Seconi, G. *Synlett* **1990**, 219–220.

(53) Chatgilialoglu, C.; Guerra, M.; Guerrini, A.; Seconi, G.; Clark, K. B.; Griller, D.; Kanabus-Kaminska, J. M.; Martinho Simões, J. A. *J. Org. Chem.*, in press.

(54) See, for example: Nagai, Y.; Yamazaki, K.; Shiojioma, I. *J. Organomet. Chem.* **1967**, *9*, P21–P24. Nagai, Y.; Matsumoto, H.; Hayashi, M.; Tajima, E.; Watanabe, H. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3113–3116. Sakurai, H.; Yamagota, M.; Murakami, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2658–2659. Sano, H.; Ogata, M.; Migita, T. *Chem. Lett.* **1986**, 77–80.

(55) Lesage, M.; Martinho Simões, J. A.; Griller, D. *J. Org. Chem.* **1990**, *55*, 5413–5414.

(56) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. Cs. *Synlett* **1991**, 435–438.

(57) Also see: Barton, D. H. R.; Jaszberenyi, J. Cs.; Tachdjian, C. *Tetrahedron Lett.* **1991**, *32*, 2703–2706. Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. Cs. *Tetrahedron Lett.* **1991**, *32*, 2569–2572.

(58) Newcomb, M.; Glenn, A. G.; Manek, M. B. *J. Org. Chem.* **1989**, *54*, 4603–4606.

(59) The rate constant for the reaction of primary alkyl radicals with t-BuSH is 8.0 × 10^6 M^{-1} s^{-1} at 25 °C.[58]

(60) Cole, S. J.; Kirwan, J. N.; Roberts, B. P.; Willis, C. R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 103–112. Kirwan, J. N.; Roberts, B. P.; Willis, C. R. *Tetrahedron Lett.* **1990**, *31*, 5093–5096. Allen, R. P.; Roberts, B. P.; Willis, C. R. *J. Chem. Soc., Chem. Commun.* **1989**, 1387–1388.

(61) Smadja, W.; Zahouily, M.; Journet, M.; Malacria, M. *Tetrahedron Lett.* **1991**, *32*, 3683–3686.

Scheme X
Propagation Steps for Silanethiol-Mediated Reduction

ever, there are several limitations and inconveniences in this otherwise attractive procedure:[60] structural restriction on starting material; impracticability of C–C bond formation; unsuitability of arenes as solvents; the need for special workup of the reaction mixture; the choice of unusual initiators; much lower yields with respect to TTMSS or the tin method.

$$R^\bullet + XSH \rightarrow RH + XS^\bullet \tag{13}$$

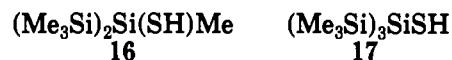$$XS^\bullet + R'_3SiH \rightarrow XSH + R'_3Si^\bullet \tag{14}$$
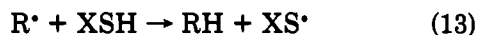
In some cases, *very fast* hydrogen donors could be of great utility; for instance, when a straightforward reduction is needed prior to any possible molecular rearrangement or, from a mechanistic point of view, when the tin method is too slow to calibrate fast "clock" substrates.[65] The facts that alkanethiols are good H-atom donors toward alkyl radicals[58] and that silyl radicals are among the most reactive known species for abstraction and addition reactions[10] suggest that any class of compounds with an appropriate molecular arrangement which allows the transformation of a thiyl to a silyl radical via a fast intramolecular rearrangement will potentially be a good radical-based reducing agent. The silanethiols 16[62] and 17[63] are found to have this property. The reductions of organic bromides, iodides, and isocyanides by tris(trimethylsilyl)silanethiol (17)

are extremely efficient processes, as the reactions are completed in 5 min, quantitatively.[63] The reaction mechanism is outlined in Scheme X.

$$\begin{array}{cc} (Me_3Si)_2Si(SH)Me & (Me_3Si)_3SiSH \\ \mathbf{16} & \mathbf{17} \end{array}$$

Concluding Remarks

Free radicals are of considerable importance in the development of organic chemistry, and the majority of their applications in synthesis have been accomplished by means of Bu_3SnH. However, there are several problems associated with triorganotin reagents. This Account indicates that silanes clearly merit much more attention than they have previously received in free-radical chemistry either as substitutes for Bu_3SnH or as reagents in novel reactions.[64] Thus, $(Me_3Si)_3SiH$ rivals Bu_3SnH in efficiency and is a superior reagent from ecological and practical perspectives. A disadvantage of TTMSS (commercially available)[15] is its cost. It is hoped that increased use will lead to reduction in price.

The Si–H bond strength in organosilanes can be modulated by the substituents, and therefore a wide range of hydrogen-donor abilities is possible. Currently, the rate constants for hydrogen abstraction from silanes by alkyl radicals cover a range of ca. 4 orders of magnitude. However, much remains to be done on the reactivity of silanes toward free radicals.

Another aspect which has received little attention is the selective use of organosilanes. The reactivity of silyl radicals could be modulated by appropriate substituents, either electrophilic or nucleophilic in character and thus affecting the outcome of a given reaction.

(62) Daroszewski, J.; Lusztyk, J.; Degueil, M.; Navarro, C.; Maillard, B. *J. Chem. Soc., Chem. Commun.* **1991**, 586–587.

(63) (a) Ballestri, M.; Chatgilialoglu, C.; Seconi, G. *J. Organomet. Chem.* **1991**, *408*, C1–C4. (b) Ballestri, M.; Chatgilialoglu, C.; Dembech, P.; Guerrini, A.; Seconi, G. In *Sulfur-Centered Reactive Intermediates in Chemistry and Biology*; Chatgilialoglu, C., Asmus, K.-D., Eds.; Plenum: New York, 1990; pp 319–325.

(64) Note added in proof: The following papers, relevant to the subject of this Account, have appeared after the submission of this Account. (a) Gerlach, M.; Jordens, F.; Kuhn, H.; Neumann, W. P.; Petersein, M. *J. Org. Chem.* **1991**, *56*, 5971–5972. (b) Dickhaut, J.; Giese, B. *Org. Synth.* **1991**, *70*, 164–168. (c) Giese, B.; Damm, W.; Dickhaut, J.; Wetterich, F.; Sun, S.; Curran, D. P. *Tetrahedron Lett.* **1991**, *32*, 6097–6100. (d) Arya, P.; Wayner, D. D. M. *Tetrahedron Lett.* **1991**, *32*, 6265–6268. (e) Barton, D. H. R.; Blundell, P.; Dorchak, J.; Jang, D. O.; Jaszberenyi, J. Cs. *Tetrahedron* **1991**, *47*, 8969–8984. (f) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. Cs. *Tetrahedron Lett.* **1991**, *32*, 7187–7190. (g) Künzer, H.; Sauer, G.; Wiechert, R. *Tetrahedron Lett.* **1991**, *32*, 7247–7250. (h) Curran, D. P.; Jasperse, C. P.; Totleben, M. J. *J. Org. Chem.* **1991**, *56*, 7169–7172.

(65) Bowry, V. W.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1991**, *113*, 5687–5698 and references cited therein.