

The Study of the Kinetics of Intramolecular Radical Cyclizations of Acylsilanes via the Intramolecular Competition Method

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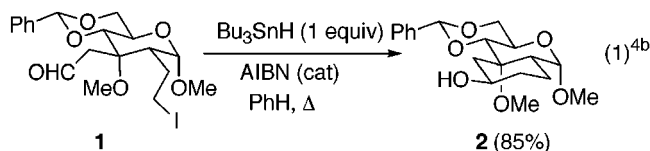
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The kinetics of the radical cyclizations of acylsilanes is probed by the construction of an intramolecular competition system. In this system, known rate constants of olefin cyclizations are used as the internal clock. At benzene reflux temperature (80 °C), the cyclization rate constants for 5-exo cyclizations of acylsilanes with primary radicals are on the order of 10^6 s^{-1} . The corresponding rate constants for 5-exo cyclizations with secondary radicals and 6-exo cyclizations with primary radicals lie on the order of 10^5 s^{-1} . The 6-exo cyclizations of acylsilanes with secondary radicals are slower and fall in the range of 10^4 s^{-1} . Substituents on the silicon of the acylsilanes affect the rates of cyclization. Large silyl groups reduce the rate, and this is more serious for the 6-exo type of cyclizations. Electron-withdrawing groups increase the rates of cyclization.

Introduction

Intramolecular radical cyclization reactions have drawn the attention of synthetic chemists in recent years because of the wide range of synthetic utilities available through this methodology.¹ An understanding of the kinetics and mechanistic aspects of these radical cyclization reactions will help the synthetic chemists to obtain better control of these processes. For this reason, the kinetics of radical cyclizations involving carbon–carbon multiple bonds have been extensively studied.²

The carbonyl functional group plays a central role in organic chemistry. Radical cyclizations involving carbonyls which produce cyclic alcohols were first reported in 1976 by Flies et al.³ and later extensively studied by Fraser-Reid⁴ and others.⁵ For example (eq 1), the cycliza-



tion of ϵ -iodo aldehyde **1** was reported to give alcohol **2** in 85% yield.^{4b} Kinetic studies^{4f,6} of this type of cycliza-

tion quickly followed the synthetic work. As shown in Scheme 1,^{6b} Beckwith and Hay showed that the k_1 value for 5-exo ring closure of 4-formylbutyl radical **3** is $8.7 \times 10^5 \text{ s}^{-1}$ at 80 °C. The k_2 value for 6-exo ring closure of 5-formylpentyl radical **5** is $1.0 \times 10^6 \text{ s}^{-1}$ at 80 °C. The values of k_1 and k_2 are very close to the value of $k_{5\text{-exo}}$ ($1.4 \times 10^6 \text{ s}^{-1}$ at 80 °C) for 5-hexenyl radical **7a**.^{6c,7,8} Interestingly, the 6-exo cyclization of 5-formylpentyl radical **5** is much faster than the corresponding cyclization of 6-heptenyl radical **7b** which carries a $k_{6\text{-exo}}$ value of $4.3 \times 10^4 \text{ s}^{-1}$ at 80 °C.^{6c,7} The 5- and 6-exo cyclizations of alkenes are, in general, irreversible.⁷ In contrast, the cyclized cyclic alkoxy radicals **4** and **6** undergo facile β -scissions to give back the ω -formyl radicals **3** and **5** with k_{-1} of $4.7 \times 10^8 \text{ s}^{-1}$ and k_{-2} of $1.1 \times 10^7 \text{ s}^{-1}$ at 80 °C, respectively. As compared with 4-formylbutyl radical **3**, because of the faster rate of 6-exo cyclization of 5-formylpentyl radical **5** and the slower rate of β -scission of cyclohexoxy radical **6**, the cyclohexanol formation is generally more efficient.⁴

Recently Curran and co-workers⁹ developed the radical cyclizations of acylgermanes. As shown in Scheme 2, in the acylgermane system, radicals **10** derived from the corresponding ω -iodo acylgermanes **9** cyclize to give β -germyl cycloalkoxy radicals **11**. Due to the presence of

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(1) (a) Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*; Wiley: New York, 1995. (b) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, *48*, 301–856.

(2) (a) Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 1, pp 161–310. (b) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 4, pp 779–831. (c) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151–1176.

(3) Flies, M. F.; Lalande, R.; Maillard, B. *Tetrahedron Lett.* **1976**, 439–442.

(4) (a) Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 2116–2117. (b) Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 8102–8104. (c) Tsang, R.; Dickson, J. K., Jr.; Pak, H.; Walton, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1987**, *109*, 3484–3486. (d) Fraser-Reid, B.; Vite, G. D.; Yeung, B.-W. A.; Tsang, R. *Tetrahedron Lett.* **1988**, *29*, 1645–1648. (e) Dickson, J. K., Jr.; Tsang, R.; Llera, J. M.; Fraser-Reid, B. *J. Org. Chem.* **1989**, *54*, 5350–5356. (f) Walton, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1991**, *113*, 5791–5799.

(5) (a) Paquette, L. A.; Ra, C. S.; Silvestri, T. W. *Tetrahedron* **1989**, *45*, 3099–3106. (b) Knapp, S.; Gibson, F. S.; Choe, Y. H. *Tetrahedron Lett.* **1990**, *38*, 5397–5400. (c) Knapp, S.; Gibson, F. S. *J. Org. Chem.* **1992**, *57*, 4802–4809. (d) Grissom, J. W.; Klingberg, D. *J. Org. Chem.* **1993**, *58*, 6559–6564. (e) Grissom, J. W.; Klingberg, D.; Meyenburg, S.; Stallman, B. L. *J. Org. Chem.* **1994**, *59*, 7876–7888. (f) Clive, D. L. S.; Postema, M. H. D. *J. Chem. Soc., Chem. Commun.* **1993**, 429–430. (g) Jung, M. E.; Choe, S. W. T. *Tetrahedron Lett.* **1993**, *34*, 6247–6250. (h) Hays, D. S.; Fu, G. C. *J. Am. Chem. Soc.* **1995**, *117*, 7283–7284. (i) Davin, P.; Fensterbank, L.; Malacria, M. *Tetrahedron Lett.* **1998**, *39*, 833–836.

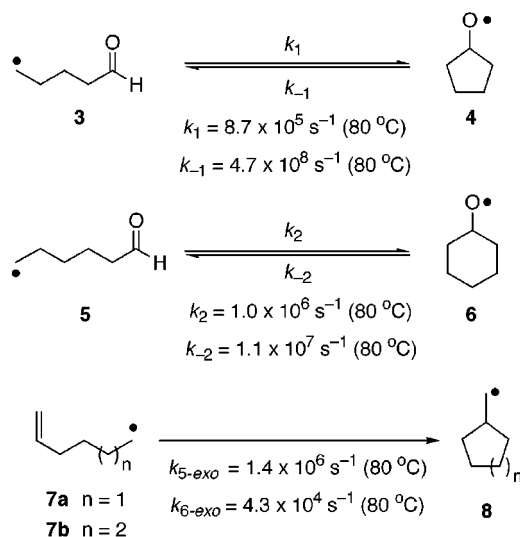
(6) (a) Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1989**, *111*, 230–234. (b) Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1989**, *111*, 2674–2681. (c) Beckwith, A. L. J.; Raner, K. D. *J. Org. Chem.* **1992**, *57*, 4954–4962.

(7) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073–3100.

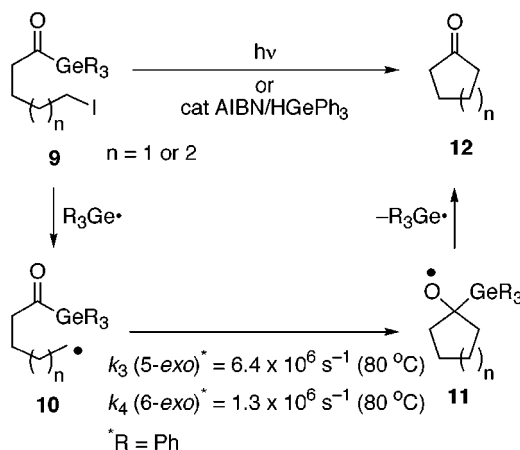
(8) Luszyk, J.; Maillard, B.; Deycard, S.; Lindsay, D. A.; Ingold, K. U. *J. Org. Chem.* **1987**, *52*, 3509–3514.

(9) (a) Curran, D. P.; Liu, H. *J. Org. Chem.* **1991**, *56*, 3463–3465. (b) Curran, D. P.; Palovich, M. *Synlett* **1992**, 631–632. (c) Curran, D. P.; Diederichsen, U.; Palovich, M. *J. Am. Chem. Soc.* **1997**, *119*, 4797–4804. (d) Diederichsen, U.; Curran, D. P. *J. Organomet. Chem.* **1997**, *531*, 9–12.

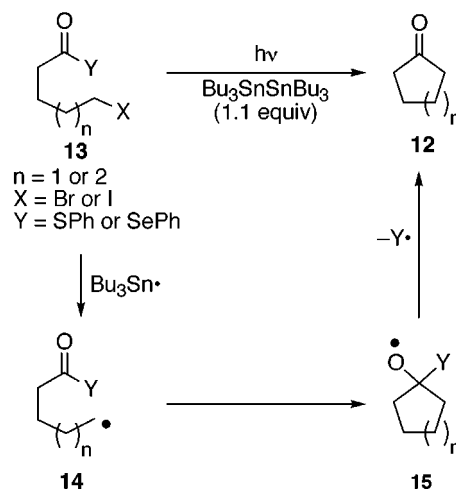
Scheme 1



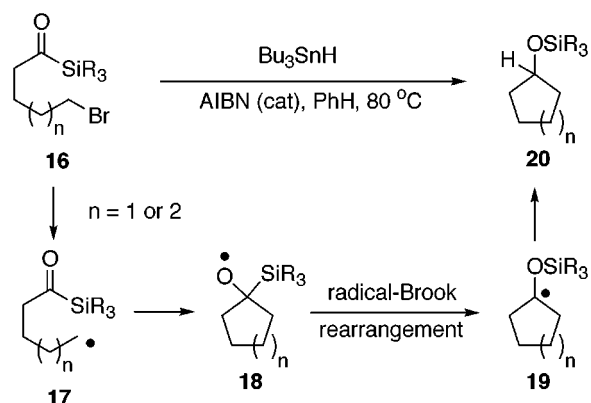
Scheme 2



Scheme 3



Scheme 4



the β -germyl group, the alkoxy radicals **11** quickly undergo a β -scission reaction to generate the cyclic ketones **12**, with concomitant formation of a germyl radical. The germyl radical reacts with the iodides **9**, constituting a unimolecular chain transfer (UMCT) reaction.¹⁰ In the case of acyltriphenylgermanes,^{9c} the rate constants of 5-exo cyclization ($k_3 = 6.4 \times 10^6 \text{ s}^{-1}$ at $80 \text{ }^\circ\text{C}$) and 6-exo cyclization ($k_4 = 1.3 \times 10^6 \text{ s}^{-1}$ at $80 \text{ }^\circ\text{C}$) are very close to the corresponding k_1 and k_2 (Scheme 1) for ω -formylalkyl radicals **3** and **5**, respectively. For 5-hexenyl radical cyclizations, it is well-known that an alkyl substituent at C(5) severely reduces the rate of 5-exo cyclizations.^{7,11} To our knowledge, 5- and 6-exo cyclizations of ketones to give tertiary cyclic alcohols are rare and can only be realized in rigid skeletons.^{5a} Therefore, the highly efficient radical cyclizations of germyl ketones are quite extraordinary. Variation of the substituents on the germanium of the acylgermanes effects the cyclization rate.^{9c} In general, an aryl substituent with an electron-withdrawing group at the para position is the most efficient. The substitution on the carbon that carries the initial radical also effects the cyclizations.^{9c} Primary radicals undergo cyclization faster.

Kim and Jon¹² reported the radical cyclizations of thioesters and selenoesters **13** (Scheme 3). Radicals **14** generated from **13** cyclize to give alkoxy radicals **15**. β -Scission of **15** gives cyclic ketones **12** with the formation of thio or seleno radicals which cannot react with the starting halides **13** to obtain radicals **14**. Therefore, 1.1 equiv of hexabutylditin is required in this system. Although the kinetics in this system is not reported, it is known that with 1,2-migrations of radicals thioester groups migrate 10^4 times slower than acyl groups.¹³

As shown in Scheme 4, we studied intramolecular radical cyclizations of acylsilanes.¹⁴ Radicals **17** derived from acylsilane **16** cyclized to give β -silyl alkoxy radicals **18**. Contrary to the germyl, thio, and seleno analogues, the β -silyl alkoxy radicals **18** undergo radical-Brook rearrangement¹⁵ to afford α -silyloxy radicals **19**. The final

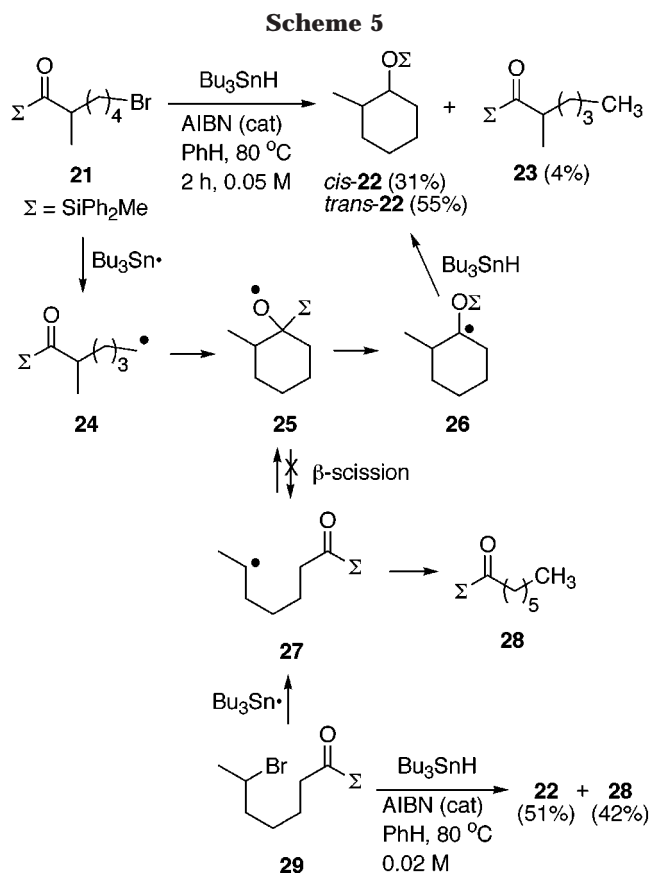
(10) (a) Curran, D. P.; Xu, J.; Lazzarini, E. *J. Am. Chem. Soc.* **1995**, *117*, 6603–6604. (b) Curran, D. P.; Xu, J. Y.; Lazzarini, E. *J. Chem. Soc., Perkin Trans. 1* **1995**, 3049–3059.

(11) Beckwith, A. L. J.; Blair, I. A.; Phillipou, G. *Tetrahedron Lett.* **1974**, 2251–2254.

(12) Kim, S.; Jon, S. Y. *J. Chem. Soc., Chem. Commun.* **1996**, 1335–1336.

(13) (a) Giese, B.; Heinrich, N.; Horler, H.; Koch, W.; Schwarz, H. *Chem. Ber.* **1986**, *119*, 3528–3835. (b) Wollowitz, S.; Halpern, J. *J. Am. Chem. Soc.* **1984**, *106*, 8319–8321. (c) Wollowitz, S.; Halpern, J. *J. Am. Chem. Soc.* **1988**, *110*, 3112–3120. (d) Lindsay, D. A.; Luszytk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1984**, *106*, 7087–7093.

(14) (a) Tsai, Y.-M.; Cherng, C.-D. *Tetrahedron Lett.* **1991**, *32*, 3515–3518. (b) Tsai, Y.-M.; Tang, K.-H.; Jiaang, W.-T. *Tetrahedron Lett.* **1993**, *34*, 1303–1306. (c) Curran, D. P.; Jiaang, W.-T.; Palovich, M.; Tsai, Y.-M. *Synlett* **1993**, 403–404. (d) Tsai, Y.-M.; Chang, S.-Y. *J. Chem. Soc., Chem. Commun.* **1995**, 981–982. (e) Chuang, T.-H.; Fang, J.-M.; Jiaang, W.-T.; Tsai, Y.-M. *J. Org. Chem.* **1996**, *61*, 1794–1805. (f) Tsai, Y.-M.; Tang, K.-H.; Jiaang, W.-T. *Tetrahedron Lett.* **1996**, *37*, 7767–7770. (g) Tsai, Y.-M.; Nieh, H.-C.; Pan, J.-S.; Hsiao, D.-D. *J. Chem. Soc., Chem. Commun.* **1996**, 2469–2470. (h) Chang, S.-Y.; Jiaang, W.-T.; Cherng, C.-D.; Tang, K.-H.; Huang, C.-H.; Tsai, Y.-M. *J. Org. Chem.* **1997**, *62*, 9089–9098.

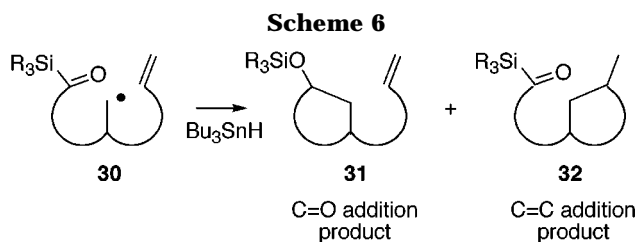


products of this process are cyclic silyl ethers **20**. With the development of this interesting reaction, it is essential to study the mechanism and kinetics of the process. In a recent paper,^{14h} we have described the qualitative aspect of this cyclization reaction. In this paper, we report the quantitative aspect of this reaction.

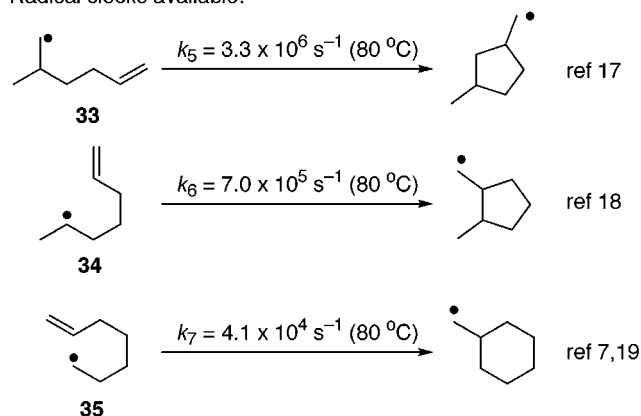
Results and Discussion

The Reversibility of Cyclization. As mentioned above, the ω -formyl radical cyclizations are reversible. To know whether the β -silyl alkoxy radicals **18** will undergo β -scission to give the ω -silylcarbonyl radicals **17** or not, we studied the cyclization of acylsilane **21** (Scheme 5). When **21** was treated with tributyltin hydride (1.2 equiv) in refluxing benzene in the presence of a catalytic amount of AIBN (0.05 equiv) as initiator, we obtained cyclic silyl ethers *cis*-**22** (31%) and *trans*-**22** (55%) as the major products. The uncyclized debrominated acylsilane **23** was isolated in 4% yield.

In this system, the ω -silylcarbonyl radical **24** was generated from the cyclization substrate **21** and cyclized to give the β -silyl alkoxy radical intermediate **25**. If this cyclization is reversible, then there are two possible routes for β -scission of alkoxy radical **25**. One route will give back the original primary radical **24**, while the other route will generate the more stable secondary radical **27**. In our previous work,^{14h} we found that secondary radicals undergo 6-exo cyclizations with acylsilanes less efficiently than primary radicals and more uncyclized reduction



Radical clocks available:



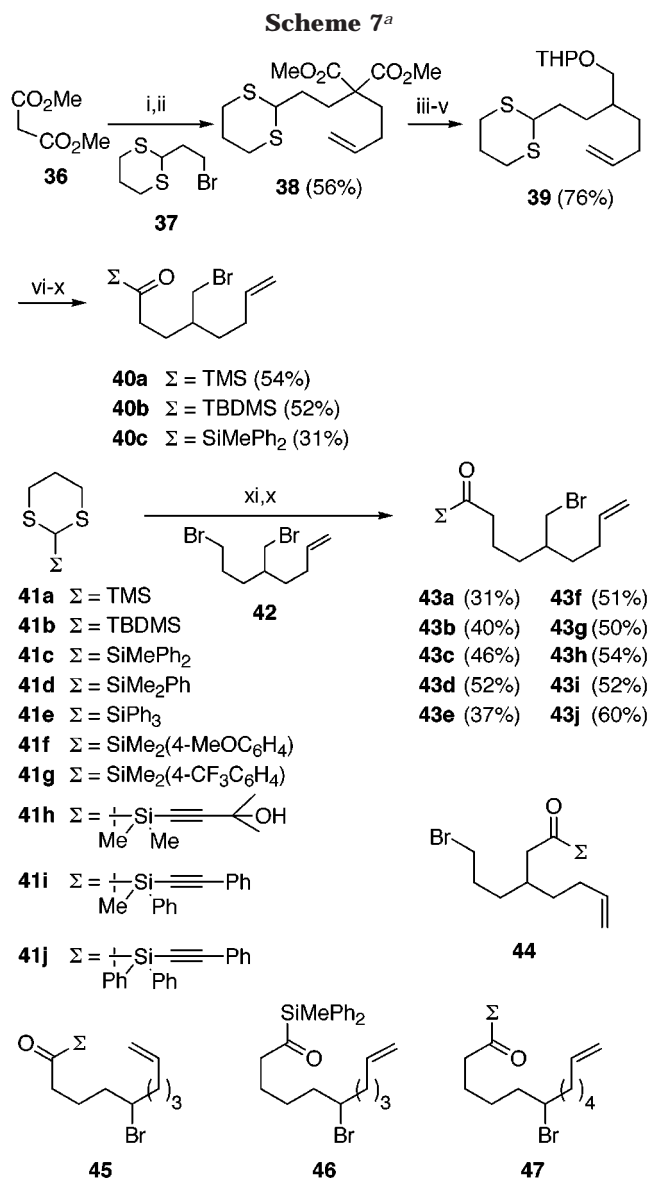
products are obtained with these cyclizations. For example, the secondary bromide **29** gave 6-exo cyclization product **22** in 51% yield along with 42% of reduction product acylsilane **28**.^{14h} Note that a more dilute condition (0.02 M) was used for cyclization of secondary bromide **29** than for that of primary bromide **21** (0.05 M). Therefore, if the cyclization of primary radical **24** is reversible, one would expect to observe the straight-chain acylsilane **28** derived from secondary radical **27**. Since we did not observe any crossover reduction product from the cyclization of primary bromide **21**, we concluded that the cyclization step is not reversible.

Harris et al. recently reported the EPR experiments on 1,2-migration of the trimethylsilyl group from carbon to oxygen.^{15b} They found that the radical-Brook rearrangement occurs very rapidly at a temperature as low as 190 K. It is likely that, once β -silyl alkoxy radical **25** is formed, the potential β -scission process is overwhelmed by the extremely facile silyl migration. As a result of the high Si–O bond strength,¹⁶ the silyl migration is most likely irreversible and serves as an excellent thermodynamic driving force for the radical cyclizations of acylsilanes.

Construction of Intramolecular Competition Systems. To probe the kinetics of the radical cyclizations of acylsilanes, we decided to use the intramolecular competition systems^{2c} such as radical **30** shown in Scheme 6 as our tools. In **30**, the radical **30** could cyclize with the acylsilane or the olefin. As mentioned above, the radical addition to acylsilane carbonyl is determined to be irreversible.⁷ The radical cyclization of an unstabilized radical with an olefin is also known to be irreversible. Therefore, the ratio of the C=O addition product **31** relative to the C=C addition product **32** should reflect the ratio of the cyclization rate constants of the two processes. In the literature, there are many fundamental radical cyclization rate constants available.² For example, the rate constants k_5 – k_7 for the cyclizations of radicals

(15) (a) Dalton, J. C.; Bourque, R. A. *J. Am. Chem. Soc.* **1981**, *103*, 699–700. (b) Harris, J. M.; MacInnes, I.; Walton, J. C.; Maillard, B. *J. Organomet. Chem.* **1991**, *403*, C25–C28. (c) Tsai, Y.-M.; Ke, B.-W. *J. Chin. Chem. Soc. (Taipei)* **1993**, *40*, 641–642. (d) Robertson, J.; Burrows, J. N. *Tetrahedron Lett.* **1994**, *35*, 3777–3780.

(16) Jackson, R. A. *J. Organomet. Chem.* **1979**, *166*, 17–19.



^a Reagents and conditions: (i) NaH, DMF; **37**; (ii) NaH, DMF; BrCH₂CH₂CH=CH₂; (iii) NaCN, DMF, 150 °C; (iv) LAH, THF; (v) TsOH, dihydropyran; (vi) BuLi, THF, 0 °C; Σ -Cl; (vii) TsOH, MeOH; (viii) MsCl, Et₃N, CH₂Cl₂; (ix) LiBr, acetone; (x) (CF₃CO₂)₂IPh for **40a**; CAN, H₂O/CH₃CN, -20 °C for **40b, c, 43**; (xi) BuLi, THF, 0 °C; **42**.

33–35, respectively, have been reported.^{7,17–19} One should be able to use these known cyclization systems as intramolecular radical clocks to extrapolate the radical cyclization rate constants for acylsilanes.

As shown in Scheme 7, the 5-exo substrates primary bromides **40** were prepared from dimethyl malonate (**36**). Alkylation of **36** sequentially with 2-(2-bromoethyl)-1,3-dithiane (**37**)²⁰ and 4-bromo-1-butene gave diester **38** in 56% yield. Decarboxylation²¹ of diester **38** gave the corresponding monoester which was reduced to an alcohol

and then converted to the tetrahydropyranyl ether **39** in 76% overall yield. Silylations of the 1,3-dithiane moiety in **39**, followed by deprotection of the tetrahydropyranyl ethers, afforded the corresponding alcohols which were then converted to the bromides. The dithiane moiety was hydrolyzed with iodobenzenebis(trifluoroacetate)²² or CAN²³ to afford acylsilanes **40**.

The 6-exo substrates primary bromides **43** were prepared by alkylations of 2-silyl-1,3-dithianes **41** with dibromide **42**. Alkylations occurred selectively at the less hindered C(8) position of **42**, and hydrolysis of the coupling products with CAN afforded acylsilanes **43**. Only trace amounts of acylsilanes **44** were observed. These regioisomers were derived from alkylation of dithianes **41** with dibromide **42** at the C(5)-bromomethyl position. In contrast, when a similar strategy was carried out in the system of acylsilanes **40**, the alkylations with 7-bromo-5-(bromomethyl)-1-heptane gave a selectivity of 20:1 in favor of C(7)-alkylations. Because the regioisomers were difficult to separate, the dibromide alkylation approach to obtaining acylsilanes **40** was abandoned. The 5-exo substrates secondary bromides **45** and 6-exo substrates secondary bromides **46** and **47** were prepared according to the methods reported previously.^{14b}

The Rates of 5-Exo Cyclizations with Primary Radicals. The cyclizations of acylsilanes **40** were performed by slow addition (1 h) of a benzene solution of tributyltin hydride (1.2 equiv) and AIBN (0.05 equiv) to a refluxing benzene solution of the acylsilane substrates. The results are summarized in Table 1. In the case of acyltrimethylsilane **40a** (entry 1), the carbonyl addition product silyl ether **48a** was obtained in 40% yield along with 23% of desilylated alcohol **49**. The desilylation of the labile trimethylsilyl group presumably occurred during silica-gel column chromatography. The olefin addition product **50a** was obtained in 24% yield. The ratio of the combined yields (63%) of silyl ether **48a** and alcohol **49** relative to the yield of acylsilane **50a** was determined to be 2.6. As mentioned above, this value should reflect the $k_{C=O}/k_{C=C}$ ratio. The olefin cyclization system in acylsilane **40** is reminiscent of the cyclization of 2-methyl-5-hexenyl radical **33** and radicals derived from acylsilanes **40** is a methyl group versus a 2-(silylcarbonyl)ethyl group. Assuming the influence of this difference on $k_{cyclization}$ is small, we used the rate constant k_5 ($3.3 \times 10^6 \text{ s}^{-1}$ at 80 °C) of the cyclization of radical **33** to extrapolate the $k_{C=O}$. Therefore, the 5-exo $k_{C=O}$ for the primary radical derived from acyltrimethylsilane **40a** was determined to be $8.6 \times 10^6 \text{ s}^{-1}$ at 80 °C.

When the silyl group was changed to a bulky *tert*-butyldimethylsilyl group in **40b** (entry 2), the ratio of $k_{C=O}/k_{C=C}$ decreased slightly to 1.5. This correlates to a $k_{C=O}$ value of $5.0 \times 10^6 \text{ s}^{-1}$ at 80 °C. This result indicates that for 5-exo cyclization of acylsilanes with primary radicals the effect of the size of the silyl group is small. This is in sharp contrast to the 5-hexenyl radical cyclization system in which an alkyl substituent at C(5) severely reduces the 5-exo cyclization rate.^{7,11}

Interestingly, acylmethyldiphenylsilane **40c** (entry 3) cyclized very efficiently to give 78% of silyl ether **48c**

(17) Beckwith, A. L. J.; Easton, C. J.; Lawrence, T.; Serelis, A. K. *Aust. J. Chem.* **1983**, *36*, 545–556.

(18) Luszytk, J.; Maillard, B.; Deycard, S.; Lindsay, D. A.; Ingold, K. U. *J. Org. Chem.* **1987**, *52*, 3509–3514.

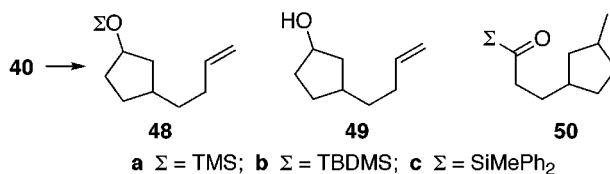
(19) Beckwith, A. L. J.; Moad, G. *J. Chem. Soc., Chem. Commun.* **1974**, 472–473.

(20) Davey, A. E.; Parsons, A. F.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1853–1858.

(21) McMurry, J. *Org. React.* **1976**, *24*, 187–224.

(22) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287–290.

(23) (a) Ho, T.-L.; Ho, H. C.; Wong, C. M. *J. Chem. Soc., Chem. Commun.* **1972**, 791. (b) Ho, H. C.; Ho, T.-L.; Wong, C. M. *Can. J. Chem.* **1972**, *50*, 2718–2721.

Table 1. The Radical Cyclizations of Acylsilanes **40** with Tributyltin Hydride^a

entry	substrates	silyl groups (Σ)	C=O addition products (% yield; cis/trans) ^b	C=C addition products (% yield; cis/trans) ^b	$k_{C=O}/k_{C=C}$ ^c	extrapolated $k_{C=O} \times 10^{-7}$ (s ⁻¹) at 80 °C ^d
1	40a	TMS	48a (40; 55/45), 49 (23) ^e	50a (24; 1/2)	2.6	0.86
2	40b	TBDMS	48b (49; 57/43)	50b (33; 1/2)	1.5	0.50
3	40c	SiMePh ₂	48c (78; 53/47)	50c (12; 1/2)	6.5	2.1

^a A benzene solution of tributyltin hydride (1.2 equiv) and AIBN (0.05 equiv) was added over 1 h to a refluxing benzene solution of the substrate. Equal amounts of benzene were used to prepare the two solutions, and the final concentration relative to the substrate was 0.05 M. ^b The cis/trans ratio was determined by ¹H NMR integration. ^c The ratio at 80 °C. ^d The rate constants were based on a $k_{C=C}$ value of 3.3×10^6 s⁻¹ at 80 °C (k_5 in Scheme 6). Inherent error exists due to the selection of this value (see text). ^e The ratio of cis/trans isomers could not be determined.

along with 12% of acylsilane **50c**, and the ratio of $k_{C=O}/k_{C=C}$ is 6.5. The $k_{C=O}$ extrapolated from this ratio is 2.1×10^7 s⁻¹ at 80 °C. Although the methyl-diphenyl group is presumably bulkier than the trimethylsilyl group, the cyclization rate constant is higher for acylmethyl-diphenylsilane **40c** than acyltrimethylsilane **40a**. We assumed that this is a result of the electronic effect of the phenyl substituents on silicon (vide infra).

Beckwith and co-workers¹⁷ studied the radical cyclizations of methyl-substituted 5-hexenyl radicals. They found that the 5-exo cyclization rate constant of 2-methyl-5-hexenyl radical **33** (Scheme 6) is greater than that of the parent 5-hexenyl radical **7a** (Scheme 1) by a factor of 2.4 at 80 °C. The acceleration effect of the 2-methyl group can be attributed to the *gem*-dialkyl effect.²⁴ Taking this factor into account and on the basis of the results shown in Table 1, the rate constants of 5-exo cyclizations for unsubstituted acylsilanes with primary radicals should lie in the area of 10^6 s⁻¹ at 80 °C. This value is similar to the kinetics value for the analogous acylgermanes reported by Curran et al. (Scheme 2).^{9c}

The assignment of the stereochemical structures of **48** was based on the comparison of their ¹H NMR spectra with that of *cis*- and *trans*-3-methylcyclopentanol (**51**).²⁵ A *cis/trans* (60/40) mixture of 3-methylcyclopentanol (**51**) was prepared from 3-methylcyclopentanone according to the literature.²⁵ The ¹H NMR absorptions of C(1)-H of *cis*-**51** appeared at higher field between δ 4.13 and 4.24, whereas that for the *trans* isomer appeared between δ 4.24 and 4.30 (entry 1, Table 2). As shown in Table 2, two sets of signals appeared in the same region for silyl ethers **48a–c**. We assigned the set of signals that appeared at higher field to the *cis* isomers analogous to the trend observed in 3-methylcyclopentanol (**51**). Mechanistically, the stereochemistry of **48** is determined at the step of hydrogen abstraction of the rearranged α -silyloxy radicals. Very little selectivity was observed in these 3-substituted cyclopentyl radicals.²⁶

The stereochemistry of acylsilanes **50** was determined by comparison of their ¹H and ¹³C NMR spectra with those of 1-*tert*-butyl-3-methylcyclopentane (**52**) reported by Beckwith²⁷ (Table 3). The chemical shifts of the methyl

Table 2. Comparison of the Characteristic ¹H NMR Absorptions of Silyl Ethers **48** with 3-Methylcyclopentanol (**51**)

entry	compounds	¹ H NMR absorptions of C(1)-H (ppm) ^a	
		<i>cis</i>	<i>trans</i> ^b
1	51	4.13–4.24 ^b	4.24–4.30
2	48a	4.14 ^c	4.19–4.28
3	48b	4.17 ^c	4.20–4.30
4	48c	4.28 ^c	4.32–4.42

^a Deuterated chloroform was used as solvent. ^b Appeared as a multiplet. ^c A quintet with $J = 6$ Hz.

Table 3. Comparison of the Characteristic ¹H and ¹³C NMR Absorptions of Acylsilanes **50** with 1-*tert*-Butyl-3-methylcyclopentane (**52**)

entry	compounds	¹ H NMR absorptions of C(3)-Me (ppm) ^a		¹³ C NMR absorptions of C(3)-Me (ppm) ^a	
		<i>cis</i>	<i>trans</i>	<i>cis</i>	<i>trans</i>
1	52^b	0.98	0.96	20.6	21.2
2	50a	0.92	0.90	20.9	21.3
3	50b	0.93	0.91	20.9	21.3
4	50c	0.91	0.88	20.9	21.3

^a Deuterated chloroform was used as solvent. ^b Ref 27.

substituent on cyclopentane for all the *cis* isomers appeared at lower field in ¹H NMR and higher field in ¹³C NMR. These data indicate that the methyl group is located at a sterically more encumbered position.²⁸ The observed 2/1 selectivity in favor of *cis*-**50** follows the normal selectivity pattern for 5-exo cyclizations of 2-substituted 5-hexenyl radicals.^{7,29}

The Rates of 6-Exo Cyclizations with Primary Radicals. To probe the 6-exo cyclization rate constants of acylsilanes with primary radicals, we studied the cyclizations of acylsilanes **43**. In **43**, an intramolecular clock of a 2-substituted 5-hexenyl radical system was used again as in the case of acylsilanes **40**. The results are shown in Table 4. In the case of acyltrimethylsilane **43a** (entry 1), desilylated cyclic alcohol *cis*-**54** was isolated in 22% yield along with 3% of silyl ether *trans*-**53a**. The

(24) (a) Beckwith, A. L. J.; Lawrence, T. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1535–1539. (b) Capon, B.; McManus, S. P. *Neighboring Group Participation*; Plenum Publishing: New York, 1976; Vol. 1, pp 58–75. (c) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183–278.

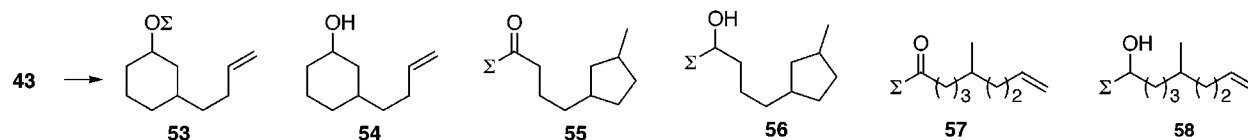
(25) Battioni, J.-P.; Chodkiewicz, W. *Bull. Soc. Chim. Fr.* **1971**, 1824–1833.

(26) For stereoselectivity of cycloalkyl radicals in general, see the following: Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: New York, 1996; Chapter 3, p 116.

(27) Beckwith, A. L. J.; Zimmermann, J. *J. Org. Chem.* **1991**, *56*, 5791–5796.

(28) Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy*, 3rd ed.; VCH: Weinheim, 1990; p 115.

(29) Beckwith, A. L. J.; Lawrence, T.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 484–485.

Table 4. The Radical Cyclizations of Acylsilanes **43** with Tributyltin Hydride^a

a Σ = TMS; b Σ = TBDMS; c Σ = SiMePh₂; d Σ = SiMe₂Ph; e Σ = SiPh₃; f Σ = SiMe₂(4-MeOC₆H₄); g Σ = SiMe₂(4-CF₃C₆H₄)

entry	substrates	silyl groups (Σ)	C=O addition products (% yield)	C=C addition products (% yield; cis/trans) ^b	$k_{C=O}/k_{C=C}$ ^c	extrapolated $k_{C=O} \times 10^{-6} (s^{-1})$ at 80 °C ^d
1	43a	TMS	<i>trans</i> - 53a (3), <i>cis</i> - 54 (22)	55a (59; 1/2)	0.42	1.4
2	43b	TBDMS	<i>cis</i> - 53b (7)	55b (65) ^e	0.11	0.36
3	43d	SiMe ₂ Ph	<i>trans</i> - 53d (6), <i>cis</i> - 54 (21)	55d (55; 1/2), 56d (4; 1/2.2)	0.46	1.5
4 ^f	43c	SiMePh ₂	<i>cis</i> - 53c (19), <i>trans</i> - 53c (5)	55c (46; 1/2.7)	0.52	1.7
5 ^g	43e	SiPh ₃	<i>cis</i> - 53e (16)	55e (41; 1/2), 56e (13; 1/2.2)	0.30	0.99
6 ^h	43f	SiMe ₂ (4-MeOC ₆ H ₄)	<i>cis</i> - 53f (19), <i>trans</i> - 53f (6), <i>cis</i> - 54 (3)	55f (59; 1/2)	0.47	1.6
7 ⁱ	43g	SiMe ₂ (4-CF ₃ C ₆ H ₄)	<i>cis</i> - 53g (16), <i>trans</i> - 53g (8), <i>cis</i> - 54 (10)	55g (44; 1/2), 56g (2) ^e	0.74	2.4
8	43h		<i>cis</i> - 54 (34), <i>trans</i> - 54 (9)	<i>j</i>	0.89 ^k	2.9
9	43i		<i>cis</i> - 53i (25), <i>trans</i> - 53i (10), <i>cis</i> - 54 (13)	<i>j</i>	1.0 ^k	3.3
10	43j		<i>cis</i> - 53j (32), <i>trans</i> - 53j (10), <i>cis</i> - 54 (15)	<i>j</i>	1.8 ^k	5.9

^a See footnote a in Table 1. ^b The cis/trans ratio was determined by ¹H NMR integration. ^c The ratio at 80 °C. ^d The rate constants were based on a $k_{C=C}$ value of $3.3 \times 10^6 s^{-1}$ at 80 °C (k_5 in Scheme 6). Inherent error exists due to the selection of this value (see text). ^e The isomeric ratio was not determined. ^f Reduction product **57c** was isolated in 6% yield. ^g Reduction product **58e** was isolated in 5% yield. ^h Reduction product **57f** was isolated in 6% yield. ⁱ Reduction products **57g** (5%) and **58g** (2%) were also isolated. ^j These addition products can be observed in the crude ¹H NMR spectrum, but we were unable to isolate them. ^k The ratio was obtained by ¹H NMR integration of the crude product.

total yield of 25% represents the fraction of 6-exo cyclization at the acylsilane part. Olefin cyclization product acylsilane **55a** was obtained in 59% yield. The ratio of C=O addition/C=C addition is 0.42. This value should reflect the ratio of the rate constants of the two cyclizations. Using the 5-exo cyclization rate constant k_5 (Scheme 6) of 2-methyl-5-pentenyl radical to represent $k_{C=C}$, the $k_{C=O}$ for acyltrimethylsilane **43a** was extrapolated to be $1.4 \times 10^6 s^{-1}$ at 80 °C. Comparing this value with the $k_{C=O}$ for the corresponding 5-exo cyclization (entry 1, Table 1) indicates that the 6-exo cyclization is slower by a factor of 6 in the case with a trimethylsilyl group.

Compared with the 5-exo cyclization, the 6-exo cyclization is also more sensitive toward steric effects as shown in entry 2. When the trimethylsilyl group was switched to a bulky *tert*-butyldimethylsilyl group, the amount of C=O addition product decreased significantly. A small amount of silyl ether *cis*-**53b** (7%) was isolated, and the major product was the acylsilane **55b** (65%). The $k_{C=O}$ in this case was extrapolated to be $3.6 \times 10^5 s^{-1}$ at 80 °C. A 4-fold drop from the case of acyltrimethylsilane **43a** was observed.

In the case of one phenyl group on silicon as in acylsilane **43d** (entry 3), silyl ether *trans*-**53d** (6%) was obtained along with 21% of desilylated alcohol *cis*-**54**. The olefin cyclization products consisted of two compounds. The major compound was acylsilane **55d** (55%), and a minor compound α -silyl alcohol **56** (4%) was also obtained. This α -silyl alcohol was presumably derived from over-reduction of acylsilane **55d** by tributyltin hydride.³⁰ Previously we have reported that the rate of reduction of an acylsilane moiety by tributyltin hydride is very close

to that of the reduction of a chloride.^{14h} The reduction of chloride by tributyltin hydride is known to be much slower than the reduction of bromide.^{30–32} Therefore, it is unlikely that **56** was derived from, first, reduction of the carbonyl in acylsilane **43d**, followed by radical cyclization of the olefin. The $k_{C=O}$ extrapolated from the cyclization of acylsilane **43d** was determined to be $1.5 \times 10^6 s^{-1}$ at 80 °C.

With two phenyl groups on silicon as in acylsilane **43c** (entry 4), the $k_{C=O}$ was determined to be $1.7 \times 10^6 s^{-1}$ (80 °C). Although the size of the silyl group in acylmethylphenylsilane **43d**, the 6-exo cyclization rate constants of the two are similar. However, when the silyl group is very large as in acyltriphenylsilane **43e** (entry 5), the $k_{C=O}$ ($9.9 \times 10^5 s^{-1}$ at 80 °C) becomes smaller than those of acylmethylphenylsilane **43c** and acylmethylphenylsilane **43d**. We believe that what we have observed in entries 3–5 is the result of two counter acting factors. The steric factor slows down the rate of cyclization as the number of phenyl groups increases from entry 3 to 5. However, the acceleration effect of the phenyl group increases the cyclization rate as the number of phenyl groups increases.

The stereochemical assignments of silyl ethers **53** and desilylated alcohols **54** were based on the analysis of their ¹H NMR spectra. As shown in Table 5, the C(1)-H absorptions of the cis isomers all appeared at higher field as triplets of triplets with a large coupling constant of ~ 10.5 Hz and a small coupling constant of ~ 4.5 Hz.

(31) Carlsson, D. J.; Ingold, K. U. *J. Am. Chem. Soc.* **1968**, *90*, 7047–7055.

(32) Beckwith, A. L. J.; Pigou, P. E. *Aust. J. Chem.* **1986**, *39*, 77–87.

(30) Ingold, K. U.; Luszyk, J.; Scaiano, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 343–348.

Table 5. ^1H NMR Absorptions of C(1)-H of Silyl Ethers **53** and Alcohols **54**^a

entry	compounds	cis isomer (ppm) ^b	trans isomer (ppm) ^c
1	53a		3.95
2	53b	3.50 ($J = 10.3, 4.2$ Hz)	
3	53c	3.66 ($J = 10.5, 4.3$ Hz)	4.12
4	53d		4.30
5	53e	3.71 ($J = 10.5, 4.2$ Hz)	
6	54	3.53 ($J = 10.7, 4.5$ Hz)	4.00

^a Deuterated chloroform was used as solvent. ^b Appeared as tt. ^c Appeared as a broad singlet.

These characteristic absorptions indicate that the hydrogens are located at the axial position. In contrast, the C(1)-H absorptions of the trans isomers appeared at lower field as broad singlets, indicating that they are located at the equatorial position. Mechanistically, the stereochemistry was determined at the hydrogen-abstraction step of the α -silyloxy radicals. It is well-known that cyclohexyl radicals prefer to abstract hydrogen from the axial site.²⁶ Therefore, the cis isomers are expected to be the major isomers. The stereochemistry of acylsilanes **55** agrees in all respects with that of acylsilanes **50**.

Probing the Electronics of the Silyl Group. To see if the electronic nature of the phenyl group on silicon will affect the cyclization or not, we studied the cyclization of acylsilanes **43f** and **43g** (entries 6 and 7, Table 4). In acylsilane **43f**, an electron-donating methoxy group is present at the 4-position of the phenyl group. The ratio of $k_{\text{C=O}}/k_{\text{C=C}}$ was determined to be 0.47 which is almost identical to that of the cyclization of acyldimethylphenylsilane **43d** (entry 3). Therefore, an electron-rich phenyl group does not affect the rate of cyclization. However, when a trifluoromethyl group is present at the 4-position of the phenyl group as in acylsilane **43g**, the ratio of $k_{\text{C=O}}/k_{\text{C=C}}$ increased 1.6-fold as compared with that of acyldimethylphenylsilane **43d**. This result indicates that the electron-withdrawing group on silicon will enhance the rate of cyclization. Presumably, as the silyl substituent becomes more electron withdrawing, the carbonyl carbon of the acylsilane will become more electropositive. The alkyl-substituted radicals involved in this work are nucleophilic and react faster with the more electrophilic carbonyls.

To further enhance the electrophilicity of the acylsilane carbonyl, we decided to attach an acetylenic group on silicon. The acetylenic group uses an sp orbital to bond with silicon and should be more electron withdrawing than the phenyl group which uses a less electronegative sp^2 orbital for bonding. We prepared three acylsilanes **43h–j** that carry an acetylenic group using the method described above (Scheme 7). The cyclization results are shown in Table 4 (entries 8–10). As a result of the enhanced electrophilicity of the acylsilane carbonyls of this type, the olefin cyclization products, acylsilanes **55h–j**, decomposed through extensive chromatography. Therefore, we determined the ratio of the carbonyl cyclization products to acylsilanes **55** by ^1H NMR integration of the cyclization crude product.

Interestingly, all the three acetylene-carrying acylsilanes **43h–j** underwent carbonyl cyclizations faster than all the other acylsilanes studied in this series (entries 1–7). Changing one methyl group on acyltrimethylsilane **43a** (entry 1) to an acetylenic group as in acylsilane **43h** (entry 8) doubled the carbonyl cyclization rate. Similarly, the same trend was observed when the cyclization results

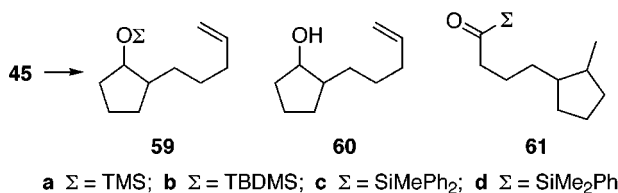
of acyldimethylphenylsilane **43d** (entry 3) and **43i** (entry 9) were compared. When the methyl group in acylmethylphenylsilane **43c** (entry 4) was changed to a phenylethynyl group as in acylsilane **43j** (entry 10), the carbonyl cyclization rate increased 3.5 times. In the case of **43j**, the carbonyl cyclization products, silyl ethers **53j** and alcohol **54**, had a total yield of 57%. This is the most efficient acylsilane cyclization in the 6-exo cyclization system. These results indicate that a directly attached acetylenic group on silicon increases the rate of acylsilane cyclization. In addition to the electronic effect of the acetylenic group, its smaller size may also play an important role in the acylsilane 6-exo cyclization system in which the cyclization is very sensitive toward the size of the silyl group. Therefore, while three phenyl groups on silicon as in acylsilane **43e** (entry 5) is a slower carbonyl cyclization system, replacement of one phenyl group with a phenylethynyl group enhances the rate 6-fold.

In Curran's acylgermane system,^{9c} it was also reported that a electron-withdrawing substituent at the 4-position of the phenyl group on germanium increases the rate of radical cyclization. As shown in Scheme 2, for acylgermanes, the 6-exo cyclization rate constant k_4 ($1.3 \times 10^6 \text{ s}^{-1}$ at 80°C) is also smaller than the 5-exo cyclization rate constant k_3 ($6.4 \times 10^6 \text{ s}^{-1}$ at 80°C). Comparing the cyclization of acyltriphenylgermane **10** ($n = 2$, $\text{R} = \text{Ph}$) and acyltriphenylsilane **43e** (entry 5, Table 4), the cyclization of **43e** is 6.5 times slower ($k_{\text{C=O}} = 9.9 \times 10^5 \text{ s}^{-1}$ at 80°C). Considering the *gem*-dialkyl effect²⁴ exerted by the 4-pentenyl substituent at the β -position of the bromo group in acyltriphenylsilane **43e**, the cyclization of the unsubstituted one should be even slower than acyltriphenylgermane **10** ($n = 2$, $\text{R} = \text{Ph}$). However, changing one phenyl group on the silicon of acylsilane **43e** to an acetylenic group, as in acylsilane **43j**, can drive the acylsilane cyclization rate constant closer to that of acyltriphenylgermane **10** ($n = 2$, $\text{R} = \text{Ph}$).

The Rate of 5-Exo Cyclizations with Secondary Radicals. To probe the 5-exo radical cyclization of acylsilanes with secondary radicals, we studied the cyclizations of bromides **45a–d** (Table 6). In this system, the olefin cyclization part involves a 1-substituted 5-hexenyl radical cyclization. Assuming that the difference between a silylcarbonylpropyl group and a methyl group is small, we used the k_6 ($7.0 \times 10^5 \text{ s}^{-1}$ at 80°C) of 1-methyl-5-hexenyl radical cyclization involving **34**, (Scheme 6) as our clock to probe the acylsilane cyclizations in bromides **45a–d**.

The cyclization of acyltrimethylsilane **45a** afforded silyl ether *cis*-**59a** (9%) and cyclic alcohols *cis*-**60** (9%) and *trans*-**60** (28%).³³ Alcohols **60** were derived from desilylation of silyl ethers **59a** during column chromatography. In addition, the olefin cyclization products **61a** were isolated in 46% yield as a mixture of *cis*/*trans* isomers. The yield of acylsilane **61a** is the same as that of the combined carbonyl cyclization products. Therefore, the extrapolated $k_{\text{C=O}}$ is $7.0 \times 10^5 \text{ s}^{-1}$ at 80°C . This rate-constant value is about 1 order of magnitude lower than that of the corresponding 5-exo cyclization of a primary radical (entry 1, Table 1) and is one-half that of the corresponding 6-exo cyclization of a primary radical (entry 1, Table 4).

(33) (a) Shono, T.; Nishiguchi, I.; Ohmizu, H.; Mitani, M. *J. Org. Chem.* **1978**, *100*, 545–550. (b) Crandall, J. K.; Magaha, H. S. *J. Org. Chem.* **1982**, *47*, 5368–5371.

Table 6. The Radical Cyclizations of Acylsilanes **45** with Tributyltin Hydride^a

entry	substrates	silyl groups (Σ)	C=O addition products (% yield)	C=C addition products (% yield; cis/trans) ^b	$k_{\text{C=O}}/k_{\text{C=C}}$ ^c	extrapolated $k_{\text{C=O}} \times 10^{-6} \text{ (s}^{-1}\text{)}$ at 80 °C ^d
1	45a	TMS	<i>cis</i> - 59a (9), <i>cis</i> - 60 (9), <i>trans</i> - 60 (28)	61a (46; 2/1)	1.0	0.70
2	45b	TBDMS	<i>cis</i> - 59b (19), <i>trans</i> - 59b (17)	61b (36; 2/1)	1.0	0.70
3	45c	SiMePh ₂	<i>cis</i> - 59c (36), <i>trans</i> - 59c (36)	61c (26; 2.3/1)	2.8	2.0
4	45d	SiMe ₂ Ph	<i>cis</i> - 59d (30), <i>trans</i> - 59d (37)	61d (29; 2/1)	2.3	1.6

^a See footnote a in Table 1. ^b The cis/trans ratio was determined by ¹H NMR integration. ^c The ratio at 80 °C. ^d The rate constants were based on a $k_{\text{C=C}}$ value of $7.0 \times 10^5 \text{ s}^{-1}$ at 80 °C (k_6 in Scheme 6). Inherent error exists due to the selection of this value (see text).

Table 7. Comparison of the Characteristic NMR Absorptions of Silyl Ethers **59** with 2-Methylcyclopentyl Methylidiphenylsilyl Ether (**62**)^a

entry	compounds	¹ H NMR absorptions of OCH (ppm)		¹³ C NMR absorptions of OCH (ppm)	
		<i>cis</i> ^b	<i>trans</i> ^c	<i>cis</i>	<i>trans</i>
1	62 ^d	4.16	3.77	<i>e</i>	81.3
2	60 ^f	4.12	3.79		
3	59b	4.05	3.67	75.0	79.6
4	59c	4.23	3.85	76.0	80.1
5	59d	4.11	3.70	75.5	79.7

^a Deuterated chloroform was used as the solvent. ^b Appeared as a broad singlet. ^c Appeared as a quartet. ^d Reference 14h. ^e Overlapped with signals of CDCl₃. ^f Reference 33.

Changing the silyl group to a bulkier *tert*-butyldimethylsilyl group as in acylsilane **45b** (entry 2) did not change the ratio of $k_{\text{C=O}}/k_{\text{C=C}}$. These results indicated that this system is not sensitive toward the steric size of the silyl group. With the presence of phenyl groups on silicon as in acylmethylidiphenylsilane **45c** (entry 3), the carbonyl cyclization rate constant is almost tripled as compared with that of acyltrimethylsilane **45a**. The rate constant of carbonyl cyclization for acyldimethylphenylsilane **45d** (entry 4) is also doubled as compared with acyltrimethylsilane **45a**.

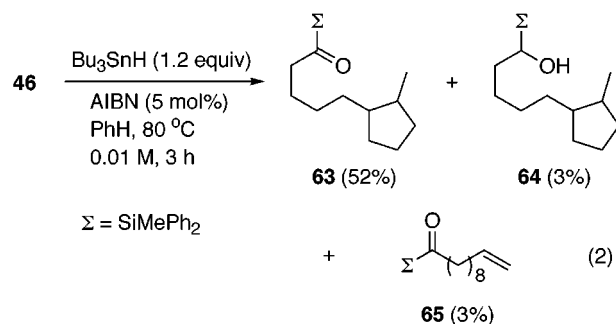
The stereochemistry of silyl ethers **59** and alcohols **60** was deduced by comparison of their NMR data with that of 2-methylcyclopentyl methylidiphenylsilyl ether (**62**).^{14h} As shown in Table 7, the ¹H NMR absorption of the C(1)-H of all the *cis*-isomers appeared at lower field and that of the *trans*-isomers appeared at higher field. In their ¹³C NMR spectra, the chemical shifts of C(1) of the *cis* isomers appeared at higher field and that of the *trans* isomers appeared at lower field. Trimethylsilyl ether *cis*-**59a** was desilylated (TBAF/THF) to give alcohol *cis*-**60** and thus secured the stereochemistry of *cis*-**59a**. As mentioned before, the stereochemical results were determined at the stage of hydrogen abstraction of the cyclized cyclic α -silyloxy radical. In the cases of the cyclizations of acylsilanes **45**, almost equal amounts of *cis*/*trans* isomers of silyl ethers **59** were obtained. These results indicate that no facial selectivity exists for this type of 2-substituted cyclopentyl radical.²⁶

The ¹³C NMR absorptions of the methyl group on the cyclopentane ring of acylsilanes *cis*-**61** all appeared at higher field at δ 14.7, indicating that the methyl groups are located at a sterically more encumbered position. In

contrast, the methyl group absorptions of the corresponding *trans* isomers appeared at lower field of δ 19.4. The *cis* selectivity observed in the formation of acylsilanes **61** is well-known for the cyclizations of 1-substituted 5-hexenyl radicals.^{7,26,29}

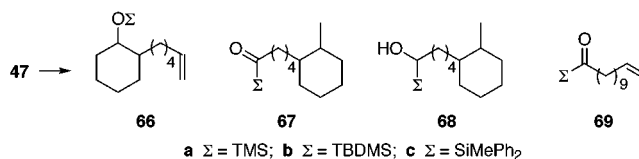
In general, the $k_{\text{C=O}}$ values for 5-exo cyclizations of acylsilanes involving secondary radicals fall in the vicinity of $1.0 \times 10^6 \text{ s}^{-1}$ at 80 °C. These values are similar to those of the acylsilane cyclizations involving 6-exo mode and primary radicals. In the acylgermane system, the cyclization of (5-bromohexenyl)triphenylgermane was estimated to have a rate constant of about $5 \times 10^6 \text{ s}^{-1}$ at 80 °C.^{9c} To compare with this acylgermane, the closest analogy that we have is the acylmethylidiphenylsilane **45c** ($k_{\text{C=O}} = 2.0 \times 10^6 \text{ s}^{-1}$ at 80 °C). The acylsilane system appears to be slower in this category.

The Rate of 6-Exo Cyclizations with Secondary Radicals. To probe the 6-exo cyclizations of acylsilanes with secondary radicals, we studied the cyclization of acylmethylidiphenylsilane **46** (eq 2). From our previous



research,^{14h} we knew that secondary radicals undergo slow 6-exo cyclizations with acylsilanes. The concentration has to be very dilute to obtain a significant amount of cyclization products. Therefore, we used a concentration of 0.01 M for the study of the cyclization of acylsilane **46**. A 1-substituted 5-hexenyl radical cyclization was used as an intramolecular clock. The cyclization reaction afforded 52% yield of cyclized acylsilane **62** and α -silyl alcohol **64** (3%). A small amount of uncyclized reduction product **65** (3%) was also isolated. There was no product derived from carbonyl cyclization. This result indicated that in acylsilane **46** the intramolecular clock is too fast to probe the acylsilane cyclization.

We next turned to the cyclization of acylsilanes **47**. In **47**, a 1-substituted 6-heptenyl radical cyclization was

Table 8. The Radical Cyclizations of Acylsilanes **47** with Tributyltin Hydride^a

entry	substrates	silyl groups (Σ)	C=O addition products (% yield; cis/trans) ^b	C=C addition products (% yield; cis/trans) ^b	$k_{C=O}/k_{C=C}$ ^c	extrapolated $k_{C=O} \times 10^{-5}$ (s ⁻¹) at 80 °C ^d
1 ^{e,f}	47a	TMS	66a (12; 1/2.7)	67a (14; 1/1)	0.86	0.35
2 ^{e,g}	47b	TBDMS		67b (18; 1/1)		
3 ^h	47c	SiMePh ₂	66c (17; 1/2)	68c (6)	2.8	1.1

^a See footnote a in Table 1. The final concentration relative to **47** was 0.01 M. ^b The cis/trans ratio was determined by ¹H NMR integration. ^c The ratio at 80 °C. ^d The rate constants were based on a $k_{C=C}$ value of 4.1×10^4 s⁻¹ at 80 °C (k_7 in Scheme 6). Inherent error exists due to the selection of this value (see text). ^e The yields were obtained by a combination of isolation and ¹H NMR integration. ^f Reduction product **69a** was also present in 59% yield. ^g Reduction product **69b** was also present in 69% yield. ^h Reduction product **69c** was isolated in 65% yield.

used as the intramolecular clock. Unfortunately, the cyclization rate constant of 1-substituted 6-heptenyl radical has not been determined in the literature. However, the 6-exo cyclization rate constant (k_7 , Scheme 6) of 6-heptenyl radical (**35**) has been reported by Beckwith^{7,19} to be 4.1×10^4 s⁻¹ (80 °C). This value was used to approximate the rate constant of the 6-heptenyl radical cyclization system present in acylsilane **47**. In the case of 5-hexenyl radical (**7a**, $n = 1$; Scheme 1), a methyl substituent at C(1) as in radical **34** (Scheme 6) decreases the k_{5-exo} value at 80 °C by one-half. Therefore, the use of k_7 to approximate the 6-exo cyclization rate constant of 1-substituted 1-heptenyl radical is likely overestimated.

As shown in Table 8, the cyclization of acyltrimethylsilane **47a** (entry 1) gave a mixture of carbonyl addition product **66a** (12%), olefin addition product **67a** (14%), and uncyclized reduction product **69a** (59%). Due to the difficulty of separation, the yields of cyclization products were calculated on the basis of ¹H NMR integration of the mixture. The $k_{C=O}$ extrapolated from this result had a value of 3.5×10^4 s⁻¹ (80 °C). As mentioned above, the actual value may be lower. This rate constant is at least 40 times slower than that of the corresponding 6-exo cyclization of a primary radical (entry 1, Table 4).

With a bulky TBDMS group as in acylsilane **47b** (entry 2), we were able to obtain a mixture of the olefin addition product **67b** (18%) and the uncyclized reduction product **69b** (69%). The carbonyl addition product was not observed. This result indicated that the acylsilane cyclization in acylsilane **47b** is much slower than that in acyltrimethylsilane **47a**.

In the case of acylmethylphenylsilane **47c** (entry 3), the cyclization gave 65% of uncyclized acylsilane **69c** along with a mixture of cyclized ether **66c** (17%) and α -silyl alcohol **68c** (6%). The $k_{C=O}$ obtained from this study gave what is presumably an overestimated value of 1.1×10^5 s⁻¹ (80 °C). This rate constant is about three times that of the acyltrimethylsilane **47a**.

In general, the 6-exo cyclizations of acylsilanes involving secondary radicals are at least an order of magnitude slower than the corresponding cyclizations of primary radicals. The 1,6-cyclization of a secondary radical with acyltriphenylgermane^{9d} was estimated to have a $k_{cyclization}$ in the range of $(5-6) \times 10^5$ s⁻¹. Therefore, again, the acyltriphenylgermane system cyclizes more efficiently than the acylsilane system.

The stereochemical assignment of the cyclized silyl ethers **66** was based on the spectroscopic data of 2-

methylcyclohexyl silyl ethers reported previously.^{14h} In acylsilanes **67a** and **67b**, two methyl doublets of equal intensity appeared at δ 0.78 and 0.84 which correlate well with those of the *cis*- and *trans*-1,2-dimethylcyclohexane³⁴ (methyl doublets at δ 0.83 for the *cis* isomer and 0.90 for the *trans* isomer). The characteristic absorptions of α -silyl alcohol **68c** contained four sets of overlapped doublets, and the isomeric ratio was not determined.

Conclusions

In this study, using the intramolecular competition experiments we were able to determine the approximate rates of radical cyclizations of acylsilanes. In general, for acylsilanes, the 5-exo cyclization rate constants involving primary radicals determined at 80 °C are approximately 10^6 s⁻¹. The rate constants for 6-exo cyclizations of primary radicals and the 5-exo cyclizations of secondary radicals are approximately 10^5 s⁻¹. The 6-exo cyclizations with secondary radicals are the slowest, and the cyclization rate constants are approximately 10^4 s⁻¹. The values of the cyclization rate constants are dependent upon the substituents on silicon. The 6-exo cyclizations are sensitive toward steric effect; therefore, a bulky silyl group reduces the cyclization rate significantly. The presence of a phenyl group on silicon increases the rate, and this effect is probably the result of the electron-withdrawing nature of the phenyl group. The acetylenic group on silicon also accelerates the cyclization, and this phenomenon is probably due to the smaller size and electron-withdrawing nature of the acetylenic group. Due to the ease of preparation, we suggest using the methylphenylsilyl group in synthetic applications of acylsilane cyclizations.

With limited kinetic data on ω -formyl radical cyclizations⁶ available for comparison, the acylsilane radical cyclizations appear to be equally fast when the right silyl group is chosen. The acylsilane system is therefore a good synthetic equivalent of the ω -formyl radical cyclizations. The advantage of the acylsilane system is the irreversible nature of the cyclization. Compared with acylgermanes,⁹ the acylgermane radical cyclizations appear to be less sensitive to the steric size of the germyl group. This may be attributed to the longer C-Ge bond. A similar electronic effect on cyclizations was also reported in the

(34) Pouchert, C. J. *The Aldrich Library of NMR Spectrum*; 2nd ed.; Aldrich Chemical: Milwaukee, 1983; 1(1), 51A, 51B.

case of acylgermanes. The radical cyclization rates of acylgermanes are also dependent on the nature of the initial radical. Although the radical cyclizations of acylgermanes and acylsilanes are similar in many ways, the two systems yield different types of end products. The acylgermanes lead to the formation of cyclic ketones, while the acylsilanes afford silyl-protected cyclic alcohols. The two systems are complementary.

Experimental Section

Melting points are uncorrected. ^1H NMR spectra were recorded at 200 or 300 MHz; ^{13}C NMR spectra were recorded at 50 or 75 MHz. Tetramethylsilane ($\delta = 0$ ppm) or CHCl_3 ($\delta = 7.24$ ppm) were used as internal standards, and CDCl_3 was used as the solvent. Benzene and THF were distilled from sodium benzophenone ketyl under N_2 . Dimethylformamide (DMF) was dried over calcium hydride. Acetone was distilled over sodium carbonate. The benzene used for cyclization reactions was deoxygenated by passing a gentle stream of argon through for 0.5 h before use. All reactions were performed under a blanket of N_2 or Ar.

Dimethyl 2-(3-Butenyl)-2-(2-(2,6-dithiacyclohexyl)ethyl)malonate (38). To a mixture of 204 mg (6.8 mmol) of sodium hydride (80% dispersion in mineral oil) in 6 mL of DMF cooled at 0°C was added dropwise over 10 min a solution of 0.71 mL (6.2 mmol) of dimethyl malonate in 3 mL of DMF. The resulting mixture was stirred at the same temperature for 10 min followed by the addition of a solution of 1.41 g (6.2 mmol) of bromide **37** in 3 mL of DMF in one portion. The reaction mixture was stirred at 80°C for 3 h and then partitioned between 100 mL of ether and 100 mL of water. The ether phase was washed with brine (100 mL), dried (MgSO_4), and concentrated in vacuo. The resulting residual oil was dissolved in 3 mL of DMF and then added dropwise over 10 min to another mixture of 204 mg (6.8 mmol) of sodium hydride (80% dispersion in mineral oil) in 6 mL of DMF at 0°C . The resulting mixture was stirred at room temperature for 10 min following which was added a solution of 0.66 mL (6.5 mmol) of 4-bromo-1-butene in 3 mL of DMF in one portion. The reaction mixture was stirred at 60°C for 2 h and then partitioned between 100 mL of ether and 100 mL of water. The ether phase was washed with brine (100 mL), dried (MgSO_4), and concentrated in vacuo. The residual oil was chromatographed over silica gel (eluted with hexane/ethyl acetate, 89/11) to give 1.14 g (56%) of **38** as a pale yellow liquid: IR (neat) 1727, 1633 cm^{-1} ; ^1H NMR (200 MHz) δ 1.55–1.70 (m, 2 H), 1.70–2.00 (m, 5 H), 2.00–2.18 (m, 3 H), 2.71–2.95 (m, 4 H), 3.68 (s, 6 H), 3.94 (t, $J = 6.9$ Hz, 1 H), 4.92 (br d, $J = 10.7$ Hz, 1 H), 4.99 (br d, $J = 16.6$ Hz, 1 H), 5.60–5.85 (m, 1 H); ^{13}C NMR (50 MHz) δ 25.7 (t), 28.2 (t), 29.6 (t), 30.0 (t), 31.6 (t), 47.0 (d), 52.2 (q), 56.7 (s), 115.0 (t), 137.0 (d), 171.3 (s); HRMS calcd for $\text{C}_{15}\text{H}_{24}\text{O}_4\text{S}_2$ m/z 332.1116, found 332.1115.

2-(3-(Tetrahydropyranoxymethyl)hept-6-enyl)-1,3-dithiane (39). To a mixture of 731 mg (14.9 mmol) of sodium cyanide in 4 mL of DMF was added in one portion a solution of 2.92 g (8.8 mmol) of malonate **38** in 5 mL of DMF. The resulting mixture was heated at 164°C for 3 h and then partitioned between 100 mL of ether and 100 mL of water. The aqueous phase was extracted with ether (100 mL). The combined ether layers were washed with brine (50 mL), dried (MgSO_4), and concentrated in vacuo. The resulting brown liquid was dissolved in 8 mL of THF and then added dropwise over 10 min to a mixture of 500 mg (13.2 mmol) of LAH in 8 mL of THF at 0°C . The reaction mixture was stirred at room temperature for 1.5 h and then diluted with 10 mL of ether. To the resulting mixture cooled at 0°C was added in sequence 0.5 mL of water, 0.5 mL of 15% sodium hydroxide solution, and 1.5 mL of water. The reaction mixture was then stirred at room temperature for 30 min, filtered, and concentrated in vacuo. To the residual oil was added a few crystals of *p*-toluenesulfonic acid monohydrate and 0.963 mL (10.6 mmol) of dihydropyran, and the resulting mixture was stirred at room

temperature for 3 h. To the resulting liquid was added one drop of triethylamine, and the resulting mixture was chromatographed over silica gel (eluted with hexane/ethyl acetate, 9/1) to give 2.2 g (76%) of **39** as a colorless liquid. This material is a mixture of two diastereomers: IR (neat) 1632 cm^{-1} ; ^1H NMR (200 MHz) δ 1.20–1.93 (m, 15 H), 2.00–2.18 (m, 2 H), 2.70–2.94 (m, 4 H), 3.21 (ddd, $J = 10.6, 5.8, 4.9$ Hz, 1 H), 3.47 (dt, $J = 11.3, 4.5$ Hz, 1 H), 3.63 (ddd, $J = 10.6, 5.3, 3.7$ Hz, 1 H), 3.81 (ddd, $J = 11.3, 6.9, 3.2$ Hz, 1 H), 4.00 (t, $J = 6.5$ Hz, 1 H), 4.53 (t, $J = 3.2$ Hz, 1 H), 4.91 (br d, $J = 10.3$ Hz, 1 H), 4.98 (br d, $J = 16.9$ Hz, 1 H), 5.77 (ddt, $J = 16.9, 10.3, 6.6$ Hz, 1 H); ^{13}C NMR (50 MHz) δ 19.4 (t), 25.5 (t), 26.0 (t), 28.5 (t), 30.4 (t), 30.6 (t), 31.0 (t), 32.9 (t), 37.4 (d), 47.9 (d), 62.0 (t), 70.0 (t), 70.2 (t), 98.9 (d), 114.3 (t), 138.9 (d); HRMS calcd for $\text{C}_{17}\text{H}_{30}\text{O}_2\text{S}_2$ m/z 330.1687, found 330.1681.

2-(2-(1-(Trimethylsilyl)-2,6-dithiacyclohexyl)ethyl)-5-hexen-1-ol. To a solution of 640 mg (1.94 mmol) of **39** in 2 mL of THF cooled at 0°C was added dropwise over 10 min a solution of 1.50 N *n*-butyllithium in hexane (1.95 mL, 2.94 mmol). The resulting solution was stirred at the same temperature for 20 min followed by the addition of a solution of 0.325 mL (2.55 mmol) of chlorotrimethylsilane in 1 mL of THF. The reaction mixture was stirred at 0°C for 2 h and then partitioned between 100 mL of ether and 100 mL of water. The ether layer was washed with brine (100 mL), dried (MgSO_4), and concentrated. The brown liquid obtained was dissolved in 5 mL of methanol with the addition of a few crystals of *p*-toluenesulfonic acid monohydrate and stirred at room temperature for 2 h. Two drops of triethylamine was added to the reaction mixture, and the resulting solution was concentrated. The resulting liquid was chromatographed over silica gel (eluted with hexane/ethyl acetate, 8/2) to give 507 mg (82%) of the alcohol as a pale yellow liquid: IR (neat) 3414, 1633 cm^{-1} ; ^1H NMR (200 MHz) δ 0.17 (s, 9 H), 1.35–1.60 (m, 5 H), 1.75–2.28 (m, 7 H), 2.43 (dt, $J = 14, 4$ Hz, 2 H), 3.00 (ddd, $J = 14, 12, 4$ Hz, 2 H), 3.58 (d, $J = 4$ Hz, 2 H), 4.94 (br d, $J = 10$ Hz, 1 H), 5.00 (br d, $J = 17$ Hz, 1 H), 5.80 (ddt, $J = 17, 10, 7$ Hz, 1 H); ^{13}C NMR (50 MHz) δ -2.4 (q), 23.4 (t), 25.1 (t), 28.5 (t), 30.2 (t), 31.2 (t), 34.3 (t), 38.9 (s), 40.5 (d), 65.3 (t), 114.6 (t), 138.7 (d); HRMS calcd for $\text{C}_{15}\text{H}_{30}\text{OS}_2\text{Si}$ m/z 318.1507, found 318.1512.

4-Bromomethyl-1-trimethylsilyl-7-octen-1-one (40a). To a solution of 259 mg (0.814 mmol) of 2-(2-(2-(trimethylsilyl)-2,6-dithiacyclohexyl)ethyl)-5-hexen-1-ol and 0.17 mL (1.22 mmol) of triethylamine in 1 mL of dichloromethane at 0°C was added 94 μL (1.22 mmol) of methanesulfonyl chloride. The resulting mixture was stirred at 0°C for 30 min and then partitioned between 50 mL of ether and 50 mL of water. The ether phase was washed with brine (50 mL), dried (MgSO_4), and concentrated. The resulting yellow liquid was dissolved in 2 mL of dry acetone and stirred with 139 mg (1.60 mmol) of lithium bromide at 80°C for 2 h. The resulting mixture was partitioned between 50 mL of dichloromethane and 50 mL of water. The organic layer was dried (MgSO_4) and concentrated to give a brown liquid. To the liquid and 121 mg (1.44 mmol) of sodium bicarbonate in a mixture of 2 mL of acetonitrile, 2 mL of THF, and 1 mL of water was added over 5 min a solution of 585 mg (1.36 mmol) of bis(trifluoroacetoxy)iodobenzene in 2 mL of acetonitrile. The resulting mixture was stirred at room temperature for 5 min and then partitioned between 50 mL of dichloromethane and 50 mL of water. The organic layer was dried (MgSO_4) and concentrated. The residual oil was chromatographed over silica gel (eluted with hexane/ethyl acetate, 96/4) to give 126 mg (54%) of **40a** as a pale yellow liquid: IR (neat) 1633 cm^{-1} ; ^1H NMR (200 MHz) δ 0.19 (s, 9 H), 1.38–1.68 (m, 5 H), 1.98–2.12 (m, 2 H), 2.44–2.73 (m, 2 H), 3.40 (d, $J = 4$ Hz, 2 H), 4.90–5.06 (m, 2 H), 5.76 (ddt, $J = 17, 10, 7$ Hz, 1 H); ^{13}C NMR (50 MHz) δ -3.2 (q), 24.9 (t), 30.7 (t), 31.7 (t), 38.2 (d), 38.5 (t), 45.1 (t), 115.0 (t), 138.1 (d), 247.4 (s); HRMS calcd for $\text{C}_{15}\text{H}_{23}^{79}\text{BrOSi}$ m/z 290.0701, found 290.0707.

5-Bromomethyl-1-trimethylsilyl-8-nonen-1-one (43a). To a solution of 608 mg (3.16 mmol) of **41a** in 6 mL of THF cooled at 0°C was added dropwise over 5 min a solution of 1.56 N *n*-butyllithium in hexane (2.40 mL, 3.74 mmol). The resulting mixture was stirred at 0°C for 30 min and then

added to a solution of 885 mg (3.11 mmol) of **42** cooled at 0 °C. The reaction mixture was stirred at 0 °C for 5 h and then partitioned between 100 mL of ether and 40 mL of water. The organic layer was washed with brine (20 mL), dried (MgSO₄), and concentrated in vacuo. The residual oil, 800 mg of Celite, and 240 mg (3.11 mmol) of sodium bicarbonate were mixed in 10 mL of acetonitrile and 2 mL of dichloromethane. The resulting mixture was cooled at -20 °C, following which a solution of 7.3 g (13 mmol) of CAN in acetonitrile/water (10 mL/1 mL) was added over a period of 2 min. The resulting mixture was stirred at -20 °C for 10 min, filtered, and partitioned between 60 mL of ether and 30 mL of water. The organic layer was washed with brine (20 mL), dried (MgSO₄), and concentrated in vacuo. The residual oil was chromatographed over silica gel (eluted with hexane/ethyl acetate, 98/2) to give 290 mg (31%) of **43a** as a pale yellow oil: IR (neat) 1636 cm⁻¹; ¹H NMR (300 MHz) δ 0.15 (s, 9 H), 1.18–1.62 (m, 9 H), 1.92–2.08 (m, 2 H), 2.57 (t, *J* = 6.9 Hz, 2 H), 3.40 (d, *J* = 4.4 Hz, 2 H), 4.93 (br d, *J* = 10 Hz, 1 H), 4.98 (br d, *J* = 17 Hz, 1 H), 5.75 (ddt, *J* = 17, 10, 7 Hz, 1 H); ¹³C NMR (50 MHz) δ -3.2, 18.9, 30.7, 31.5, 32.0, 38.7, 38.8, 48.3, 114.8, 138.1; HRMS calcd for C₁₃H₂₅⁷⁹BrOSi *m/z* 304.0858, found 304.0851.

General Procedure for Radical Cyclizations of Bromoacylsilanes 40, 43, 45, and 47. To a refluxing benzene (10-mL) solution of the bromoacylsilane (1 mmol) was added via syringe pump over 1 h a benzene (10-mL) solution of tributyltin hydride (1.2–1.5 mmol) and AIBN (0.05 mmol). The resulting solution was heated at 80 °C for 1 h more and concentrated in vacuo. To the residual liquid was added a few drops of wet triethylamine,³⁵ and the resulting mixture was chromatographed over silica gel (eluted with hexane/ethyl acetate) to isolate the products. The results are shown in Tables 1, 4, 6, and 7. The cyclization of bromoacylsilane **40c** is shown below as an example.

(35) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140–3154.

Radical Cyclization of 40c. cis/trans-3-(3-Butenyl)-cyclopentylmethylidiphenylsilyl Ether (48c) and cis/trans-3-(3-Methylcyclopentyl)-1-(methylidiphenylsilyl)propan-1-one (50c). According to the general procedure for radical cyclization, starting from 394 mg (0.95 mmol) of **40c**, 0.31 mL (1.14 mmol) of tributyltin hydride, and 7.7 mg (0.047 mmol) of AIBN, we obtained 249 mg (78%) of **48c** (cis/trans = 53/47) as a colorless liquid and 38 mg (12%) of **50c** (cis/trans = 1/2) as a colorless liquid. **48c**: IR (neat) 1634 cm⁻¹; ¹H NMR (300 MHz) δ 0.62 (s, 3 H), 0.98–2.25 (m, 11 H), 4.28 (q, *J* = 6.0 Hz, 0.53 H, cis isomer), 4.32–4.42 (m, 0.47 H, trans isomer), 4.85–5.05 (m, 2 H), 5.68–5.91 (m, 1 H), 7.28–7.52 (m, 6 H), 7.50–7.62 (m, 4 H); HRMS calcd for C₂₂H₂₈OSi *m/z* 336.1909, found 336.1903. **50c**: IR (neat) 1633 cm⁻¹; ¹H NMR (200 MHz) δ 0.74 (s, 3 H), 0.88 (d, *J* = 6.4 Hz, 2 H, trans isomer), 0.91 (d, *J* = 5.4 Hz, 1 H, cis isomer), 0.95–1.12 (m, 2 H), 1.15–1.28 (m, 2 H), 1.44 (quintet, *J* = 7.3 Hz, 2 H), 1.56–2.08 (m, 4 H), 2.63 (t, *J* = 7.4 Hz, 2 H), 7.30–7.46 (m, 6 H), 7.54–7.62 (m, 4 H); HRMS calcd for C₂₁H₂₅OSi *m/z* 321.1675, found 321.1673.

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Supporting Information Available: Details of compound characterization of **40b**, **c**, **43b–j**, **45a–d**, **46**, **47a–c**, **48a, b**, **49**, **50a, b**, *trans*-**53a, c, d, f, g, i, j**, *cis*-**53b, c, e, f, g, i, j**, *cis*-**54**, *trans*-**54**, **55a–g**, **56d, e, g, 57c, 58e**, *cis*-**59a–d**, *trans*-**59b–d**, **61a–d**, **63–65**, **66a, c**, **67a, b**, **68c** and **69a–c**, and ¹H and ¹³C NMR spectra of new compounds (77 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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