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Radical Cyclizations of Acylgermanes. New Reagent Equivalents of the Carbonyl Radical Acceptor Synthon

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Abstract: An in depth study of the capability of acylgermanes to function as acceptors in radical cyclizations is reported. Radicals add to acylgermanes, and rapid fragmentation of the resulting α-germylalkoxy radicals provides ketones and germyl radicals. The germyl radicals in turn propagate the chain by addition or abstraction, so the reaction occurs by a unimolecular chain transfer (UMCT) process. In contrast, acylsilanes also function as radical acceptors, but they do not participate in UMCT processes because a "radical-Brook" rearrangement intervenes. Cyclizations in 5-*exo* and 6-*exo* modes show good to excellent scope, and rate constants for cyclization can be varied over 2 orders of magnitude by changing the germanium substituents. Acyltriarylgermanes are among the best radical acceptors yet identified, and this quality makes them superior reagent equivalents of the carbonyl radical acceptor synthon. Parent cyclizations in the 4-*exo* and 7-*exo* modes fail. Attempted 3-*exo* cyclization results in a 1,2-acyl shift, which can be conducted alone or in tandem with a subsequent cyclization to the rearranged acylgermane. The results provide a foundation for future synthetic applications of radical cyclizations to acylgermanes.

Introduction

Early synthetic applications of radical cyclizations relied heavily on the use of carbon−carbon double bonds as radical acceptors.[1] But more recently[2] a wide assortment of carbon−carbon (alkynes,[3] allenes,[4] aromatic rings[5]) and carbon−nitrogen (imines,[6] hydrazones,[7] oximes,[8] nitriles,[9] heteroaromatic rings[10]) multiple bonds have been used as radical acceptors in diverse

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(1) (a) Curran, D. P. *Synthesis* **1988**, 419. (b) Curran, D. P. *Synthesis* **1988**, 487.

(2) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, p 779.

(3) (a) Clive, D. L. J.; Manning, H. W. *J. Chem. Soc., Chem. Commun.* **1993**, 666. (b) Clive, D. L. J.; Tao, Y.; Khodabocus, A.; Wu, Y. J.; Angoh, A. G.; Bennett, S. M.; Boddy, C. N.; Bordeleau, L.; Kellner, D.; Kleiner, G.; Middleton, D. S.; Nichols, C. J.; Richardson, S. R.; Vernon, P. G. *J. Am. Chem. Soc.* **1994**, *116*, 11275.

(4) (a) Crandall, J. K.; Ayers, T. A. *Tetrahedron Lett* **1991**, *32*, 3659. (b) Ziegler, C. B., Jr. *J. Org. Chem.* **1990**, *55*, 2983. (c) Apparu, M.; Crandall, J. K. *J. Org. Chem.* **1984**, *49*, 2125.

(5) (a) Bowman, W. R.; Heaney, H.; Jordan, B. M. *Tetrahedron* **1991**, *47*, 10119. (b) Ziegler, F. E.; Harran, P. G. *J. Org. Chem.* **1993**, *58*, 2768.

(6) (a) Tomaszewski, M. J.; Warkentin, J.; Werstiuk, N. H. *Aust. J. Chem.* **1995**, *48*, 291. (b) Bowman, W. R.; Stephenson, P. T.; Young, A. R. *Tetrahedron Lett.* **1995**, *36*, 5623. (c) Bowman, W. R.; Stephenson, P. T.; Young, A. R. *Tetrahedron* **1996**, *52*, 11445.

(7) (a) Bernardhenriet, C. D.; Grimaldi, J. R.; Hatem, J. M. *Tetrahedron Lett.* **1994**, *35*, 3699. (b) Bowman, W. R.; Stephenson, P. T.; Terrett, N. K.; Young, A. R. *Tetrahedron Lett.* **1994**, *35*, 6369. (c) Bowman, W. R.; Stephenson, P. T.; Terrett, N. K.; Young, A. R. *Tetrahedron* **1995**, *51*, 7959. (d) Sturino, C. F.; Fallis, A. G. *J. Org. Chem.* **1994**, *59*, 6514. (e) Kim, S.; Cheong, J. H.; Yoon, K. S. *Tetrahedron Lett.* **1995**, *36*, 6069. (f) Kim, S.; Kee, I. S. *Tetrahedron Lett.* **1993**, *34*, 4213.

(8) (a) Bartlett, P. A.; McLaren, K. L.; Ting, P. C. *J. Am. Chem. Soc.* **1988**, *110*, 1633. (b) Della, E. W.; Knill, A. M. *Aust. J. Chem.* **1994**, *47*, 1833. (c) Hatem, J.; Henriet-Bernard, C.; Grimaldi, J.; Maurin, R. *Tetrahedron Lett.* **1992**, *33*, 1057. (d) Marco-Contelles, J.; Destabel, C.; Chiara, J. L.; Bernabe, M. *Tetrahedron-Asymmetry* **1995**, *6*, 1547. (e) Naito, T.; Tajiri, K.; Harimoto, T.; Ninomiya, I.; Kiguchi, T. *Tetrahedron Lett.* **1994**, *35*, 2205.

(9) (a) Griller, D.; Schmid, P.; Ingold, K. U. *Can. J. Chem.* **1979**, 57, 831. (b) Clive, D. L. J.; Beaulieu, P. L.; Set, L. *J. Org. Chem.* **1984**, 49, 1313.

(10) Murphy, J. A.; Sherburn, M. S. *Tetrahedron* **1991**, *47*, 4077.

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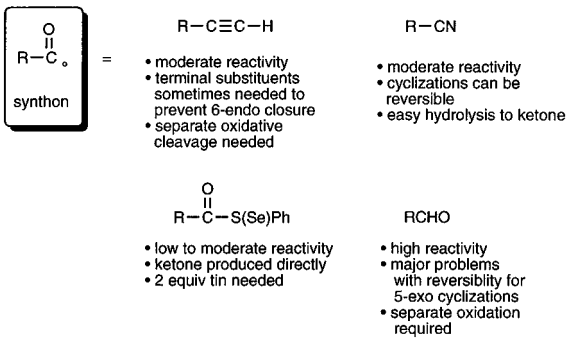
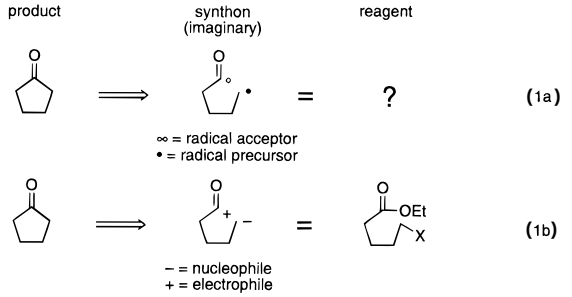


Figure 1. Existing reagent equivalents of carbonyl radical acceptors.

settings. Indeed, the variety of radical acceptors that can be used in radical cyclizations is a major synthetic attraction.[11]

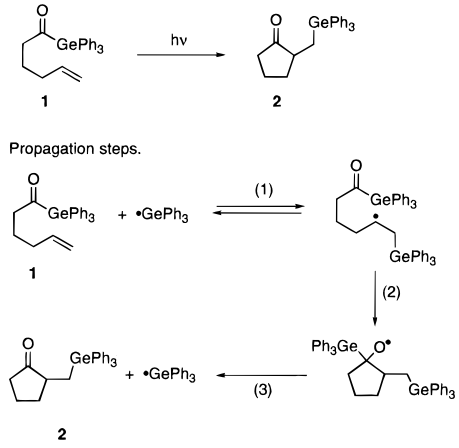
The carbonyl group is one of the central functional groups in organic chemistry, and this renders the development of radical cyclizations to make carbonyl compounds an important goal. Equation 1a depicts a strategy[12] for formation of a cyclopentanone by reaction of an alkyl radical precursor with a carbonyl radical acceptor. The strategy complements the traditional ionic route, eq 1b, which is an intramolecular acylation.[13] The



functional group tolerance of radical methods could make a radical-based strategy the method of choice for many synthetic applications. The alkyl radical can readily be prepared from a variety of standard precursors including halides. The problem with the strategy in eq 1a is that reagent equivalents of the carbon radical acceptor synthon are often lacking in one or more respects. In contrast, carbonyl radical precursors[14] (acyl halides, sulfides, selenides, tellurides, cobalts, etc.) are readily available, and the derived acyl and related radicals provide powerful synthetic options in a number of settings.

Existing reagent equivalents of the carbonyl radical acceptor synthon are summarized in Figure 1. Cyclizations to alkynes have often been used,[3] and oxidative cleavage is required to reveal the ketone. This is a valuable strategy when ketone protection before and after the radical cyclization is desired, and it has added flexibility because the terminal alkyne substituents can be chosen to accelerate the radical cyclization (TMS and Ph are popular choices). However, the strategy is indirect, ranks low on the "atom economy" scale, and sacrifices

Scheme 1



the bond-forming capabilities of the carbonyl group (because it is masked). A more direct route involves cyclizations to nitriles;[9] the intermediate imines are easily hydrolyzed by mild acid. But nitriles are very modest radical acceptors which are useful only for fairly rapid cyclizations, and attempts to form bridged or other moderately strained rings usually result in fragmentation (nitrile transfer).[15]

Direct equivalents of the carbonyl radical acceptor are lacking because functional groups like amides and esters are inert to radical addition.[16] Recently, acyl sulfides and selenides have been used with some success.[17] As anticipated from studies in the vitamin B_{12} area,[17b] acyl sulfides have relatively low reactivity, but acyl selenides show more potential. For these substrates, a reagent like hexabutylditin is required in stoichiometric amounts to propagate chains. Carbon monoxide adds to reactive radicals at high CO pressures, but it obviously cannot be used as a radical acceptor in cyclizations. However, it is very useful in radical additions and in tandem reactions of all sorts.[18] Aldehydes are excellent radical acceptors,[19] and the resulting alcohols can be oxidized to ketones under mild conditions. The problem here is that radical cyclizations to carbonyl groups are reversible, and trapping of the closed product is not always easy. In general, cyclohexanols can be made by radical cyclizations to aldehydes, but attempts to form other ring sizes often results in migration or ring expansion. These reactions are of significant preparative interest in their own right.[20]

In 1990, Kiyooka and co-workers[21] reported the discovery of an interesting reaction of unsaturated acylgermanes, the simplest example of which is shown in Scheme 1. Photolysis of **1** with a UV lamp provided **2** in 92% yield. This isomerization took place under very mild conditions and had good generality, although some limitations were identified. A mechanism was posited in which the acylgermane behaved as the radical precursor and the alkene behaved as the radical acceptor. We were intrigued by these observations, and we soon garnered strong experimental support for the alternative mech-

(11) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237.

(12) For retrosynthetic planning with radical reactions, see: Curran, D. P. *Synlett* **1991**, 63.

(13) For example, see: Molander, G. A.; Harris, C. R. *J. Am. Chem. Soc.* **1995**, *117*, 3705. Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1993**, *58*, 7216.

(14) (a) Lucas, M. A.; Schiesser, C. H. *J. Org. Chem.* **1996**, *61*, 5754. (b) Chen, L.; Gill, G. B.; Pattenden, G.; Simonian, H. *J. Chem. Soc., Perkin Trans. 1* **1996**, 31. (c) Batsanov, A.; Chen, L.; Gill, G. B.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1996**, 45. (d) Penn, J. H.; Liu, F. *J. Org. Chem.* **1994**, *59*, 2608. (e) Gill, G. B.; Pattenden, G.; Reynolds, S. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 369. (f) Chen, C.; Crich, D. *Tetrahedron Lett.* **1993**, *34*, 1545. (g) Chen, C.; Crich, D.; Papadatos, A. *J. Am. Chem. Soc.* **1992**, *114*, 8313. (h) Crich, D.; Yao, Q. *J. Org. Chem.* **1996**, *61*, 3566.

(15) Curran, D. P.; Seong, C. M. *Tetrahedron* **1992**, *48*, 2175.

(16) For the only known exception, see: Lee, E.; Yoon, C. H.; Lee, T. H. *J. Am. Chem. Soc.* **1992**, *114*, 10981.

(17) (a) Kim, S.; Jon, S. Y. *Chem. Commun.* **1996**, 1335. (b) Dowd, P. *Sel. Hydrocarbon Act.* **1990**, 265. (c) For related bimolecular reactions to oxime ethers, see: Kim, S.; Lee, I. Y.; Yoon, J. Y.; Oh, D. H. *J. Am. Chem. Soc.* **1996**, *118*, 5138.

(18) (a) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177. (b) Ryu, I.; Sonoda, N. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1051.

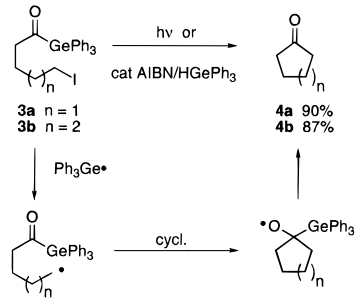
(19) (a) Walton, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1991**, *113*, 5791. (b) Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1989**, *111*, 2674.

(20) Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091.

(21) Kiyooka, S.; Kaneko, Y.; Matsue, Y.; Hamada, M.; Fujiyama, R. *J. Org. Chem.* **1990**, 55, 5562.

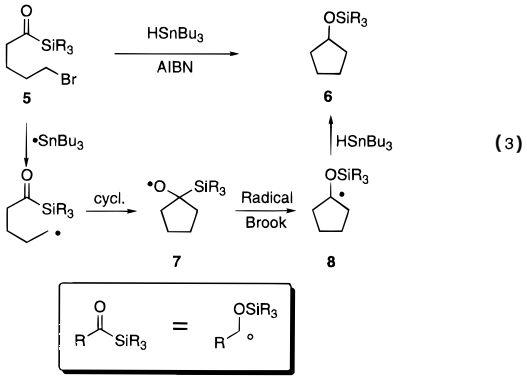
anism shown in Scheme 1.[22] In this mechanism, the alkene behaves as a radical precursor, reversibly adding the triphenylgermyl radical (step 1), and the acylgermane behaves as the radical acceptor (step 2). The key fragmentation (step 3) occurs not with cleavage of a carbon−carbon bond (as happens with radical cyclizations to aldehydes and ketones) but instead with cleavage of the carbon−germanium bond. This step transfers the chain, so the overall transformation requires only initiation. The reaction is a heteroatom analog of the well-known cyclization of vinylstannanes.[23] The chain transfer process is unimolecular, conferring on this transformation all the advantages associated with unimolecular chain transfer (UMCT) reactions.[24]

These results suggested that acylgermanes, and possibly silanes and stannanes as well, showed potential as reagent equivalents of the carbonyl radical acceptor synthon. Indeed, in preliminary experiments[25] we showed that cyclizations of **3a** and **3b** to cyclopentanone **4a** and cyclohexanone **4b** occurred rapidly and in very high yield (eq 2). Estimates of rate constants suggested that the acylgermanes were much more reactive towards radicals than most other acceptors.



(2)

Our preliminary studies of acylsilanes were preempted by a report of Tsai,[26] who observed that acylsilanes are indeed excellent radical acceptors, yet they do not behave like acylgermanes. UMCT reactions will not propagate, but haloacylsilanes**5** can be reductively cyclized with reagents like tin hydride to give silylcyclopentanols **6** (eq 3). The difference in reaction

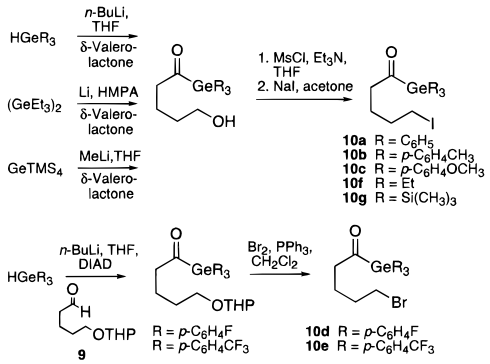


(3)

mode between the acylsilanes and acylgermanes can be traced to the high bond strength of the silicon-oxygen bond. The silyl radical is not easily released from **7**, but instead undergoes a "radical-Brook" rearrangement to give **8**, which in turn abstracts hydrogen from tin hydride in a standard bimolecular chain process. Acylsilanes are thus reagent equivalents of the hydroxyalkyl radical acceptor synthon. In this respect, they resemble aldehydes, but with two significant advantages: (1) the radical-Brook rearrangement prevents fragmentation, and (2) the rearranged radical **8** can be used for additional transformations.[26]

(22) Curran, D. P.; Liu, H. *J. Org. Chem.* **1991**, 56, 3463.

Scheme 2



Herein we report the full details of our studies on the scope and limitations of radical cyclization reactions of acylgermanes. These studies have focused on how the germanium and radical substituents and the ring size affect the radical cyclization. These areas were chosen because other substituent effects in radical cyclizations are well understood and can be superposed on acylgermane reactions once the unique features of acylgermanes are evident. Acylgermanes are indeed excellent radical acceptors. As far as we know, radical cyclizations of acylstannanes have still not been reported, but it seems highly probable that they will be good radical acceptors that undergo reactions analogous to those of the acylgermanes, not silanes.

Results and Discussion

Synthesis of Acylgermanes. Acylgermanes have been much less widely synthesized and studied than their acylsilane and stannane counterparts, but the syntheses of all three classes of compounds are conceptually similar.[27] Scheme 2 illustrates the synthesis of the acylgermanes that were used in rate studies to uncover the effects of germane substitution. One of two pathways was generally followed. In the first route a germyllithium species[28] (generated by deprotonation or transmetalation,[29] depending on the germanium substituents) was reacted with δ-valerolactone, and the resulting unstable hydroxylacylgermane was mesylated and converted into the iodide. This route was not successful for substrates bearing electron poor aromatic rings, and these were made instead by addition of the germyllithium to an aldehyde followed by DIAD oxidation according to Marshall for acylstannane synthesis.[30]

Other acylgermanes used for the ring size studies were made by one of these two routes, and complete details of all of these

(23) Some examples: (a) Gomez, A. M.; Lopez, J. C.; Fraser-Reid, B. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1689. (b) Curran, D. P.; van Elburg, P. A. *Tetrahedron Lett.* **1989**, *30*, 2501. (c) Ardisson, J.; Ferezou, J. P.; Julia, M.; Li, Y.; Liu, L. W.; Pancrazi, A. *Bull. Soc. Chim. Fr.* **1992**, *129*, 387. (d) Kinney, W. A. *Tetrahedron Lett.* **1993**, *34*, 2715. (e) Harris, F. L.; Weiler, L. *Tetrahedron Lett.* **1987**, *28*, 2941. (f) Lowinger, T. B.; Weiler, L. *J. Org. Chem.* **1992**, *57*, 6099. (g) Jasperse, C. P.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 5601.

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

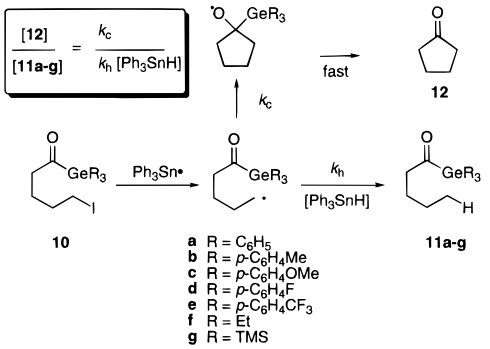
(25) Curran, D. P.; Palovich, M. *Synlett* **1992**, 631.

(26) (a) Tsai, Y. M.; Cherng, C. D. *Tetrahedron Lett* **1991**, *32*, 3515. (b) Tsai, Y.-M.; Tang, K.-H.; Jiaang, W.-T. *Tetrahedron Lett.* **1993**, *34*, 1303. (c) Curran, D. P.; Jiaang, W.-T.; Palovich, M.; Tsai, Y.-M. *Synlett* **1993**, 403. (d) Tsai, Y. M.; Chang, S. Y. *J. Chem. Soc., Chem. Commun.* **1995**, 981.

(27) (a) Cirillo, P. F.; Panek, J. S. *Org. Prep. Proced. Int.* **1992**, *24*, 555. (b) Qi, H.; Curran, D. P. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Elsevier Science: Oxford, U.K., 1995; Vol. 5, p 409.

(28) The desired germanes have been prepared starting with tetrasubstitution of germanium(IV) chloride by Grignard reaction followed by bromination and LAH reduction of the monobrominated derivative. For the synthesis of Ph_3GeH, see: Harris, D. M.; Nebergall, W. H.; Johnson, O. H. *Inorg. Synth.* **1957**, *5*, 76.

Scheme 3



syntheses are contained in the Supporting Information. Yields for the formation of the acylgermanes were typically in the 50−65% range, although a few instances of both higher and lower yields were encountered. The acylgermanes for kinetic studies were purified by flash chromatography and/or recrystallization. Some of the acylgermanes may not be completely stable to flash chromatography (as determined by rechromatography of pure samples), but for the kinetic experiments, sample purity took priority over yield. These acyltriphenylgermanes proved reasonably stable to atmospheric oxygen (in contrast to acylstannanes, many of which are readily air oxidized). The compounds were handled with no special precautions; however, long-term storage requires chilling under nitrogen or argon.

Effects of the Substituents on Germanium. To determine the effects of the substituents on germanium on the rate constant for 5-*exo* radical cyclization, we selected five triarylgermanes of varying electronic properties along with a triethylgermane and a tris(trimethylsilyl)germane (Scheme 3). Rate constants were estimated by conducting standard competition kinetic studies[31] in the presence of 1.3 equiv of triphenyltin hydride. Reactions (1−3 trials) were conducted at both 25 and 80 °C at three or four different concentrations in C_6D_6 in sealed NMR tubes, and the ratio of the reduced product **11** to cyclopentanone (**12**) was measured by ^{1}H NMR integration of the methylene resonances adjacent to the carbonyl. This is facile since the CH_2 group α to the carbonyl group of acylgermanes **10** is considerably further downfield from that of cyclopentanone. The competition involved between cyclization (a unimolecular chain transfer process[24]) and reduction (a bimolecular chain transfer process) is a standard one, as shown in Scheme 3.

The data from one representative set of experiments (with **10a**) are shown in Table 1. Analogous tables in the Supporting Information provide the data for all the other substrates. No other products were detected in any of the experiments. Furthermore, all the acylgermanes provided cyclopentanone and the corresponding germyl iodide in high yield (>95%) on both thermal and photochemical initiation (in the absence of tin hydride). Therefore, the competition experiments were not standardized; we assume that the combined yield of the two products is 100%.

The calculated rate constants of all the substrates are compiled in Table 2. These should be considered estimates for (at least) two reasons: (1) the precision of the base rate constant—hydrogen abstraction from triphenyltin hydride[32] —is not as high as that with tributyltin hydride (which could not be used because it interfered with integration of the cyclopentanone CH_2 resonance), and (2) the reactions are not pseudo-first order.[33] However, that the different reaction concentrations consistently produced the same rate constant within experimental error suggests that the error introduced by using non-first-order conditions is not very significant. Rate constants at 25 °C were consistently about 1 order of magnitude below those at 80 °C.

Table 1. 5-*exo* Cyclization Rate Constant of I(CH2)4COGePH3 (**10a**)

entry	temp, °C	[$HSnPh_3$], M	[**12**]/[**11a**][a]	k_c, s^{-1}
1	80	0.23	1.39	6.5×10^6
2	80	0.13	2.32	6.7×10^6
3	80	0.065	4.12	6.2×10^6
4	80	0.033	7.75	6.0×10^6
5	25	0.29	0.53	6.0×10^5
6	25	0.14	0.96	6.0×0^5
7	25	0.07	1.90	6.1×0^5
8	25	0.036	4.00	6.7×0^5
5-*exo* cyclization				k_c(80 °C) = 6.4×10^6 s^{-1} k_c(25 °C) = 6.2×10^5 s^{-1}

[a] Average of 2−3 trials.

Table 2. Rate Constants for 5-exo Radical Cyclizations of Acylgermanes

entry	R	k_c(25 °C), s^{-1}	k_c(80 °C), s^{-1}
1	C_6H_5	6.2×10^5	6.4×10^6
2	p-C_6H_4Me	5.1×10^5	5.0×10^6
3	p-C_6H_4OMe	4.8×10^5	4.9×10^6
4	p-C_6H_4F	1.0×10^6	1.3×10^7
5	p-$C_6H_4CF_3$		2.7×10^7
6	Et	2.9×10^5	2.9×10^6
7	TMS	2.7×10^4	3.1×10^5

These competition experiments show that the cyclization rate is dependent on the germanium ligand. Compared to the phenyl derivative **10a** [k_c(80 °C) = 6.4×10^6 s^{-1}], we observed a slightly decreased cyclization rate for the *p*-tolylacylgermane **10b** [k_c(80 °C) = 5.0×10^6 s^{-1}] and the *p*-anisyl derivative **10c** [k_c(80 °C) = 4.9×10^6 s^{-1}]. On the other hand, the fluorinated acylgermanes **10d** [k_c(80 °C) = 1.3×10^7 s^{-1}] and **10e** [k_c(80 °C) = 2.7×10^7 s^{-1}] were slightly more reactive. This trend supports a standard picture in which the LUMO energy of the carbonyl group is an important factor; lowering the LUMO accelerates the cyclization.

The 5-*exo* cyclization rate constants of the aromatic acylgermanes correlate roughly linearly with the pK_a value of the acids $(XC_6H_4)_3GeCOOH$[34] as well as with the Hammett constant σ_{para}. Plots of the cyclization rate constants against the ^{13}C NMR chemical shifts of the respective carbonyl carbon are also nearly linear (graphs shown in the Supporting Information). On the other hand, correlation with the Hammett constants representing the inductive effect σ_I or the mesomeric effect σ_M alone are not linear. This indicates that both effects influence the radical acceptor reactivity.

In addition to these trends, the absolute magnitude of these rate constants is also noteworthy. These acylgermanes are among the most reactive radical acceptors known for 5-*exo* cyclizations. Cyclizations to acylgermanes are about 1 order

(29) (a) Brook, A. G.; Dillon, P. J.; Pearce, R. *Can. J. Chem.* **1971**, *49*, 133. (b) Brook, A. G.; Abdesaken, F.; Söllradl, H. *J. Organomet. Chem.* **1986**, *299*, 9. (c) Kraus, C. A.; Flood, E. A. *J. Am. Chem. Soc.* **1932**, *54*, 1635. (d) Anderson, H. H. *J. Am. Chem. Soc.* **1957**, *79*, 326.

(30) (a) Marshall, J. A.; Welmaker, G. S.; Gung, B. W. *J. Am. Chem. Soc.* **1991**, 113, 647. (b) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31.

(31) Newcomb, M. *Tetrahedron* **1993**, 49, 1151.

(32) (a) Carlsson, D. J.; Ingold, K. U. *J. Am. Chem. Soc.* **1968**, *90*, 7047. (b) Walling, C.; Cioffari, A. *J. Am. Chem. Soc.* **1972**, *94*, 6059. We used k_H [$HSnPh_3$, 80 °C] = 2.5×10^7 M^{-1} s^{-1}.

(33) As usual, the "effective tin hydride concentration" was estimated as the concentration of tin hydride at 50% conversion of the acylgermane.

(34) Steward, O. W.; Dziedzic, J. E.; Johnson, J. S.; Frohliger, J. O. *J. Org. Chem.* **1971**, *36*, 3480.

of magnitude faster than similar reactions of aldehydes and alkenes, and closer to 2 orders of magnitude faster than additions to nitriles and unactivated alkynes. More sterically correct comparisons, for example, with 2-substituted alkenes or ketones, are even more impressive. For example, simple 5-*exo* cyclizations to unactivated ketones do not occur at all, so the acylgermanes are probably at least 10^4 or 10^5 times more reactive than the corresponding methyl ketones. Acylgermanes react at rates comparable to those of some of the best radical acceptors including hydrazones and activated alkenes. Unfortunately, these high rate constants for 5-*exo* cyclizations did not translate into successful bimolecular reactions. Chains did not propagate in attempts to add several halides to a few simple acylgermanes.[35]

The nonaromatic germanium ligands exhibited lower reactivity than the triphenylgermane group. The radical derived from triethylacylgermane **10f** [k_c(80 °C) = 2.9×10^6 s^{-1}] cyclized about 3 times more slowly while that derived from tris(trimethylsilyl) derivative **10g** [k_c(80 °C) = 3.1×10^5 s^{-1}] cyclized about 20 times more slowly. Nonetheless, in the yield experiments described above (which are directly relevant to synthetic applications), both compounds provided cyclopentanone in >95% yield. The decreased reactivity of these two substrates could be due to a higher LUMO energy or to a steric effect (or both).

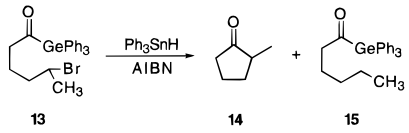
Because acylgermanes operate by a UMCT mechanism, they effectively combine the radical cyclization and chain transfer steps. The rate constants for these processes are crucial in many applications. Excellent tuning of the radical acceptor reactivity in 5-*exo* cyclizations of acylgermanes is available by varying the germanium ligands. The efficiency of the radical acceptor can readily be varied over about 2 orders of magnitude without changing the yield of the final product. While a reactive acceptor is desired for many processes, tandem reactions often require radical traps of lower reactivity to allow time for intermediate radicals to do other reactions prior to chain transfer. In this respect, acylgermanes should be excellent reagents for radical cascades.

Ring Size and Radical Substituent Effects. To study the scope of acylgermane radical cyclizations, we prepared a series of substrates in which both the substitution of the radical (primary, secondary, tertiary) and the chain length connecting the radical and the acylgermane were varied. The preparation of the precursors for these experiments is fully described in the Supporting Information. Preparative experiments (usually by sunlamp photolysis) were conducted to determine the yield of cyclization. Because the products of these simple substrates are volatile, yields were usually determined by ^{1}H NMR against internal standards. Competitive experiments were conducted with triphenyltin hydride to estimate rate constants for cyclization. With these substrates, the competitive experiments were not as extensive. Typically one or two trials at two or three different concentrations were conducted. All competitive experiments were carried out at 80 °C.

The results of the preparative cyclization with the secondary radical precursor **13** are shown in eq 4a. Cyclization of **13** by photolysis with a sunlamp proceeded smoothly over the course of 30 min at room temperature and provided 2-methylcyclopentanone (**14**) in 80% yield (as measured by ^{1}H NMR against an internal standard). The competition experiments with triphenyltin hydride (Table 3) provided an estimated rate constant for cyclization of about 5×10^6 s^{-1}. This is comparable to the rate constant for cyclization of the primary radical (entry 1 in Table 2).

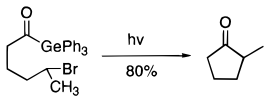
(35) Curran, D. P.; Diederichsen, U. *J. Organomet. Chem.*, in press.

Table 3. Competitive Rate Experiments with **13**

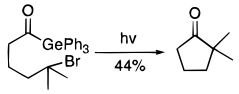


13 **14** **15**

experiment	concn of **13**, M	ratio **14**/**15**	k_c, s^{-1}
1	0.1	3.03/1	5.0×10^6
2	0.1	2.70/1	4.4×10^6
3	0.2	1.53/1	4.6×10^6
4	0.2	1.71/1	5.2×10^6



13 **14** (4a)



16 **17** (4b)

In contrast to the good results with the secondary radical precursor **13**, the cyclization of the tertiary radical precursor **16** was not nearly as efficient. Photolysis of the acylgermane **16** with a sunlamp for 30 min at room temperature resulted in only 44% yield of 2,2-dimethylcyclopentanone (**17**) as measured by ^{1}H NMR (eq 4b). The proton NMR spectrum showed that the acylgermane **16** was consumed, but no other products besides **17** were evident.

The results of the competition experiments performed with acylgermane **16** are shown in Table 4. From these experiments, the rate constant was calculated to be about $(1-2) \times 10^4$ s^{-1} at 80 °C. This is over 2 orders of magnitude lower than the primary and secondary 5-*exo* cyclization rate constants. These experiments have considerably more error than the prior competition experiments for two reasons. First, there is a problem with integrating the proton signals of the cyclic product **17** because even at low reaction concentrations it is formed in only small amounts. Increasing the reaction concentration from 0.003 to 0.005 M should result in a decrease in the ratio of the products, not an increase as was found in the two experiments (Table 4). Second, the assumption that the mass balance of the two products in the competition experiments is 100% may not be a good one in this case. Considering these problems, the estimated rate constant is probably on the high end. Errors aside, the bottom line is clear: the tertiary radical generated from **16** is at least 2 orders of magnitude less reactive that its primary and secondary counterparts.

The reason for the dramatic rate reduction in the cyclization of the tertiary radical is not immediately clear. FMO effects cannot be invoked since the tertiary radical has a higher SOMO than either primary or secondary radicals, and should therefore be expected to cyclize more rapidly. It is possible that steric effects are in play as suggested by the transition state models shown in Figure 2. It is possible that the rate constant for cyclization decreases when the R^1 substituent facing the large triphenylgermanium group is not hydrogen.

This analysis suggests that there is a high preference in secondary radicals for the methyl group to occupy a position trans to the triphenylgermyl group. If, on top of this, the acylgermane exhibited a high preference for either a "boatlike" or "chairlike" orientation, then high stereoselectivity would be expected in the cyclization. The stereoselectivity of the cyclization of a simple acylgermane cannot be probed directly (because the stereocenter bearing the α-germylalkyl radical is

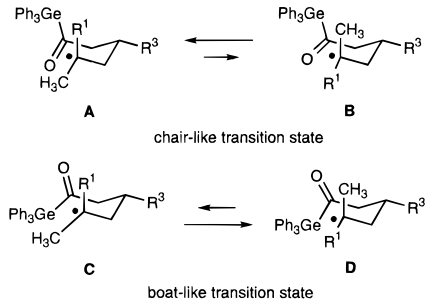
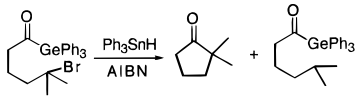


Figure 2. Transition state models for acylgermane radical cyclizations.

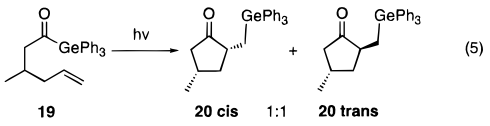
Table 4. Competitive Rate Experiments with **16**



experiment	concn of **16**, M	ratio **17**/**18**	k_c, s^{-1}
1	0.003	0.24/1	9.4×10^3
2	0.005	0.38/1	2.6×10^4

rapidly lost by fragmentation), but it can be probed indirectly simply by adding a substituent to the chain. According to the calculations of Houk and Spellmeyer,[36] C3 substituents have a good "pseudoequatorial" preference (see R^3 in Figure 2) so they should provide a good probe.

To test this idea, we prepared the unsaturated acylgermane **19** and cyclized it according to the procedure of Kiyooka (eq 5).[21] It follows from the above analysis that the trans product should predominate if a chairlike transition state is favored and the cis product should predominate if a boatlike transition state is favored. Unfortunately, the results were not very informative.

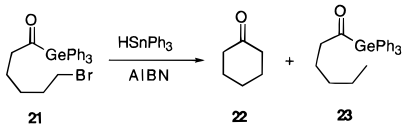


Cyclization of **19** by sunlamp (30 min) or sunlight (8 h) photolysis provided a 1/1 mixture of stereoisomers **20** in good yield. In view of the low selectivity, no attempt was made to separate the isomers or assign the configuration. Assuming that the C3 methyl group does indeed have a reasonable pseudoequatorial preference, the results could mean that this cyclization occurs competitively through boatlike and chairlike transition states, or they could mean that the postulate that the C1 substituent and the triphenylgermyl group must be trans in the cyclization is incorrect.

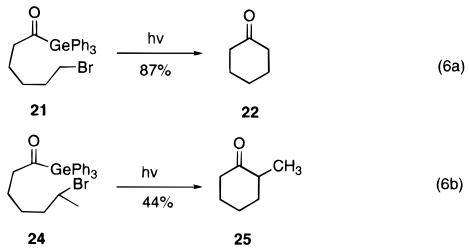
To investigate the potential for 6-*exo* radical cyclization to an acylgermane, the preparative and competitive cyclizations of the acylgermane **21** were studied (eq 6a). When the acylgermane **21** was photolyzed with a sunlamp in benzene for 30 min at room temperature, an 87% yield of cyclohexanone (**22**) was found. No other products were evident in the proton ^{1}H NMR spectrum. Table 5 shows the results of the competition experiments performed on the acylgermane **21** following the standard competition experimental procedure. From these experiments, the cyclization rate constant was estimated to be 1.3×10^6 s^{-1} at 80 °C. Therefore, the 6-*exo* primary radical cyclization is just as efficient as the primary and secondary 5-*exo* radical cyclizations.

These results are reminiscent of the radical cyclizations of aldehydes, where rate constants for 5-*exo* and 6-*exo* cyclizations of the parent substrates are very similar. This behavior of

Table 5. Competitive Rate Experiments with **21**



experiment	concn of **21**, M	ratio **22**/**23**	k_c, s^{-1}
1	0.05	0.93/1	1.1×10^6
2	0.05	1.10/1	1.4×10^6
3	0.20	0.26/1	1.4×10^6



carbonyl acceptors is in direct contrast to that of alkenes and alkynes, where 5-*exo* cyclizations are typically significantly faster than 6-*exo* cyclizations. The rapidity of the 6-*exo* cyclizations of aldehydes has been attributed to the "tighter" transition states in radical additions to carbonyl groups due to the stronger SOMO/LUMO interaction. In particular, the forming bond in cyclizations to carbonyls is calculated to be significant shorter than its counterpart in cyclizations to alkenes.[19b] In a simple picture,[36b] the "looser" transition states of alkenes (with their long forming bonds) resemble cycloheptane in ring strain while the tighter transition states in 6-*exo* cyclizations of carbonyl compounds more closely resemble the cyclohexane product. This analysis is also consistent with the postulate that the triphenylgermyl group prefers to be adjacent to a hydrogen atom in a cyclization with a tight transition state.

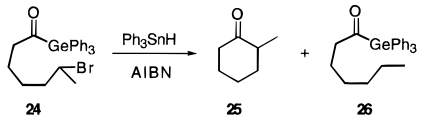
The cyclizations of the secondary 6-*exo* substrate **24** were not as well behaved as the primary one. Preparative cyclization of **24** provided 2-methylcyclohexanone (**25)** in only 44% yield (eq 6b). Furthermore, the rate constant measurements (Table 6) provided cyclization rate "constants" that decreased with decreasing tin hydride concentration.[37] Taken together, these observations suggest that 1,5-hydrogen transfer is competing with cyclization. If we assume that the ratio of cyclized to reduced products is equal to the ratio $k_c/k_{1,5}$, we can estimate that k_c is in the vicinity of $(5-6) \times 10^5$ s^{-1} and $k_{1,5}$ is about $(2-3) \times 10^5$ s^{-1}. These are just approximations; however, even simple comparison of the yields of the primary and secondary 6-*exo* cyclizations suggests that more 1,5-hydrogen transfer occurs in the secondary case. This is surprising. Competing 1,5-hydrogen transfer is a common problem in 6-*exo* cyclizations of all sorts, and it also competes to some extent in the radical cyclization reactions of acylsilanes. However, in both cases, the cyclization products seem to predominate. In view of the poor results with the tertiary 5-*exo* substrate **16**, a tertiary 6-*exo* analog was not investigated.

Attempts to conduct the parent 4-*exo* and 7-*exo* cyclizations were not successful (eqs 7a,b). Irradiation of **27** for 30 min resulted in its complete consumption, but the crude product exhibited a complex ^{1}H NMR spectrum in which the protons

(36) (a) Houk, K. N.; Paddon-Row, M. N.; Spellmeyer, D. C.; Rondan, N. G.; Nagase, S. *J. Org. Chem.* **1986**, *51*, 2874. (b) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions: Concepts, Guidelines, and Synthetic Applications*; VCH: Weinheim, 1996, p 283.

(37) This could also be shown by labeling experiments with Bu_3SnD. See: Palovich, M. Ph.D. Thesis, University of Pittsburgh, 1996.

Table 6. Competitive Rate Experiments with **24**



24 **25** **26**

experiment	concn of **24**, M	ratio **25**/**26**	k_c, s^{-1}
1	0.02	1.12/1	3.2×10^5
2	0.01	1.73/1	2.6×10^5
3	0.005	2.11/1	1.6×10^5

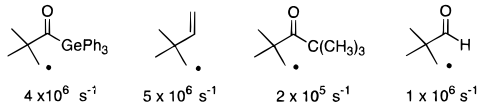
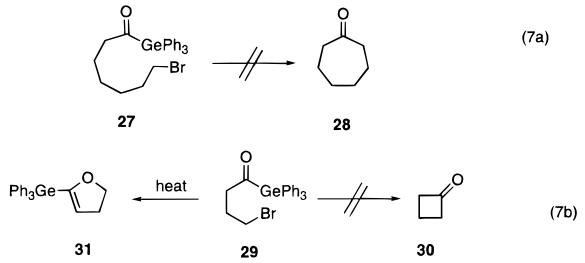


Figure 3. Comparison of 3-*exo* cyclization rate constants at 25 °C.

of cycloheptanone (**28**) could not be identified. Attempts at

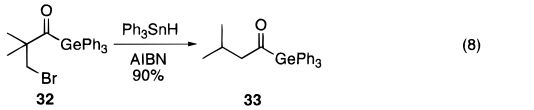


27 **28** **31** **29** **30**

thermal initiation at 80 °C with AIBN and 5% Ph_3GeH returned starting material even after 12 h. Chain propagation did not occur. Reduction of **27** with a stoichiometric quantity of triphenyltin or triphenylgermanium hydride cleanly provided the product of reductive debromination (not shown). All these results suggest that the 7-*exo* cyclization rate constant is below the limit needed to propagate a chain in solution (probably $<10^3$ s^{-1}).

The 4-*exo* cyclization precursor exhibited behavior similar to that of **27**, except that it underwent slow, thermal cyclization to germyltetrahydrofuran **31**. This reaction probably occurs by S_N2 substitution, and may be a useful method to prepare such cyclic germyl enol ethers. Analogous reactions of acylsilanes are known.[38]

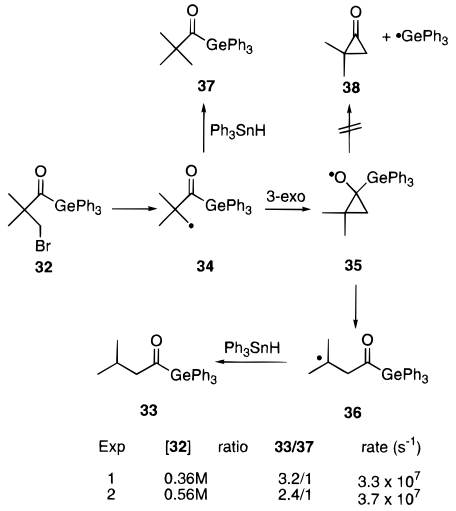
In contrast to these disappointments, the 3-*exo* cyclization precursor **32** provided especially interesting results. We choose the *gem*-dimethyl-substituted precursor to preclude any possibility of β-elimination of the radical precursor in the acylgermane. Due to the Thorpe−Ingold effect, this group will also dramatically accelerate the 3-*exo* cyclization. Attempts to isomerize **32** by using a catalytic amount of Ph_3SnH were not successful; as with the 7-*exo* and 4-*exo* cases, **32** was not consumed. However, when **32** was reduced with 1.3 equiv of Ph_3SnH at 0.05 M, a smooth reductive rearrangement occurred, as shown in eq 8. Acylgermane **33** was isolated in 90% yield by flash chromatography.



32 **33**

The mechanism for the formation of **33** is shown in Scheme 4. Radical generation followed by 3-*exo* cyclization provides **35**, which apparently does not eliminate the triphenylgermyl radical to provide cyclopropanone **38**. Instead, **35** fragments

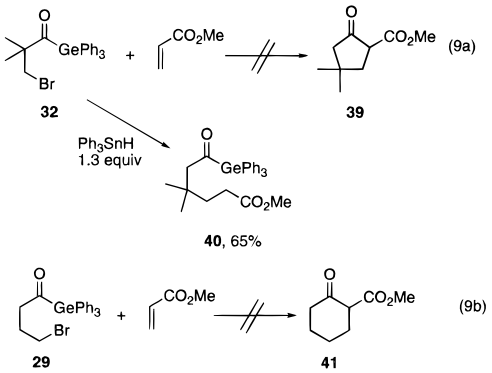
Scheme 4



to provide a tertiary radical, **36**, which is then reduced by triphenyltin hydride. Thus, the triphenylgermyl group is not involved in the radical chemistry, and the acylgermane simply participates in the standard 1,2-shift observed with many other types of multiply bonded functional groups. The rate constant for this shift was estimated as about 3×10^7 s^{-1} by the competition experiments shown at the bottom of Scheme 4.

Comparison rate constants for related shifts are provided in Figure 3.[39] This comparison is done at 25 °C, and to estimate the rate constant for the acylgermane at this temperature, we simply divided the 80 °C rate constant by 10. Once again, the acylgermane proves to be an excellent radical acceptor in comparison with alkenes, ketones, and aldehydes.

Because unimolecular chain transfer reactions are especially powerful for conducting cascade radical reactions,[24] we closed the basic study of acylgermane radical cyclizations with a few preliminary tandem reactions. Two attempts to develop radical annulations were not successful, as summarized in eq 9a,b.



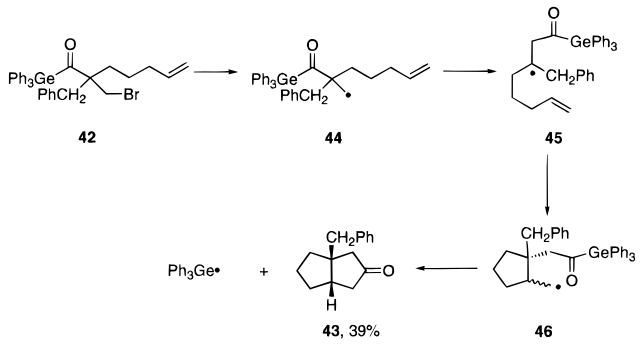
Attempts to initiate chain reactions with either **32** or **29** and methyl acrylate resulted only in very slow conversions to mixtures of products. However, reductive addition of **32** to methyl acrylate by the standard (stoichiometric) tin hydride gave **40** in 65% isolated yield. This product results from a 1,2-shift followed by addition to methyl acrylate and hydrogen transfer. This result suggests that the annulation fails because the ester-substituted radical does not add to the acylgermane.

In contrast, an intramolecular variant of this type of sequence was successful. Radical precursor **42** was readily available from dimethyl malonate by a series of standard alkylation reactions

(38) Tsai, Y. M.; Nieh, H. C.; Cherng, C. D. *J. Org. Chem.* **1992**, 57, 7010.

(39) Giese, B.; Heinrich, N; Horler, H.; Koch, W; Schwarz, H. *Chem. Ber.* **1986**, 119, 3528.

Scheme 5



to introduce the side chains followed by conversion of the final aldehyde to an acylgermane. Irradiation of β-bromoacylgermane for 30 min followed by flash chromatography provided bicyclic ketone **43** in 39% yield through the sequence of steps indicated in Scheme 5. The modest yield in this cyclization is almost certainly attributed to the expected lack of stereoselectivity in the 5-*exo* cyclization step.[36b] The trans isomer of **46** is reluctant to cyclize to a trans-fused diquinane and probably decomposes via other pathways.

Conclusions

The results of this study suggest that acylgermanes are indeed suitable equivalents of the carbonyl radical acceptor synthon for many synthetic applications. For primary radicals at least, acylgermanes are among the best of the known classes of radical acceptors. The speed of the cyclizations suggests that many types of 5-*exo* and 6-*exo* cyclizations will be possible, including those which are generally considered to be slow. The simple 4-*exo* and 7-*exo* cyclizations did not work, though in especially favorable cases it is probably possible to use acylgermanes in these types of reactions as well. The ability to tune the rate constant for cyclization over a wide range by varying the germanium substituent is an asset. The reactions occur by a mechanism analogous to that for vinylstannanes, but they are tin free. Preparative experiments are very easy to conduct, and separation of the R_3GeX byproduct by chromatography did not prove difficult. Finally, the combination of good radical-accepting properties and the UMCT chain mechanism[21] makes acylgermanes good candidates for conducting sequences of radical reactions.

Limitations are also suggested by this work, and these involve mainly the character of the attacking radical. Tertiary radicals do not appear to be good candidates for these types of cyclizations, and the presence of electron-withdrawing groups on the radical may also cause problems. More work is needed to better ascertain what radical substituent pairs work well with acylgermane acceptors and why.

The complementary nature of acylgermane and acylsilane radical reactions is an especially valuable asset. These functional groups can be prepared in similar ways, have similar properties, and have grossly similar behavior in nonradical reactions. However, their radical chemistry is very different. Both are excellent radical acceptors, but the subsequent evolution of products in acylsilane chemistry is dictated by the radical-Brook rearrangement and ultimately produces alcohols, while acylgermanes undergo simple fragmentation to ketones.

Acknowledgment. We thank the National Science Foundation for support of this work. U.D. thanks the Deutsche Forschungsgemeinschaft for a postdoctoral fellowship.

Supporting Information Available: Full experimental details for all the reactions and compounds reported in the paper (30 pages). See any current masthead page for ordering and Internet access instructions.

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