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Kinetics of 5-*exo* Cyclizations of *N*-Alkyl-4-pentenaminyl Radicals and β-Fragmentations of β-(Dialkylamino)alkyl Radicals

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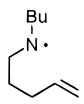
Abstract: The kinetic conclusions of a recent report by Maxwell and Tsanaktsidis (*J. Am. Chem. Soc.* **1996**, *118*, 4276) were investigated. The kinetics of ring opening of the (*N*-butyl-2-pyrrolidinyl)methyl radical (**2**) to the *N*-butyl-4-pentenaminyl radical (**1**) and the reverse reaction, 5-*exo* cyclization of **1** to **2**, were determined at 50 and 80 °C by competitive Bu_3SnH trapping. Rate constants for 5-*exo* cyclization of a dialkylaminyl radical and for β-fragmentation of a β-(dialkylamino)ethyl radical were measured by direct laser flash photolysis (LFP) methods. In contrast to the conclusions of Maxwell and Tsanaktsidis, all of these radical reactions were facile with rate constants of at least 1×10^4 s^{-1}. The claim by Maxwell and Tsanaktsidis that bis(tributyltin oxide) catalyzes dialkylaminyl radical reactions was investigated by LFP kinetic studies of the 5-*exo* cyclization of the *N*-methyl-5,5-diphenyl-4-pentenaminyl radical (**20**) in the presence of the additive which demonstrated that $(Bu_3Sn)_2O$ does not have a catalytic effect on the reaction. Computations of the energies of the *N*-methyl analogs of radicals **1** and **2** with a high level of theory (fourth-order Møller−Plesset perturbation theory) and by a hybrid density functional theory with a very large basis set indicate that the cyclization reaction is expected to be slightly exergonic at 298 K. This work demonstrates that the kinetic results reported by Maxwell and Tsanaktsidis were spurious. We speculate that impurities of dichalcogens in their radical precursor samples were reduced by Bu_3SnH to highly reactive chalcogen hydrides (arylthiols and benzeneselenol) in their kinetic studies.

In recent publications, Maxwell and Tsanaktsidis reported[1] useful extensions of benzenesulfenamides[2] as precursors to dialkylaminyl radicals. They also reported the results of kinetic studies of cyclization of the *N*-butyl-4-pentenaminyl radical (**1**) to radical **2** in competition with trapping by Bu_3SnH.[1] They found that the relative rate constants for cyclization and tin hydride trapping were variable; they claimed that cyclization of **1** was very slow, ascribed the unusual kinetic behavior to Lewis acid activation of the cyclization of **1** by impurities in the tin hydride, and concluded that $(Bu_3Sn)_2O$ acted as a Lewis acid catalyst for the cyclization of **1**. They also claimed that the cyclization of radical **1** was not reversible; specifically, they generated radical **2** in the presence of tin hydride and found no ring-opened product.[1] In another report, Maxwell *et al.* claimed



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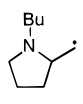

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[⊗] Abstract published in *Advance ACS Abstracts*, May 1, 1997.

(1) (a) Maxwell, B. J.; Tsanaktsidis, J. *J. Chem. Soc., Chem. Commun.* **1994**, 533−534. (b) Maxwell, B. J.; Tsanaktsidis, J. *J. Am. Chem. Soc.* **1996**, *118*, 4276−4283.

(2) (a) Bowman, W. R.; Clark, D. N.; Marmon, R. J. *Tetrahedron Lett.* **1991**, *32*, 6441−6444. (b) Beckwith, A. L. J.; Maxwell, B. J.; Tsanaktsidis, J. *Aust. J. Chem.* **1991**, *44*, 1809−1812. (c) Bowman, W. R.; Clark, D. N.; Marmon, R. J. *Tetrahedron Lett.* **1992**, *33*, 4993−4994. (d) Bowman, W. R.; Clark, D. N.; Marmon, R. J. *Tetrahedron* **1994**, *50*, 1295−1310. (e) Bowman, W. R.; Clark, D. N.; Marmon, R. J. *Tetrahedron* **1994**, *50*, 1275−1294.

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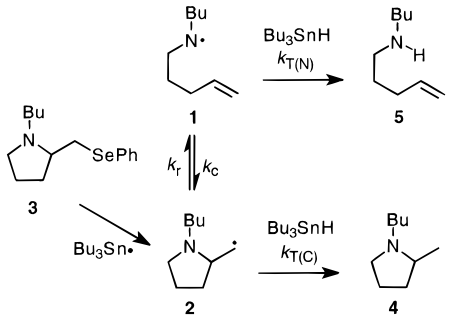
Scheme 1



that the experimental results with radicals **1** and **2** were supported by *ab initio* calculations.[3] As Maxwell and Tsanaktsidis noted,[1] their kinetic conclusions contradict previously reported work by our group in which the cyclization of **1** to **2** in competition with tin hydride trapping was found to give reproducible relative rate constants and the ring-opened product was found from reaction of radical **2** in the presence of tin hydride.[4]

Maxwell and Tsanaktsidis discussed conflicting reports regarding the efficiency of dialkylaminyl radical cyclizations in support of their claims, but their conclusions require that cyclizations of *N*-alkyl-4-pentenaminyl radicals are inherently too slow to be useful for synthesis (this point is further developed in the Discussion). Accordingly, many reported[5] cyclizations of such radicals produced in chain reactions involving Bu_3SnH would have to be ascribed to a highly unlikely fortuitous contamination of the commercial and prepared samples of tin hydride employed by an impurity that acted as a catalyst. For cases where simple *N*-alkyl-4-pentenaminyl radical cyclizations occurred but tin hydride was not employed in the reactions, the factors that might have resulted in successful cyclizations are more obscure. Further confusing the issue, recent direct laser flash photolysis kinetic studies of dialkylaminyl radical reactions[6] including 5-*exo* cyclizations showed that, whereas the aminyl radical reactions are not as fast as those of the isostructural carbon radical analogs, they are not slower by several orders of magnitude as suggested by Maxwell and Tsanaktsidis.

Because of the obvious conflicts in the kinetic studies and the resulting uncertainty this produces in predicting the outcome of dialkylaminyl radical reactions, we have revisited the kinetics of reactions of the simple aminyl radicals **1** and **2**. We report that the kinetic conclusions in the papers[1] by Maxwell and Tsanaktsidis cannot be substantiated. Specifically, we describe herein studies that show (1) that the initial report that radical **2** ring opens to radical **1** in competition with tin hydride trapping is reproducible, (2) that the rate constants for ring opening of radical **2** to **1** and for cyclization of radical **1** to radical **2** were accurately determined in the earlier work, (3) that a 5-*exo* cyclization of an *N*-alkyl-4-pentenaminyl radical is rapid as determined by direct laser flash photolysis (LFP) kinetic studies, (4) that a β-fragmentation of a β-(dialkylamino)ethyl radical is similarly rapid as determined by direct LFP kinetic studies, (5) that LFP kinetic studies of a 5-*exo* cyclization of a dialkylaminyl radical in the presence of $(Bu_3Sn)_2O$ reveal no measurable acceleration in contradistinction to the results obtained with Lewis acid catalysts, and (6) that the free energy difference between analogs of **1** and **2** predicted computationally either with a high level of theory or with a very large basis set is small. We conclude that the kinetic results of Maxwell and Tsanaktsidis were spurious, and we speculate that they resulted from dichalcogen impurities in the radical precursor samples that reacted with Bu_3SnH to give highly reactive chalcogen hydrides. The possibility of such contamination should be an important consideration whenever dialkylaminyl radicals are produced from arenesulfenamide precursors.

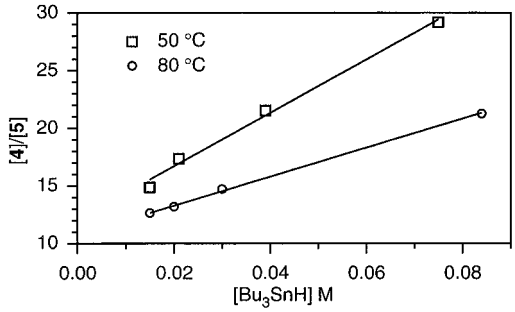


Figure 1. Ratios of products **4** and **5** formed in Bu_3SnH reductions of radical precursor **3** at 50 and 80 °C.

Results

Indirect Kinetic Studies. Maxwell and Tsanaktsidis[1] claimed that pyrrolidine **4** but no ring-opened product **5** was obtained when radical **2** was produced in the presence of Bu_3SnH (Scheme 1). Previously, this reaction had been reported to give acyclic amine **5**.[4] We have performed a series of studies of radical **2** similar to those reported.[1,4] The source of radical **2** was *N*-butyl-2-[(phenylselenyl)methyl]pyrrolidine (**3**), the same precursor as used previously. The method of preparation of radical precursor **3** is noteworthy in that it might be important for explaining the unusual results of Maxwell and Tsanaktsidis (see the Discussion). Two routes for preparation of compound **3** were described in earlier reports;[4,7] in this work, we produced **3** by intramolecular amidoselenylation of *N*-(4-pentenyl)-butanamide followed by $LiAlH_4$ reduction of the acylpyrrolidine.

Reactions of precursor **3** with Bu_3SnH in benzene were conducted at 50 and 80 °C. Product identities were confirmed by GC−mass spectral comparisons with authentic samples, and product yields were determined by GC. Both pyrrolidine **4** and acyclic amine **5** were obtained in these reactions. The relative yields of products observed at 50 °C were consistent with those previously reported for studies at this temperature.[4] Figure 1 shows the results. At 50 °C, the slope of the plot in Figure 1 is 231 ± 26 M^{-1} and the intercept is 12.1 ± 1.2; at 80 °C, the slope is 126 ± 4 M^{-1} and the intercept is 10.8 ± 0.2. (Stated uncertainties in this work are at 2σ.)

For the case of reversible first-order reactions with second-order trapping reactions and with entry to the radical manifold via radical **2** (*i.e.*, Scheme 1), the ratio of products [**4**]/[**5**] is described[8] by eq 1 where $k_{T(C)}$ and $k_{T(N)}$ are the rate constants

$$[\mathbf{4}]/[\mathbf{5}] = (k_{T(C)}/k_r)(k_c/k_{T(N)}) + (k_{T(C)}/k_r)[Bu_3SnH] \quad (1)$$

for Bu_3SnH trapping of the carbon-centered radical **2** and the nitrogen-centered radical **1**, respectively, k_r is the rate constant

(3) Maxwell, B. J.; Schiesser, C. H.; Smart, B. A.; Tsanaktsidis, J. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2385−2387. Correction: Maxwell, B. J.; Schiesser, C. H.; Smart, B. A.; Tsanaktsidis, J. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1245.

(4) Newcomb, M.; Deeb, T. M.; Marquardt, D. J. *Tetrahedron* **1990**, *46*, 2317−2328.

(5) Mackiewicz, P.; Furstoss, R. *Tetrahedron* **1978**, *34*, 3241−3260. Stella, L. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 337−350. Esker, J. L.; Newcomb, M. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic: San Diego, 1993; Vol. 58, pp 1−45.

(6) Musa, O. M.; Horner, J. H.; Shahin, H.; Newcomb, M. *J. Am. Chem. Soc.* **1996**, *118*, 3862−3868.

(7) Newcomb, M.; Marquardt, D. J.; Kumar, M. U. *Tetrahedron* **1990**, *46*, 2345−2352.

(8) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151−1176.

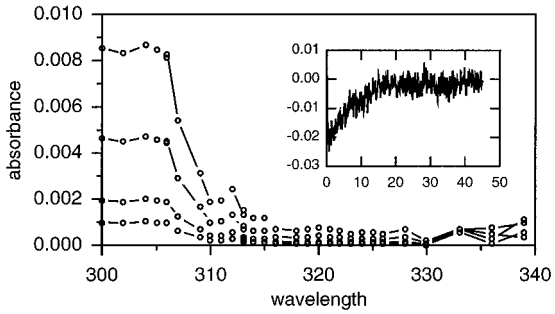


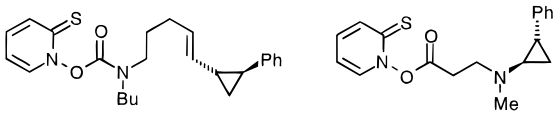
Figure 2. Time-resolved spectrum of product formed after laser flash irradiation of radical precursor **7** in THF at 57 °C. The increasing signal intensities are for 0.15, 0.25, 2.0, and 6.0 μs after laser irradiation with the intensity measured 0.10 μs after irradiation subtracted to give a baseline. The inset shows a kinetic trace recorded at 307 nm with time in microseconds.

for ring opening of **2**, k_c is the rate constant for cyclization of **1**, and [Bu_3SnH] is the concentration of tin hydride.

The slopes in Figure 1 provide rate constants for the ring-opening reaction of **2**. From these slopes and with the assumption that the rate constant for tin hydride trapping of radical **2** is equal to that for trapping a primary alkyl radical[9] and error free, the rate constant for ring opening of **2** at 50 °C is $(1.7 \pm 0.2) \times 10^4$ s^{-1} and the rate constant for ring opening of **2** at 80 °C is $(5.1 \pm 0.2) \times 10^4$ s^{-1}. The rate constant at 50 °C is in good agreement with the value previously reported.[4]

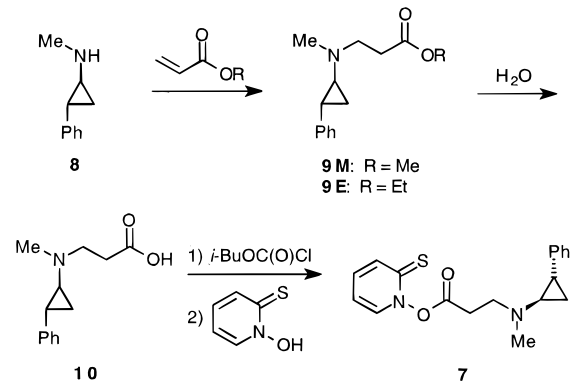
The intercepts in Figure 1 divided by the slopes can provide the rate constants for the cyclization of **1** if the data are precise enough. The ratio of the intercept to the slope (equal to $k_c/k_{T(N)}$; see eq 1) was 0.052 ± 0.011 M at 50 °C, and the corresponding value at 80 °C was 0.086 ± 0.004 M. Combining these values with the rate constants[6] for reaction of dialkylaminyl radicals with Bu_3SnH and again assuming the kinetics of the trapping reactions are error free, the rate constants for cyclization of **1** are $(5 \pm 1) \times 10^4$ s^{-1} at 50 °C and $(14.6 \pm 0.6) \times 10^4$ s^{-1} at 80 °C. The rate constant at 50 °C is in excellent agreement with the value of $(3.9 \pm 0.7) \times 10^4$ s^{-1} at this temperature which is calculated from previously reported data (see the Discussion).

Direct Kinetic Studies. Direct observations of both a 5-*exo* cyclization of a 4-pentenaminyl radical and a β-fragmentation of a β-(dialkylamino)ethyl radical were achieved in LFP studies employing "reporter group" methodology.[10] The radical precursors employed for these studies were the PTOC carbamate **6** and the PTOC ester **7**.[11] The synthesis of the PTOC carbamate

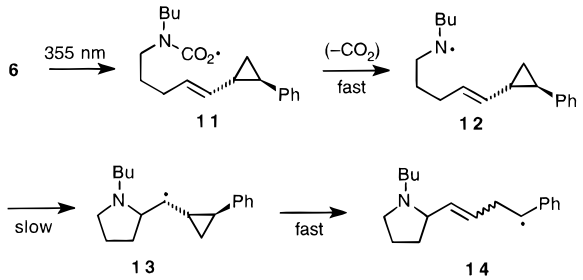


6 has been reported.[10] PTOC ester **7** was prepared by the route shown in Scheme 2. The known[6] *N*-methyl-*N*-(*trans*-2-phenylcyclopropyl)amine (**8**) reacted with methyl acrylate and with ethyl acrylate as expected. Hydrolysis of esters **9** was monitored carefully because decomposition of the desired product occurred upon extended reaction. The difficult reaction in the sequence was the final production of the PTOC ester[11] **7** from the β-amino acid **10** by the method of Barton *et al.*[12] The esters **9M** and **9E** and acid **10** were characterized by NMR spectroscopy and high-resolution mass spectrometry. Unfortunately, PTOC ester **7** decomposed upon attempted chromatography, but the crude product was characterized by ^{1}H NMR spectroscopy. From the NMR spectrum, the sample of **7** was judged to be 50% pure. PTOC esters from β-dialkylaminocarboxylic acids have been reported previously, but these reactive species were not isolated.[13]

Scheme 2



Scheme 3



LFP studies with PTOC carbamate **6** involve the sequence of reactions shown in Scheme 3. Homolytic cleavage of **6** by a 355 nm laser pulse gives (aminoacyl)oxyl radical **11** in addition to the 2-pyridylthiyl radical which absorbs with λ_{max} at 490 nm. Radical **11** decarboxylates with a rate constant exceeding 1×10^8 s^{-1} at ambient temperature[6] to give the target radical for the kinetic study, dialkylaminyl radical **12**. Cyclization of radical **12** gives **13** which will rapidly ring open to the UV-observable product **14**. Because the final ring-opening reaction of **13** to **14** is known to have a rate constant exceeding 1×10^{11} s^{-1} at ambient temperature,[14] this reaction has no effect on the kinetic measurements and serves only as a "reporter" by providing a UV-detectable product.

PTOC ester **7** reacts by a similar sequence (Scheme 4). The laser photolysis gives (alkylacyl)oxyl radical **15** which decarboxylates with $k > 1 \times 10^9$ s^{-1} at ambient temperature[15] to give the target radical **16**. A β-fragmentation of radical **16** gives dialkylaminyl radical **17** which is known to ring open to the reporting benzylic radical **18** with a rate constant exceeding 1×10^{11} s^{-1} at ambient temperature.[6]

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

(10) Newcomb, M.; Tanaka, N.; Bouvier, A.; Tronche, C.; Horner, J. H.; Musa, O. M.; Martinez, F. N. *J. Am. Chem. Soc.* **1996**, *118*, 8505−8506.

(11) The acronym PTOC derives from pyridine-2-thione oxycarbonyl. PTOC esters are actually anhydrides of a carboxylic acid and the thiohydroxamic acid *N*-hydroxypyridine-2-thione, and PTOC carbamates are anhydrides of a carbamic acid and the thiohydroxamic acid.

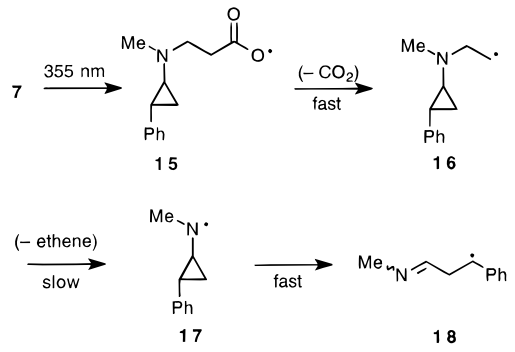
(12) Barton, D. H. R.; Hervé, Y.; Potier, P.; Thierry, J. *Tetrahedron* **1988**, *44*, 5479−5486.

(13) Castagnino, E.; Corsano, S.; Barton, D. H. R. *Tetrahedron Lett.* **1989**, *30*, 2983−2986.

(14) Newcomb, M.; Johnson, C. C.; Manek, M. B.; Varick, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 10915−10921.

(15) Falvey, D. E.; Schuster, G. B. *J. Am. Chem. Soc.* **1986**, *108*, 7419−7420. DeCosta, D. P.; Pincock, J. A. *J. Am. Chem. Soc.* **1989**, *111*, 8948−8950.

Scheme 4



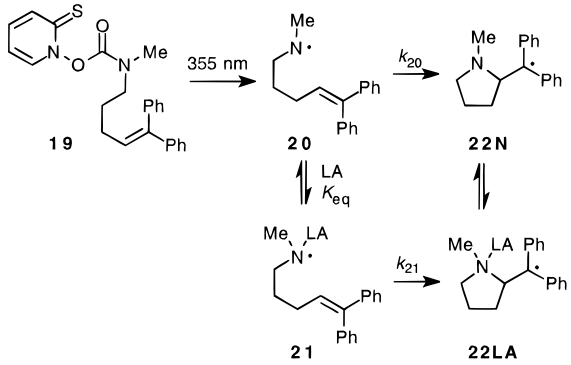
LFP studies of the cyclization of dialkylaminyl radical **12** in THF were conducted at 50 °C. A weak signal from benzylic radical **14** grew in over the 300−320 nm range with an observed rate constant at all wavelengths in this range of $(3 \pm 0.5) \times 10^4$ s^{-1}. LFP studies of radical **16** were conducted in THF at 27 and 58 °C. A time-resolved spectrum of the reaction products indicated formation of benzyl radical **18** with the long-wavelength band extending beyond 310 nm (Figure 2). The observed rate constants obtained by monitoring the signal growth at ca. 310 nm were 9×10^4 s^{-1} at 27 °C and 1.6×10^5 s^{-1} at 58 °C.

The cyclization of radical **12** and β-fragmentation of radical **16** are implicated by the ultimate production of benzylic radicals **14** and **18** because other reasonable pathways for formation of benzylic radicals do not exist. Second-order hydrogen atom abstractions from the benzylic positions of the precursors or bimolecular addition of a radical to the alkene moiety in **6** are not expected to be extremely fast, and the low concentrations of precursors employed in the LFP studies assure that pseudo-first-order rate constants for these bimolecular reactions will be unobservable by the LFP method ($k < 10$ s^{-1}). However, the observed rate constants for formation of radicals **14** and **18** are only upper limits for the rate constants of the cyclization of **12** and β-fragmentation of **16**. These measured values are actually the sums of the first-order and pseudo-first-order rate constants for all reactions that consume **12** and **16**, and both the cyclization and the fragmentation reactions are slow enough such that bimolecular reactions of **12** and **16** with residual oxygen and radical−radical coupling reactions will be competitive. Specifically, we have shown that bimolecular consumption of radicals occurs with pseudo-first-order rate constants in the 10^4 s^{-1} range at ambient temperature in the LFP experimental design we employ.[6]

The total signal growths observed in the LFP studies with precursors **6** and **7** were about 30% and 40%, respectively, of the signal growth we typically have observed by LFP when other PTOC ester precursors to radicals that give, ultimately, benzylic radical products were employed in otherwise similar studies. If we assume that the quantum yields for homolysis in the laser photolyses of these precursors are similar to those we typically obtain with PTOC precursors and that the benzyl radical products **14** and **18** have approximately the same molar absorptivity as other benzylic radicals, then one concludes that the cyclization of **12** and β-fragmentation of **16** accounted for only 30% and 40% of the total reactions of this species. Accordingly, we estimate that the rate constant for cyclization of **12** is approximately 1×10^4 s^{-1} at 50 °C and the rate constants for fragmentation of radical **16** are approximately 4×10^4 s^{-1} at 27 °C and 6×10^4 s^{-1} at 58 °C.

LFP studies of acid-catalyzed cyclizations of radical **12** were more precise and served to support the approximate rate constant for cyclization of the neutral species. When dialkylaminyl radical **12** was produced by LFP in THF at 20 °C in the presence of 0.2 M BF_3, a demonstrated catalyst for dialkylaminyl radical reactions,[16] the observed rate constant for formation of the benzylic radical product was 6.8×10^5 s^{-1}. This rate constant is large enough such that interfering reactions with residual oxygen cannot contribute significantly to the observed kinetics. In a similar manner, observed rate constants for cyclization of **12** in the presence of protic acid in acetonitrile at 10 °C are in the 10^7−10^8 s^{-1} range and are accurately measured.[10] The implications of these measured rate constants for acid-catalyzed cyclizations of **12** are presented in the Discussion.

Scheme 5



LFP Studies of Potential Catalysis by $(Bu_3Sn)_2O$. An important experimental observation in the study by Maxwell and Tsanaktsidis that led to the conclusion that cyclization of radical **1** was slow was the fact that the amounts of cyclic product **5** relative to acyclic product **4** increased when $(Bu_3Sn)_2O$ was present in the reaction mixture containing Bu_3SnH. They concluded that the tin oxide acted as a Lewis acid catalyst for the cyclization reaction. Studies designed to demonstrate catalysis were not performed,[1] but in any event, attempts to demonstrate catalysis by competition reactions involving product ratios would be difficult to interpret given that both of the competing reactions could be affected by the additive.

Lewis acid catalysis of dialkylaminyl radical cyclization reactions has been known qualitatively for more than two decades[5] and specifically demonstrated for the cyclization of radical **1** with a number of Lewis acids.[16,17] Recently, we established an LFP-based method for quantitative evaluations of Lewis acid catalysis of dialkylaminyl radical reactions that has been applied to BF_3, $MgBr_2$, and $LiBF_4$ catalysis.[16] One of the reactions studied was the 5-*exo* cyclization of dialkylaminyl radical **20** which gives a UV-detectable product radical with a convenient rate constant for LFP studies. We have now directly evaluated the effect of $(Bu_3Sn)_2O$ on the rate of cyclization of **20**.

Scheme 5 shows the reaction sequence possible when radical **20** is generated from its PTOC carbamate[11] precursor **19** in the presence of a Lewis acid. Complexation of radical **20** with the Lewis acid to give the complex **21** can occur reversibly, and cyclic products can be formed from both **20** and **21**. The total velocity of formation of cyclic products **22** is the sum of the velocities of cyclization of **20** and **21**; the observed rate constants are described by eq 2 where F_X is the fraction of species X. If complex **21** reacts substantially faster than the uncomplexed radical **20** ($k_{21} \gg k_{20}$), then the observed kinetics are effectively only those of the complex, and the observed kinetics reduce to eq 3. Further, if the complexation equilibrium is rapidly obtained, then the overall rate of the reaction is described by

(16) Ha, C.; Musa, O. M.; Martinez, F. N.; Newcomb, M. *J. Org. Chem.* **1997**, *62*, 0000−0000.
(17) Newcomb, M.; Ha, C. *Tetrahedron Lett.* **1991**, *32*, 6493−6496.

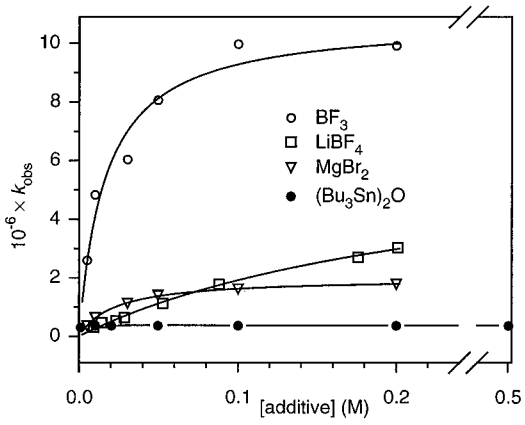


Figure 3. LFP observed rate constants (s^{-1}) for product formation from radical **20** in THF at 20 °C in the presence of additives. The data for BF_3, $LiBF_4$, and $MgBr_2$ are from ref 16. The lines are the fits from nonlinear regression analyses according to eq 4.

eq 4 where K_{eq} is the equilibrium constant for formation of the

$$k_{obs} = k_{20}F_{20} + k_{21}F_{21} \quad (2)$$

$$k_{obs} = k_{21}F_{21} \quad (3)$$

$$k_{obs} = k_{21}K_{eq}[LA]/(1 + K_{eq}[LA]) \quad (4)$$

Lewis acid complex and [LA] is the concentration of Lewis acid. For studies with BF_3, $MgBr_2$, and $LiBF_4$ in solvent THF, rapid equilibrations between dialkylaminyl radical **20** and its Lewis acid complexes **21** and catalysis of the cyclization reaction by each Lewis acid were demonstrated.[16] The observed rate constants for cyclization were functions of the Lewis acid concentrations and displayed typical saturation kinetic behavior according to eq 4. Nonlinear regression analyses of the kinetic results provided both the equilibrium constants for complexation and the rate constants for cyclization of the Lewis acid complexes **21**.[16]

Using the same experimental design as employed with Lewis acids,[16] the cyclization of radical **20** in THF at 20 °C in the presence of $(Bu_3Sn)_2O$ was studied. For concentrations of $(Bu_3Sn)_2O$ ranging from 0.001 to 0.50 M, effectively no kinetic acceleration in the cyclization of **20** was observed. The results are shown graphically in Figure 3 where we have also shown the results[16] of actual Lewis acid catalysis of the cyclization of radical **20**. The data for the tin oxide are consistent with two explanations; specifically, either (1) the tin oxide does not complex strongly with the aminyl radical or (2) the tin oxide complexes with the radical, but the complex does not react significantly faster than the uncomplexed radical. What is clear, however, is that $(Bu_3Sn)_2O$ does not complex strongly with the dialkylaminyl radical *and also* accelerate the 5-*exo* cyclization reaction considerably; that is, there is no catalytic effect for the tin oxide.

The above results were obtained in THF so that the behavior of **20** in the presence of $(Bu_3Sn)_2O$ could be compared directly to its behavior in the presence of actual Lewis acid catalysts. The results reported by Maxwell and Tsanaktsidis[1] were for studies in solvent benzene, however. Therefore, the cyclization of **20** in benzene in the presence of the tin oxide also was studied by LFP. The observed rate constant for cyclization of **20** at 20 °C was 4.1×10^5 s^{-1} in benzene in the absence of an additive and an unchanging 4.2×10^5 s^{-1} in the presence of 0.02, 0.05, 0.10, and 0.20 M $(Bu_3Sn)_2O$. There was no measurable catalysis of the dialkylaminyl radical cyclization by the tin oxide.

Table 1. Calculated Free Energies (ΔG_{298}) for Aminyl Radical Reactions[a]

theory	**1M** → **2M**[b]	eq 5[c]
UHF/3-21G	−4.7	−3.6
UHF/6-31G*	−0.5	−3.6
UMP2/6-31G*//UHF/6-31G*	−11.8	
UMP2/6-31G*	−11.8	−11.8
BLYP/6-31G*	0.4	−7.8
B3LYP/6-31G*	−2.7	−10.4
CBS-4	−10.8	−11.7
G2		−9.3
UMP4SDTQ/6-31G//UMP2/6-31G*	−1.0	
B3LYP/6-311+G(3df,2df,2p)//B3LYP/6-31G*	0.0	

[a] Zero-point energies and thermal corrections were obtained from UHF/6-31G* level frequency calculations. Free energies are in kilocalories per mole. [b] Free energy for cyclization of **1M** to **2M**. [c] Free energy for addition of $H_2N^{\bullet}$ to ethylene.

Computational Studies. Maxwell and Tsanaktsidis[1b] supported their claims that the cyclization of dialkylaminyl radical **1** to radical **2** was both slow and irreversible with results of theoretical calculations of the energies of the *N*-methyl analogs of both radicals (*i.e.*, **1M** and **2M**) and the transition state for

1M **2M**

the cyclization that were given in an earlier report.[3] In the original theoretical paper,[3] the structures of **1M** and **2M** and the transition state for the 5-*exo* cyclization were optimized at the UHF/6-31G* level of theory, and energies also were reported from MP2/6-31G*//UHF/6-31G* (*i.e.*, single-point MP2 calculations on the UHF-optimized geometries). In the recent report,[1b] Maxwell and Tsanaktsidis discussed only the energies obtained from the MP2 calculations (apparently without zero-point and thermal corrections). They claim that the activation energy (labeled ΔE) for cyclization is 14.1 kcal/mol and that the reaction exothermicity (labeled ΔH) is −14.8 kcal/mol. We have repeated and extended the computations of species **1M** and **2M** (Table 1).

The ΔE values (without zero-point or thermal corrections) for the cyclization that we obtained from UHF/6-31G* calculations and from the single-point MP2/6-31G* calculations on the UHF-optimized structures were similar to those previously reported;[3] specifically ΔE was −3.5 and −14.8 kcal/mol, respectively. This large difference in energies from the two sets of calculations on the same structures was disconcerting. Therefore, the energies for **1M** and **2M** were calculated at different levels of theory. In addition to the unrestricted Hartree−Fock computations with the 3-21G and 6-31G* basis sets, complete optimizations were obtained for second-order Møller−Plesset perturbation theory (UMP2/G-31G*), for a density functional theory (DFT) (BLYP/6-31G*), and for a hybrid DFT (B3LYP/6-31G*). The energies for **1M** and **2M** were also computed with the complete basis set method CBS-4. Zero-point energy and thermal corrections were incorporated to give values for the free energy change at 25 °C (ΔG_{298}) that are listed in Table 1.

The scatter in the results from the different approaches using the 6-31G* basis set was unsatisfying. The MP2 and CBS-4 results are similar, but this is to be expected because the CBS-4 method heavily weights MP2 calculations.[18] The DFT and hybrid DFT methods group together, and this also is not surprising.

(18) Foresman, J. B.; Frisch, Æ. *Exploring Chemistry with Electronic Structure Methods*, 2nd ed.; Gaussian, Inc.: Pittsburgh, 1996.

In an attempt to test the various approaches against a very high standard, we computed the free energy change for the addition of the aminyl radical to ethylene (eq 5). This simple

$$H_2N^{\bullet} + CH_2{=}CH_2 \rightarrow H_2NCH_2CH_2^{\bullet} \qquad (5)$$

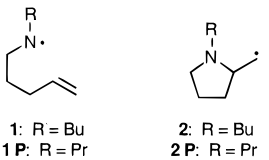
model reaction, which contains some of the elements of the cyclization reaction of **1M**, is small enough to permit calculations by the G2 method.[19] The free energies for the reaction in eq 5 obtained at each level are listed in Table 1. All approaches using the 6-31G* basis set except UHF were in reasonable agreement with one another and also with the G2 value although there might be a hint that the MP2 calculations estimated that the reaction was too exothermic. Given the limitations of the model reaction in eq 5, we conclude that the difference in results between MP2 and DFT for the cyclization of **1M** apparently involves the energies of the dialkylaminyl radical and/or the trialkylamine.[20]

Finally, the energies of **1M** and **2M** were computed at the effective limits of the available resources. Single-point calculations were performed with a high level of theory (fourth-order Møller−Plesset perturbation theory) using a modest basis set, and with the hybrid DFT B3LYP using a large basis set, 6-311+G(3df,2df,2p). The latter approach has been found to have a mean average deviation in results slightly greater than that obtained with G2.[18,19] The results of these two sets of calculations, included in Table 1, are in excellent agreement.

From the computational results for the cyclization of **1M** to **2M**, we conclude that the weight of the evidence indicates that the reaction is predicted to be slightly exergonic, in good agreement with the experimental result that ΔG for cyclization of **1** at 50 °C is −0.6 kcal/mol. A considerable error for the free energy change of the cyclization reaction apparently was introduced in the MP2 calculations with the 6-31G* basis set, a point which might be addressed by theoreticians. This possible error was compounded somewhat (3 kcal/mol) by Maxwell *et al.* who apparently reported ΔE or ΔH values rather than ΔG values.[3] Given the apparent poor performance of MP2 in the computation of the total energy change, the transition state energy for cyclization of **1M** computed by Maxwell *et al.* with MP2 theory also should be considered suspect.

Discussion

Cyclization of Radical 1. The kinetics of dialkylaminyl radical reactions have been the subject of study for many years. In early work, Maeda and Ingold failed to observe an ESR signal from cyclic radical **2P** in a low-temperature kinetic ESR study of **1P**.[22] They assumed that the cyclization reaction of **1P** did not occur to a measurable extent at low temperature, estimated an upper limit for the rate constant for cyclization at low temperature, and extrapolated their results to give an estimated upper limit for the rate constant for cyclization of **1P** at room temperature of $<5\ s^{-1}$.[22] This result was cited by Maxwell and Tsanaktsidis as support for their conclusion that cyclization of radical **1** was slow.[1]



1: R = Bu
1P: R = Pr
2: R = Bu
2P: R = Pr

Maeda and Ingold might have failed to observe an ESR signal from **2P** because the cyclization reaction of **1P** is reversible. Irrespective of the reasons for the absence of an ESR signal for **2P**, however, the cyclization of **1P** cannot possibly be as slow as they concluded on the basis of the demonstrated product throughput of dialkylaminyl radical reactions. This point was noted previously.[4] Specifically, if the rate constant for cyclization of **1** or **1P** was $<5\ s^{-1}$ at ambient temperature, then radical concentrations would have to be maintained below 1×10^{-9} M so that cyclization could compete with diffusion-limited radical−radical reactions. In turn, this would require that a total reaction velocity of $<1 \times 10^{-8}$ M s^{-1} was achieved experimentally in order to obtain a predominance of cyclic products. In the case of an initial precursor concentration of 0.1 M, the reaction would have to be performed over a period of several months. In practice, radical chain reactions involving **1** and related species are typically completed within minutes and give fair to good yields of cyclic products when reactive trapping agents are not present.[5] In fact, cyclic products were formed when radical **1P** and the *N*-butyl-5-methyl-4-hexenaminyl radical were produced by decomposition of the respective symmetrical tetrazenes, nonchain situations in which the radical concentrations must have been relatively large.[23ab] Thus, a rate constant for cyclization of **1P** of $<5\ s^{-1}$ at 25 °C is not possible.

All reliable experimental evidence available, including some of the data reported by Maxwell and Tsanaktsidis, indicates that the rate constants for cyclization of the simple *N*-alkyl-4-pentenaminyl radical **1** are reasonably accurately measured in the previous[4] and present work. The relative rate constants at 50 °C for trapping of **1** by Bu_3SnH and cyclization were found[4] to be $k_T/k_c = 23 \pm 4\ M^{-1}$ (error at 2σ) which can be combined with the rate constant for tin hydride reaction with a dialkylaminyl radical at 50 °C to give a rate constant for cyclization of **1**. An early, approximate value for the rate constant of Bu_3SnH trapping of a dialkylaminyl radical at 50 °C determined by a series of indirect kinetic studies was $k_T \approx 8 \times 10^4\ M^{-1}\ s^{-1}$,[23c] but the original basis radical reaction rate constant used for this series of studies is now known to be only a lower limit.[6] A recently reported detailed study of Bu_3SnH trapping of the directly calibrated dialkylaminyl radical clock **20** gave the value $k_T = 9 \times 10^5\ M^{-1}\ s^{-1}$ at 50 °C.[6] Using the recently obtained value of k_T and the ratio of rate constants from the competition studies and assuming that the trapping rate constant is error free, the rate constant for cyclization of **1** at 50 °C is calculated to be $k_c = (3.9 \pm 0.7) \times 10^4\ s^{-1}$. The kinetic study in this work, where the reaction manifold was entered from radical **2**, gave a rate constant for cyclization of **1** of $(5 \pm 1) \times 10^4\ s^{-1}$ at 50 °C. The weighted average value is $k_c = (4.3 \pm 0.6) \times 10^4\ s^{-1}$.

From the studies of radical **2** in the present work, we find a rate constant for cyclization of **1** at 80 °C of $(14.6 \pm 0.6) \times 10^4\ s^{-1}$. This value is consistent with that one would estimate using a rate constant of $4.3 \times 10^4\ s^{-1}$ for cyclization of **1** at 50 °C and a log *A* value for **1** equal to that measured[6] for the 5-*exo* cyclization of aminyl radical **20**; specifically, one would thus

(19) The G2 (Gaussian-2) method was found to give a mean absolute error of only 1.3 kcal/mol for a test set of 125 well-characterized energy differences; see: Curtiss, L. A.; Raghavachari, K.; Trucks, G. W.; Pople J. A. *J. Phys. Chem.* **1990**, *94*, 7221−7230.

(20) A related effect might be seen in the evaluation of DFT methods for calculation of nitrogen bond energies recently reported by Jursic.[21] MP2 and BLYP calculations of the N−H bond energies of NH_3, CH_3NH_2, and $(CH_3)_2NH$ differed by 5, 2, and 1 kcal/mol, respectively, but the N−C bond energies for CH_3NH_2, $(CH_3)_2NH$, and $(CH_3)_3N$ computed by these two methods differed by 25, 21, and 17 kcal/mol, respectively.

(21) Jursic, B. S. *J. Mol. Struct.: THEOCHEM* **1996**, *366*, 103−108.

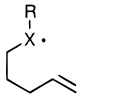
(22) Maeda, Y.; Ingold, K. U. *J. Am. Chem. Soc.* **1980**, *102*, 328−331.

(23) (a) Michejda, C. J.; Campbell, D. H.; Sieh, D. H.; Koepke, S. R. In *Organic Free Radicals*; Pryor, W. A., Ed.; American Chemical Society: Washington, DC, 1978; Chapter 18. (b) Newcomb, M.; Burchill, M. T. *J. Am. Chem. Soc.* **1983**, *105*, 7759−7760. (c) Newcomb, M.; Park, S.-U.; Kaplan, J.; Marquardt, D. J. *Tetrahedron Lett.* **1985**, *26*, 5651−5654.

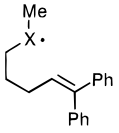
estimate that the rate constant for cyclization of **1** at 80 °C is 11×10^4 s^{-1}.

The rate constant for cyclization of **1** at 80 °C is actually supported in a qualitative sense by some of the results of Maxwell and Tsanaktsidis.[1] It seems obvious that they had an impurity or side-product problem that gave erratic results in the absence of added $(Bu_3Sn)_2O$, but their results when $(Bu_3Sn)_2O$ was added seem to be relatively consistent. We conclude that the tin oxide served to destroy or sequester an impurity or side product, and we speculate on this possibility below. In any event, because the tin oxide is demonstrated in the present work to have no measurable catalytic effect on the kinetics of a dialkylaminyl radical reaction, their data obtained in the presence of this agent might be evaluated in regard to the rate constant of the dialkylaminyl radical cyclization. The data in Figures 3 and 4 of their recent paper[1b] for studies in the presence of tin oxide give slopes for k_T/k_c of about 15 and 65 M^{-1}, respectively, at 80 °C which, when combined with the rate constant for tin hydride reacting with a dialkylaminyl radical at that temperature, give 11×10^4 and 3×10^4 s^{-1} for the rate constant for cyclization of **1** at 80 °C.

Rate constants for cyclization of radical **1** in the range of 4×10^4 s^{-1} at 50 °C and 15×10^4 s^{-1} at 80 °C are also consistent with the kinetics of other radical reactions. For example, dialkylaminyl radical **20** cyclizes with a rate constant of 8×10^5 s^{-1} at 50 °C as determined from the Arrhenius function obtained from direct LFP studies.[6] For the carbon-centered radicals isostructural with **1** and **20**, the rate constant for 5-*exo* cyclization of radical **23** at 50 °C is about 2 orders of magnitude smaller than that for radical **24**.[24] If the kinetic effect of the 1,1-diphenylethene moiety is similar in the carbon and nitrogen radical cases, then one would estimate that radical **1** should have a rate constant for cyclization at 50 °C on the order of 1×10^4 s^{-1}.



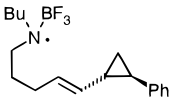
1: X = N, R = Bu
23: X = CH, R = Me



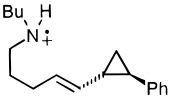
20: X = N
24: X = CH

The approximate rate constant for cyclization of dialkylaminyl radical **12** determined by LFP was 1×10^4 s^{-1} at 50 °C. The precision in this kinetic measurement is poor due to the fact that cyclization of **12** and its consumption by other processes are competitive, but this kinetic value does establish the order of magnitude for the rate of the cyclization reaction in a direct LFP study.

Rate constants for the acid-catalyzed cyclizations of dialkylaminyl radical **12** provide important support for the approximate rate constant found for reaction of the neutral radical. The equilibrium constant for complexation of BF_3 with a dialkylaminyl radical in THF at 20 °C is 56 M^{-1}, and the complexation and decomplexation reactions have been shown to be fast with respect to cyclization of dialkylaminyl radical **20**, a reaction that is considerably faster than cyclization of **12**.[16] Thus, eq 4 can be used with the observed rate constant for cyclization of **12** in the presence of 0.2 M BF_3 at 20 °C ($k_{obs} = 6.8 \times 10^5$ s^{-1}) to calculate the rate constant for cyclization of the **12BF$_3$** complex; the resulting value is $k = 7.4 \times 10^5$ s^{-1}. In previous work,[10] the protonated counterpart of radical **12**, *i.e.*, the aminium cation radical **12H$^+$**, was found to cyclize in acetonitrile at 10 °C with a rate constant of 1×10^8 s^{-1}. It is known that the 5-*exo* cyclization of radical **20** is accelerated by a factor of 35 for the BF_3 complex and a factor of about 30 000 for the aminium cation from protonation of **20**.[6,16] If one assumes that the catalytic accelerations of the 5-*exo* cyclization reactions of **12** are the same as those observed for the 5-*exo* cyclizations of **20**, then one would estimate that the rate constant for cyclization of neutral radical **12** at 20 °C is about 2×10^4 s^{-1} (**12BF$_3$** results) and that for cyclization of **12** at 10 °C is about 3×10^3 s^{-1} (**12H$^+$** results). Of course, the catalytic effects on **12** and **20** are unlikely to be exactly the same, but this exercise demonstrates the internal consistency of the measured rate constants for cyclization of neutral radical **12** and its BF_3-complexed and protonated counterparts.

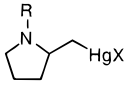


12BF$_3$

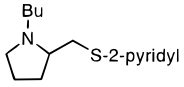


12H$^+$

Ring Opening of Radical 2. In regard to the fragmentation reaction of radical **2**, the reports by Maxwell and Tsanaktsidis[1] contradicted the kinetic results our group had reported and also indirectly contradicted the observations of several synthetic groups who have found that reductions of β-amino organometallic compounds under radical-producing conditions result in fragmentations. For example, reduction of 2-(mercuriomethyl)-pyrrolidines **25** by $NaBH_4$ (a radical chain process of the first formed mercuric hydride) can result in extensive ring opening, and the development of new reducing conditions that prevented fragmentation was the subject of a recent synthetic study by the Tordo group.[25] In a similar manner, treatment of pyrrolidine **26** with Raney nickel and with $NiCl/NaBH_4$ resulted in 25% and 75% ring opening, respectively, apparently via the intermediacy of radical **2**.[7]



25



26

Our observation in this work that acyclic product **5** was formed in reactions of precursor **3** in the presence of Bu_3SnH at low concentrations essentially reproduces the results previously reported[4] for studies at 50 °C but with a higher level of precision. Rate constants for the fragmentation reaction of radical **2** were $(1.7 \pm 0.2) \times 10^4$ s^{-1} at 50 °C and $(5.1 \pm 0.2) \times 10^4$ s^{-1} at 80 °C, in reasonable agreement with the previously reported value at 50 °C.[4]

The direct observation of fragmentation of β-amino radical **16** in the LFP studies is a more dramatic demonstration that the reaction occurs relatively rapidly. Again, however, the directly measured rate constants for fragmentation of **16** are less precise than those measured indirectly for ring opening of **2** because bimolecular reactions competed with the unimolecular process of interest. From the results obtained at 27 and 58 °C, the estimated rate constant for fragmentation of **16** at 50 °C is about 5×10^4 s^{-1} which is similar to the rate constant for fragmentation of radical **2** determined at 50 °C.

A Possible Resolution of the Conflicting Results. One should ask how such diametrically opposed results were obtained by our group and by Maxwell and Tsanaktsidis who reported extremely low yields of cyclic products from radical **1** in the presence of tin hydride and no measurable amount of ring-

(24) Newcomb, M.; Horner, J. H.; Filipkowski, M. A.; Ha, C.; Park, S. U. *J. Am. Chem. Soc.* **1995**, *117*, 3674−3684.

(25) Roubaud, V.; Lemoigne, F.; Mercier, A.; Tordo, P. *Synth. Commun.* **1996**, *26*, 1507−1516.

opened product from radical **2** when as little as 0.005 M Bu_3SnH was employed.[1] A suggestion as to the origin of the conflicting results was offered to us by Professor David Crich.[26]

Crich and co-workers developed a convenient synthetic technique wherein the highly reactive hydrogen atom transfer agent PhSeH is produced *in situ* by reduction of Ph_2Se_2 by Bu_3SnH and a constant concentration of PhSeH is subsequently maintained by rapid reaction of $PhSe^•$ with the sacrificial tin hydride.[27] They also reported that Bu_3SnH reacts rapidly with the benzenethiyl radical to regenerate PhSH.[27] One also can regenerate a reactive alkanethiol employed in catalytic amounts with a sacrificial metal hydride such as Et_3SiH.[28] It is quite likely that regeneration of any arylthiol by reaction of Bu_3SnH with $ArS^•$ will occur given that the tin hydride is demonstrated to react with the $PhS^•$ radical and the more stable $PhSe^•$ radical.[27] In each case, the sacrificial metal hydride reacts with the chalcogen-centered radical to give a species that reacts with an alkyl radical much faster than does the sacrificial metal hydride; PhSH and PhSeH react with alkyl radicals at 25 °C about 60 and 900 times faster, respectively, than does tin hydride.[8] The chalcogen hydrides are also much more reactive toward dialkylaminyl radicals than is tin hydride; specifically, PhSH and PhSeH are 240 and 4500 times more reactive at 25 °C toward $R_2N^•$, respectively, than is Bu_3SnH.[6]

On the basis of the suggestion by Professor Crich, we speculate that arylthiol and PhSeH might have been produced by Bu_3SnH reduction of impurities in the samples used by Maxwell and Tsanaktsidis.[1] In the method of preparation of arenesulfenamides, the final synthetic step involves reaction of a dialkylamine with a sulfenyl chloride that is prepared *in situ* from a disulfide.[1,2] One can readily envision that a small impurity of disulfide could be carried on in the chromatographic purification of the arenesulfenamide. Similarly, the sample of precursor **3** prepared by Maxwell and Tsanaktsidis could have been contaminated, in this case with Ph_2Se_2. They stated[1b] that **3** was prepared by a method reported in an earlier publication but gave no experimental details. In the work they cited, **3** was prepared by cyclization of aminyl radical **1** in the presence of acid and Ph_2Se_2,[7] and one can imagine that this method might result in a sample containing an impurity of Ph_2Se_2. The more circuitous method for production of **3** employed in the present work, an amidoselenylation reaction followed by $LiAlH_4$ reduction, was used because chromatographic separation of the amide intermediate from Ph_2Se_2 is likely to be efficient and a second reaction and purification step follow the introduction of the phenylselenyl group.

Thus, small amounts of disulfide and diselenide might have been present in the radical precursors used by Maxwell and Tsanaktsidis. Contamination by these agents at the level of a few percent would be undetectable by NMR spectroscopy because the impurity signals overlap with those of the products, and even a low level of contamination could explain their unusual product ratio results. For example, in their studies of radical **2**, a concentration of 0.0005 M PhSeH, continually regenerated by rapid reaction of $PhSe^•$ with Bu_3SnH,[27] would have trapped the cyclic radical with 99% efficiency. Depending upon the amount of substrate employed, such a concentration could easily be achieved with a small amount of Ph_2Se_2 in the sample of **3**.[29]

The potential for contamination of arenesulfenamides by disulfides might be critically important for synthetic applications involving nitrogen-centered radicals. For example, in addition to the results of Maxwell and Tsanaktsidis, radical **1** was reported by Bowman *et al.* to give "poor yields" of cyclic pyrrolidine when produced from the benzenesulfenamide precursor in the presence of Bu_3SnH,[2e] and one might question whether or not this resulted from Ph_2S_2 contamination of the precursor sample. The arenesulfenamides[2] as a general class are attractive as dialkylaminyl radical precursors due to the ease of their preparation. If they are to be used for production of dialkylaminyl radicals, which has only been demonstrated to occur in chain reactions with Bu_3SnH mediation, one must be concerned with the possibility that small amounts of disulfide impurities could produce disastrous results.

There is a positive note for the use of arenesulfenamides as aminyl radical precursors, however. Assuming that our speculation concerning diselenide and disulfide impurities is correct and given that $(Bu_3Sn)_2O$ is demonstrated in this work to have no catalytic effect on a dialkylaminyl radical reaction, the results of Maxwell and Tsanaktsidis suggest that $(Bu_3Sn)_2O$ reacted with arylthiol to form a stannyl sulfide. There is precedent for such a reaction in that thiols, including thiophenol, are known to react with $(R_3Sn)_2O$ to give trialkylstannyl alkyl (aryl) sulfides (R_3SnSR').[30] Addition of tin oxide to an arenesulfenamide reaction might be considered as a precautionary measure.

Experimental Section

General Procedures. Samples of *N*-butyl-4-pentenamine (**5**) and *N*-butyl-2-methylpyrrolidine (**4**) were prepared as previously reported.[4] *N*-Butyl-2-[(phenylselenyl)methyl]pyrrolidine (**3**) was prepared by intramolecular amidoselenylation of *N*-(4-pentenyl)butanamide followed by $LiAlH_4$ reduction of the resulting *N*-butanoyl-2-[(phenylselenyl)-methyl]pyrrolidine as previously described;[4] the ^1H and ^{13}C NMR spectra of compound **3** matched those reported.[4] The PTOC carbamates **6** and **19** were prepared as previously reported.[10,31] Bu_3SnH was prepared by the method of Hayashi *et al.*[32] and freshly distilled before use. *N*-Hydroxypyridine-2-thione was prepared from an aqueous solution of the sodium salt (Olin Chemical Co.). $(Bu_3Sn)_2O$ and all other reagents listed were obtained from Aldrich Chemical Co. and used as obtained.

Ethyl 3-[*N*-methyl-*N*-(*trans*-2-phenylcyclopropyl)amino]propanoate (**9E**) was prepared by a method similar to that reported by Horsma and Nash for a related amino ester.[33] *N*-Methyl-*N*-(*trans*-2-phenylcyclopropyl)amine was prepared as previously described.[6] A mixture of 1.31 g (8.9 mmol) of this amine and 1.1 mL (9.8 mmol) of ethyl acrylate was stirred at room temperature for 5 days. Excess ethyl acrylate was removed by distillation to give the desired ester (1.78 g, 7.3 mmol, 81%). ^1H NMR: δ 0.97 (m, 1H), 1.11 (m, 1H), 1.27 (t, $J = 6.9$ Hz, 3H), 1.87 (m, 1H), 1.99 (m, 1H), 2.39 (s, 3H), 2.52 (m, 2H), 2.91 (m, 2H), 4.13 (q, $J = 7.2$ Hz, 2H), 7.1−7.3 (m, 5H). ^{13}C NMR: δ 14.22, 17.19, 25.44, 32.78, 42.36, 48.77, 53.15, 60.29, 125.57, 125.91, 128.23,

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(29) The potential for contamination to be the origin of the observations of Maxwell and Tsanaktsidis[1] was readily demonstrated. A sample of **3** was intentionally contaminated with 5% Ph_2Se_2 and subjected to reduction by a deficient amount of Bu_3SnH at 50 °C (0.03 M substrate and 0.02 M Bu_3SnH). Under these conditions, one would expect to observe about 10% yield of ring-opened product **5** if the diselenide was not present. In fact, GC analysis indicated the formation of **4** in 90% yield based on the limiting tin hydride, and ring-opened product **5** was not observed at a detection limit of 0.1%.

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141.98, 172.54. MS: *m/z* (rel intens) 247 (46.2), 174 (10.0), 160 (100), 156 (95.3), 146 (63.2), 144 (26.0), 117 (71.7), 115 (28.4), 104 (16.3), 91 (36.5). HRMS: calcd for $C_{15}H_{21}NO_2$, 247.1572; found, 247.1576.

Methyl 3-[*N*-methyl-*N*-(*trans*-2-phenylcyclopropyl)amino]propanoate (**9M**) was prepared by the same method as above from 0.53 g (3.6 mmol) of the amine and 0.36 mL (4.0 mmol) of methyl acrylate to give the desired amino ester (0.71 g, 3.1 mmol, 85%). ^{1}H NMR: δ 0.98 (m, 1H), 1.11 (m, 1H), 1.86 (m, 1H), 1.97 (m, 1H), 2.39 (s, 3H), 2.53 (m, 2H), 2.91 (m, 2H), 3.66 (s, 3H), 7.05 (m, 2H), 7.14 (m, 1H), 7.26 (m, 2H). ^{13}C NMR: δ 17.16, 25.46, 32.55, 42.39, 48.77, 51.51, 53.15, 125.58, 125.89, 128.25, 141.94, 172.97. MS: *m/z* (rel intens) 233 (58.3), 160 (88.5), 146 (53.4), 144 (32.7), 142 (100), 117 (80.5), 115 (33.4), 104 (14.4), 91 (41.9),77 (11.1). HRMS: calcd for $C_{14}H_{19}NO_2$, 233.1416; found, 233.1412.

3-[*N*-Methyl-*N*-(*trans*-2-phenylcyclopropyl)amino]propanoic acid (**10**) was prepared from both the methyl and ethyl esters. The above methyl ester (0.24 g, 1.03 mmol) was dissolved in water (12 mL). The resulting solution was heated at 70 °C for 48 h, after which ca. 75% of the solvent was removed at reduced pressure. The concentrated mixture was washed with ether to remove unhydrolyzed ester, and the aqueous layer was concentrated under reduced pressure to give the desired acid as a solid which was recrystallized from ether to give **10** (0.21 g (0.96 mmol, 93%). A similar preparation from the above ethyl ester gave **10** in 90% yield. Mp: 55−57 °C. ^{1}H NMR: δ 1.14 (m, 1H), 1.29 (m, 1H), 2.11 (m, 1H), 2.19 (m, 1H), 2.54 (m, 5H), 2.97 (m, 2H), 6.89 (bs, 1H), 7.04 (m, 2H), 7.25 (m, 3H). ^{13}C NMR: δ 16.08, 24.46, 30.49, 41.21, 48.49, 53.11, 125.89, 126.29, 128.51, 140.10, 173.40. MS: *m/z* (rel intens) 219 (41.0), 172 (10.8), 160 (41.2), 146 (31.8), 144 (11.0), 128 (100.0), 117 (61.0), 104 (13.7), 91 (51.5), 86 (15.5), 77 (17.4), 44 (60.0). HRMS: calcd for $C_{13}H_{17}NO_2$, 219.1259; found, 219.1260.

[[[2-[*N*-Methyl-*N*-(*trans*-2-phenylcyclopropyl)amino]ethyl]carbonyl]-oxy]-2(1*H*)-pyridinethione (**7**) was prepared by the method of Barton *et al.*[12] To a solution of acid **10** (167 mg, 0.76 mmol) in THF (15 mL) at −15 °C were added *N*-methylmorpholine (0.083 mL, 0.76 mmol) and isobutyl chloroformate (0.10 mL, 0.76 mmol) under nitrogen. The solution was stirred at −15 °C for 5 min. All procedures from this point were conducted in flasks shielded from light. A solution of *N*-hydroxy-2-thiopyridone (0.12 g, 0.916 mmol) and Et_3N (0.128 mL, 0.92 mmol) in THF (8 mL) was added. The solution was stirred at −15 °C under nitrogen for 2 h. The precipitate of *N*-methylmorpholine hydrochloride was filtered and washed with THF. Dilution of the filtrate with ether (20 mL) gave an organic phase which was washed with 3 × 10 mL of saturated aqueous $NaHCO_3$ and 3 × 10 mL of saturated aqueous NaCl solution. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give **7** as a heavy oil, 0.183 g (0.56 mmol, 73%). Attempted chromatography on silica gel resulted in decomposition of the sample. On the basis of the integration of the PTOC ester signals at δ 6.62 versus that for the entire aliphatic region, the crude sample was judged to be 50% pure. The ^{1}H NMR spectrum of **10** exhibited a number of broadened peaks due to slow dynamic processes. ^{1}H NMR: δ 0.98 (br m, 6H), 1.31 (br m, 1H), 1.61 (br m, 3H), 2.02 (br m, 3H), 2.49 (s, 3H), 2.95 (m, 4H), 3.5−4.2 (m, 3H), 6.62 (dt, J = 6.9, 1.8 Hz, 1H), 7.15−7.29 (m, 6H), 7.49 (d, J = 6.0 Hz, 1H), 7.70 (dd, J = 6.9, 1.2 Hz, 1H).

Indirect Kinetic Studies. Solutions containing 0.02 mmol of **3** in benzene were equilibrated at the desired temperature under nitrogen. A stock solution of Bu_3SnH and AIBN was added such that the total volume of the resulting solution was 2.0 mL. The reactions were monitored for loss of **3** by TLC. After consumption of **3**, the cooled solutions were extracted with HCl solution (3 × 2 mL). The acidic aqueous phase was basified (NaOH) and extracted with benzene (3 × 2 mL). A measured amount of internal standard (pentadecane) was added, and the mixtures were analyzed by an FID-equipped gas chromatograph on a 15 m, wide-bore capillary column with a low-polarity bonded phase (Alltech, SE-30). The yields of products were determined with response factors measured on the same instrument with authentic samples. Because the concentrations of Bu_3SnH were relatively low, the mean concentrations of tin hydride during the course of the reaction were calculated; this procedure introduces an insignificant error for the concentrations employed. The ratios of products obtained from the GC analyses are shown in Figure 1.

Direct Kinetic Studies. Laser flash photolysis kinetic studies employed an Applied Photophysics LK50 kinetic spectrometer with a Spectron Nd-YAG laser. The methods employed were the same as previously reported.[6,16,31] Kinetic traces were obtained following laser irradiation of He-sparged and thermostated solutions of precursors that were flowing through a flow cell in the spectrometer. The observed rate constants typically had errors of 2−5% at the 95% confidence interval. For studies of radical **20** with $(Bu_3Sn)_2O$, the radical precursor **19** was added to THF or benzene solutions containing the stated concentrations of the additives before sparging. The study of radical **12** in the presence of BF_3 was conducted in the same manner as those of **20** with BF_3.[16] Concentration changes due to sparging were judged to be minimal on the basis of the observation that doubling and trebling the sparging time of a test sample containing BF_3, the Lewis acid with the largest catalytic effect, resulted in no appreciable change in the observed rate constants for cyclization of **20**.[16]

Computations were performed with the Gaussian 94 series of programs.[34] Fully optimized structures of **1M** and **2M** were obtained by *ab initio* methods at the unrestricted Hartree−Fock (UHF)[35] level of theory with the 3-21G[36] and 6-31G*[37] basis sets and by second-order Møller−Plesset perturbation theory (UMP2/6-31G*).[38] The energies of **1M** and **2M** were also obtained by the complete basis set extrapolation method CBS-4.[39] Optimized structures were also obtained by the density functional theory BLYP/6-31G* and the hybrid density functional theory B3LYP/6-31G*.[40] Single-point calculations of the energies of **1M** and **2M** were obtained with fourth-order Møller−Plesset perturbation theory (UMP4/6-31G//UMP2/6-31G*) and hybrid density functional theory (B3LYP/6-311+G(3df,2df,2p)//B3LYP/6-31G*). Vibrational frequencies were calculated at the UHF/6-31G* level of theory in order to characterize the minima and compute zero-point energies. Thermal corrections from UHF/6-31G* level frequency calculations were used to calculate enthalpies and free energies with the appropriate scaling factor.[18] Energies and coordinates for the optimized structures of **1M** and **2M** are provided in the Supporting Information.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **9M**, **9E**, and **10**, ^{1}H NMR spectrum of **7**, and energies and Cartesian coordinates for structures of **1M** and **2M** at various levels of theory (18 pages). See any current masthead page for ordering and Internet access instructions.

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