Intramolecular Cyclization of Radicals Generated from α-Halomethylsulfonamides

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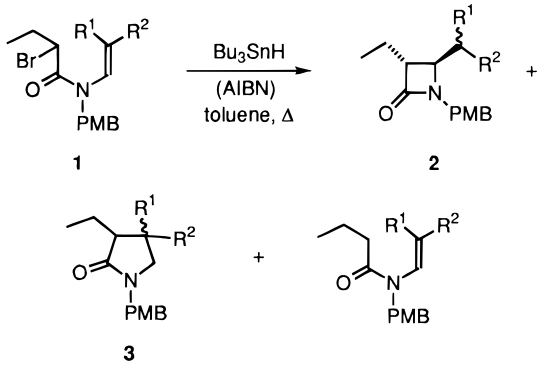
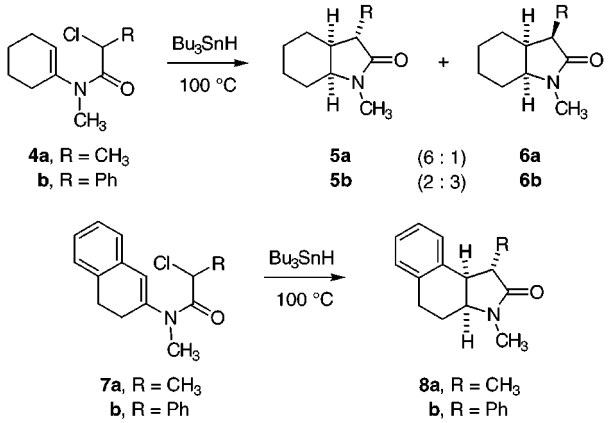
A series of homologous α-sulfonamidyl radicals has been generated by reaction of α-halomethyl precursors with tri-*n*-butyltin hydride under AIBN catalysis. The intramolecular cyclization capability of these highly reactive intermediates has been evaluated. Where possible, five-membered sultams are formed by 5-exo transition states. The longer $C-SO_2$ and SO_2-NR_2 bonds have little demonstrable effect on this pathway. In larger systems, however, the 7-endo option predominates over the 6-exo alternative. A preparatively useful route to sultams has emerged from this investigation.

With the dramatic increase in the synthetic application of radical-induced cyclization reactions has come a number of broad generalizations.[1] Indeed, it is now widely recognized that ring closures via 3-exo, 5-exo, and 6-exo pathways operate readily. Examples of other reaction trajectories are feasible, particularly when substitution or other structural features such as ring strain render these alternatives conducive to operation. These general features have been extended only to a limited degree to carboxamides, and not at all to sulfonamides. The two bromine-substituted butanamides **1a** and **1b** represent



an informative pair of examples. When heated with tri-*n*-butyltin hydride and a catalytic amount of AIBN in toluene, **1a** gave both *β*-lactam **2a** and *γ*-lactam **3a** (ca. 1:1, 31%), with the reduction product formed predominantly (41%).[2] In contrast, the more highly activated system **1b** was transformed into *β*-lactam **2b** (diastereomeric ratio of 2.7:1, 56%) more efficiently and with only a trace of reduction product and no detectable **3b**.[2,3]

The extent to which enamides are prone to undergo uncommon 5-endo radical ring closure has been noted.[1a,4] Although the bicyclic lactams **5** and **6** formed from **4a** and **4b** are produced with variable stereoselectivities, their tricyclic congeners **7** cyclize to give only **8**.[5]



The preceding observations show that substitution of a radical center by the carbonyl group of an amide linkage lends itself quite suitably to the controlled formation of nitrogen heterocycles. It is consequently surprising that carbon-centered electrophilic radicals positioned α to sulfonamide sulfur have not received prior attention in carbon−carbon bond-forming reactions.

Steric and polar effects have long been recognized to cause α-halo sulfones to be very resistant toward substitution by external nucleophiles.[6,7] For this reason, carbon−carbon bond formation involving such compounds has historically been carried out via the alkylation of α-sulfonyl carbanions typified by $ArSO_2CH^-X$. Once ESR spectroscopy had been applied to sulfonylated

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(2) Ishibashi, H.; Kodama, K.; Kameoka, C.; Kawanami, H.; Ikeda, M. *Synlett* **1995**, 912.

(3) For additional related examples, consult: (a) Ishibashi, H.; Kameoka, C.; Sato, T.; Ikeda, M. *Synlett* **1994**, 445. (b) Ishibashi, H.; Kameoka, C.; Kodama, K.; Ikeda, M. *Tetrahedron* **1996**, *52*, 489. (c) Ishibashi, H.; Kameoka, C.; Kodama, K.; Kawanami, H.; Hamada, M.; Ikeda, M. *Tetrahedron* **1997**, *53*, 9611.

(4) (a) Ishibashi, H.; Nakamura, N.; Sato, T.; Takeuchi, M.; Ikeda, M. *Tetrahedron Lett.* **1991**, *32*, 1725. (b) Sato, T.; Nakamura, N.; Ikeda, K.; Okada, M.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2399.

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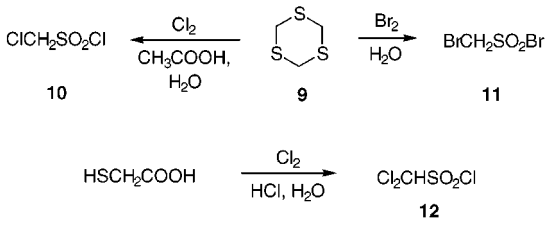
radicals and indicated that minimal stabilization was offered by the sulfur functionality,[8] this class of intermediates was recognized to be sufficiently reactive to enter into intramolecular cyclizations. Several reports had foreshadowed this conclusion.[9] In the ensuing decade, substantial use has been made of α-sulfonyl radicals in a variety of synthetic applications.[10]

As a prelude to work directed toward the first synthesis of bridgehead bicyclic sultams,[11] we initiated a systematic study to explore the kinetic preferences of intramolecular cyclization within halomethylsulfonamides substituted at nitrogen with unsaturated chains of varying length. In the present paper, we describe our observations in this area, which shed light on the feasibility of several cyclization pathways. Comparison is made with the chemistry of sulfur-centered radicals.[12]

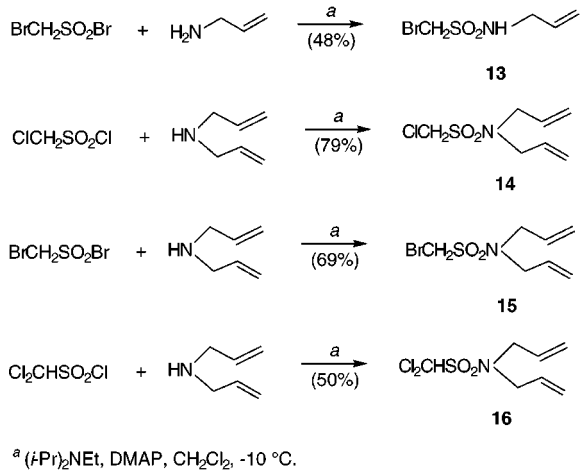
Results and Discussion

Chloromethanesulfonyl chloride (**10**)[13] and bromomethanesulfonyl bromide (**11**)[14] were prepared by the halogenation of *s*-trithiane (**9**) under aqueous conditions as previously described. The dichloro derivative **12** was obtained from thioglycolic acid in the manner reported by Kempe and Norin.[15] The readiness with which **10**−**12** are transformed into halosulfenes in the presence of



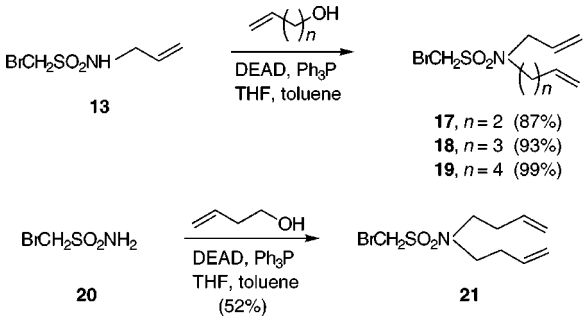
base[16,17] and the polymerizability of these intermediates prompted the development of a reproducible protocol for production of the requisite sulfonamides. Our requirements were best met by reaction with a primary or secondary amine in CH_2Cl_2 containing both DMAP and Hünig's base at −10 °C (Scheme 1). Although similar yields were realized with sodium 2-ethylhexanoate in THF,[18] this base is soluble in the common organic solvents and chromatographic separation is required. No comparable purification is necessary in the first instance.

Scheme 1



[a] (*i*-Pr)$_2$NEt, DMAP, CH_2Cl_2, -10 °C.

Scheme 2



Sulfonamide **13** was chosen as the building block to which terminally unsaturated chains of different length would be bonded to nitrogen. The exposure of **13** to Mitsunobu conditions[19] with 3-buten-1-ol, 4-penten-1-ol, and 5-hexen-1-ol as coreactants gave rise to **17**−**19** in high yield (Scheme 2). The symmetrical dibutenyl derivative **21** was accessed by comparable treatment of the known[20] bromomethanesulfonamide **20** with the proper alkenol. Despite the fact that this transformation is not as efficient as the others, it serves to exemplify a very direct synthetic route to the radical precursors of interest.

Although α-sulfonyl radicals lack stability[21] and have on occasion been deemed to be difficult to generate,[10b] reaction of the several halomethylsulfonamides with 1.1−3 equiv of tri-*n*-butyltin hydride and 0.07−0.47 equiv of AIBN in refluxing benzene by means of a syringe pump

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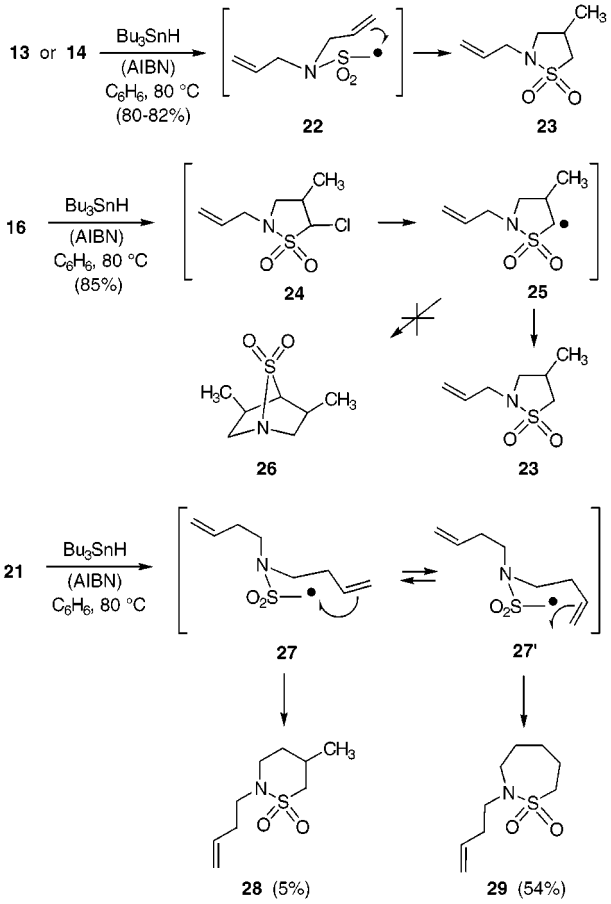
Scheme 3

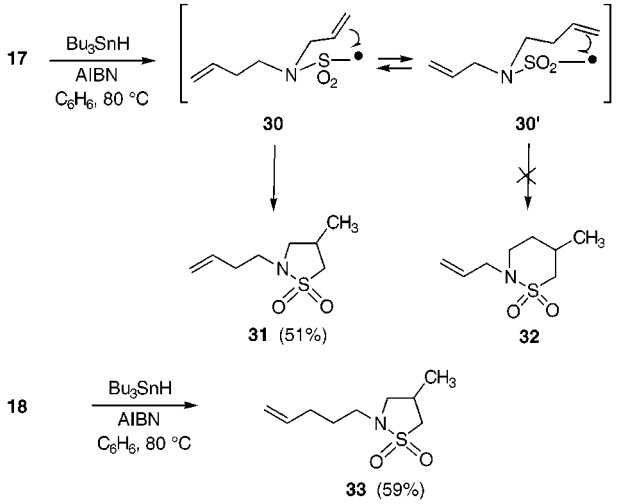


resulted in the ready consumption of starting materials. For **14** and **15**, the conversion uniquely to **23** proceeded in excess of 80% yield (Scheme 3). The identity of this product was established unambiguously by analysis of its ^{1}H and ^{13}C NMR spectra, scrutiny of which immediately reveals the presence of a methyl group. Accordingly, both **14** and **15** are transformed into the α-sulfonamidyl radical **22**, which smoothly cyclizes in 5-exo fashion.[22,23] No evidence was found for operation of the 6-endo option, presumably as the result of its higher energy costs.

The dichloro analogue **16** is assumed to follow the same initial reaction pathway and produce initially the cyclized monochloro sultam **24**. From this point, generation of a second α-sulfonamidyl radical is induced. However, this intermediate is ultimately converted by hydrogen atom transfer into **23** (85%). Further second-stage cyclization to generate the bicyclic bridgehead sulfonamide **26** does not operate because of the high-level strain resident therein.[11]

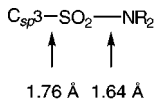
Bromomethylsulfonamide **21** was the next to be examined. As shown in Scheme 3, this reactant can cyclize in 6-exo (see **27**) or 7-endo fashion (as in **27′**). Although the first of these alternatives is commonly followed in hydrocarbon networks,[1a] only 5% of **28** was isolated. The heavy predominance of **29** (54%) indicates that adoption of the 7-endo reaction trajectory is favored by more than 10-fold over **27**.

Scheme 4



The **17**−**19** triad brings into focus the opportunity for direct intramolecular competition between two or more transition structures, one of which is necessarily the 5-exo cyclization mode (Scheme 4). In the ring closure of **17**, the results indicate that adoption of transition state **30** is preferentially adopted, in that the five-membered ring sultam was the only characterizable product isolated (51%). When **18** was similarly transformed uneventfully into **33**, we saw no cause to investigate the behavior of **19**.

All of the transition state models evaluated in this study[24] feature a sulfonamide unit whose bond lengths are significantly larger than those associated with the C−C bonds in hydrocarbon prototypes. While conventional $C_{sp^3}-C_{sp^3}$ bonds are fairly constant in length at 1.51−1.52 Å, those of the type in question are significantly longer (see **34** for average values).[25] One of these



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values is comparable to that associated with the $C_{sp^3}-S-C_{sp^3}$ length of 1.82 Å, and direct comparison with the cyclization of sulfur-centered radicals seems therefore warranted.[12] The intramolecular ring closure of the pent-4-enylthiyl radical (**35**) holds particular relevance (Scheme 5).[26] This species is recognized to cyclize reversibly and to deliver the six-membered species **37** in much higher yield than the tetrahydrothiophene **36**. This product distribution is a reflection of thermodynamic control and therefore holds a direct relationship to the longer C−S bonds. The almost exclusive conversion of **38** to cepham **39** at low concentrations[27] illustrates the synthetic utility of this process.

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(24) These include **22**, **25**, **27**, **27′**, **30**, and **30′**.

(25) *CRC Handbook of Chemistry and Physics*; Lide, D. R., Ed., CRC Press: Boca Raton, FL.

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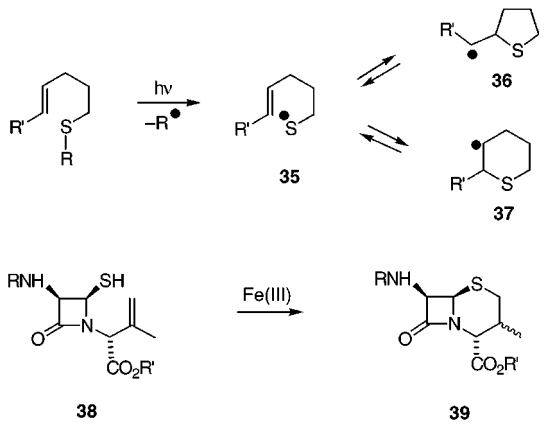
Scheme 5



Although bond construction in the present examples is not operating at a heteroatomic site, the forming sultam ring does incorporate two long bonds. The parallel to **37** is an obvious one. Nonetheless, no overriding tendency for six-membered ring formation is seen. Rather, the relative rate profile is of the form 5-exo > > > 7-endo > 6-exo.

On this basis, the sulfonamide group is seen to impose only very modest control over the regioselectivity of this group of radical reactions. This is likely because of the high reactivity of the electrophilic α-sulfonamidyl radicals, which are trapped very rapidly under kinetic control. Seemingly, the transition states that result in 5-exo cyclization are not disadvantaged to an extent sufficient to warrant a kinetic crossover. Moving beyond this level, the extent to which the 7-endo trajectory is adopted is taken as an indication that the generation of seven-membered sultams benefits from a decrease in the associated activation barriers. This feature could have important synthetic ramifications.

Experimental Section

General Methods. Melting points are uncorrected. The column chromatographic separations were performed with Woelm silica gel (230−400 mesh). Solvents were reagent grade and in most cases dried prior to use. The purity of all compounds was shown to be >95% by TLC and high field ^{1}H and ^{13}C NMR. The high-resolution and fast-atom-bombardment spectra were recorded at The Ohio State University Campus Chemical Instrumentation Center. Elemental analyses were performed at Atlantic Microlab, Inc., Norcross, GA.

General Procedure for Sulfonamide Formation. *N*-Allyl Bromomethanesulfonamide (13). A solution of allylamine (1.28 mL, 16.8 mmol), diisopropylethylamine (2.98 mL, 16.8 mmol), and DMAP (85 mg) in CH_2Cl_2 (20 mL) was cooled to −10 °C and treated slowly with bromomethanesulfonyl bromide (3.30 g, 13.9 mmol) dissolved in CH_2Cl_2 (1 mL). The reaction mixture was allowed to warm slowly to 20 °C, stirred overnight, and quenched with saturated $NaHSO_4$ solution. The aqueous phase was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried, and evaporated. Flash chromatography of the residue on silica gel (elution with 5:1 to 1:1 hexanes/ethyl acetate containing 5% of triethylamine) gave 1.41 g (48%) of **13** as white crystals: mp 33−34 °C (from ether); IR ($CHCl_3$, cm^{-1}) 1646, 1329, 1206, 1151; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91−5.80 (m, 1 H), 5.33 (dd, J = 17.0, 1.0 Hz, 1 H), 5.22 (dd, J = 10.2, 1.0 Hz, 1 H), 5.08 (br, 1 H), 4.42 (s, 2 H), 3.81 (t, J = 6.0 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.9, 118.2, 46.3, 42.0; HRMS (EI) m/z (M^+) calcd 212.9459, obsd 212.9482. Anal. Calcd for $C_4H_8BrNO_2S$: C, 22.44; H, 3.77. Found: C, 22.89; H, 3.79.

14: reaction of diallylamine (1.08 mL, 8.8 mmol) with chloromethanesulfonyl chloride (1.19 g, 8.0 mmol) in the predescribed manner afforded 1.33 g (79%) of **14** as a colorless oil; IR ($CHCl_3$, cm^{-1}) 1644, 1442, 1421, 1352; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88−5.75 (m, 2 H), 5.32−5.29 (m, 2 H), 5.27−5.25 (m, 2 H), 4.50 (s, 2 H), 3.96 (d, J = 4.2 Hz, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.3, 119.4, 56.1, 50.0; HRMS (EI) m/z (M^+) calcd 209.0277, obsd 209.0266. Anal. Calcd for $C_7H_{12}ClNO_2S$: C, 40.10; H, 5.77. Found: C, 40.20; H, 5.83.

15: pale yellowish crystals, mp 22−24 °C (69% yield); IR ($CHCl_3$, cm^{-1}) 1643, 1421, 1348, 1147, 1097; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94−5.73 (m, 2 H), 5.29−5.23 (m, 4 H), 4.39 (s, 2 H), 3.93 (d, J = 6.3 Hz, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.3, 119.5, 50.2, 42.2; HRMS (EI) m/z (M^+) calcd 252.9772, obsd 252.9772. Anal. Calcd for $C_7H_{12}BrNO_2S$: C, 33.08; H, 4.76. Found: C, 33.30; H, 4.87.

16: colorless oil (50%); IR ($CHCl_3$, cm^{-1}) 1644, 1442, 1420, 1364, 1264, 1048; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.22 (s, 1 H), 5.78 (m, 2 H), 5.26 (m, 4 H), 3.98 (d, J = 6.4 Hz, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.0, 120.1, 78.6, 50.7; HRMS (EI) m/z (M^+) calcd 244.9858, obsd 244.9875. Anal. Calcd for $C_7H_{11}Cl_2NO_2S$: C, 34.44; H, 4.54. Found: C, 34.73; H, 4.58.

General Mitsunobu Procedure. To a magnetically stirred solution of **13** (1 mmol), the alcohol (1 mmol), and triphenylphosphine (1.2 mmol) in toluene (2 mL) and THF (2 mL) was added diethyl azodicarboxylate (1.2 mmol, 40% in toluene) over a 15-min period. After an additional 30 min of agitation, the reaction mixture was placed on top of a column of silica gel. Elution with 2:1 hexanes/ethyl acetate afforded product, which was further purified by flash chromatography.

17: use of 312 mg of **13** afforded 337 mg (87%) of **17** as white crystals; mp 15−16 °C; IR ($CHCl_3$, cm^{-1}) 1642, 1454, 1420, 1345, 1240, 1205, 1144; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92−5.67 (m, 2 H), 5.33−5.06 (m, 4 H), 4.39 (s, 2 H), 3.95 (d, J = 6.5 Hz, 2 H), 3.39 (t, J = 7.4 Hz, 2 H), 2.35 (q, J = 7.2 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.2, 132.7, 119.4, 117.5, 50.8, 47.5, 41.8, 32.9; HRMS (EI) m/z (M^+) calcd 266.9929, obsd 266.9868. Anal. Calcd for $C_8H_{14}BrNO_2S$: C, 35.83; H, 5.26. Found: C, 36.08; H, 5.33.

18: 93% yield; white crystals, mp 22−23 °C (from CH_2Cl_2); IR ($CHCl_3$, cm^{-1}) 1641, 1446, 1419, 1344, 1285, 1204, 1144, 1098; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94−5.71 (m, 2 H), 5.33−5.24 (m, 2 H), 5.07−4.97 (m, 2 H), 4.39 (s, 2 H), 3.94 (d, J = 6.4 Hz, 2 H), 3.32 (dd, J = 7.5, 7.9 Hz, 2 H), 2.06 (m, 2 H), 1.71 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 132.8, 119.3, 115.4, 50.8, 47.8, 41.6, 30.5, 27.5; HRMS (EI) m/z (M^+) calcd 283.0064, obsd 283.0068. Anal. Calcd for $C_9H_{16}BrNO_2S$: C, 38.31; H, 5.71. Found: C, 38.51; H, 5.61.

19: 99% yield; colorless oil; IR (film, cm^{-1}) 1640, 1444, 1419, 1382, 1348, 1206, 1145, 1097; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91−5.70 (m, 2 H), 5.32−5.24 (m, 2 H), 5.03−4.94 (m, 2 H), 4.38 (s, 2 H), 3.93 (d, J = 6.4 Hz, 2 H), 3.31 (t, J = 7.7 Hz, 2 H), 2.10−2.03 (m, 2 H), 1.65−1.55 (m, 2 H), 1.45−1.34 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 132.7, 119.3, 114.9, 50.6, 48.0, 41.7, 33.1, 27.6, 25.6; HRMS (EI) m/z (M^+) 295.0242, obsd 295.0242. Anal. Calcd for $C_{10}H_{18}BrNO_2S$: C, 40.55; H, 6.12. Found: C, 40.67; H, 6.16.

21: reaction in this case involved 139 mg (0.80 mmol) of **20**, 140 mL (1.6 mmol) of 3-buten-1-ol, 312 mL (1.92 mmol) of DEAD, and 504 mg (1.92 mmol) of triphenylphosphine; 52% yield; colorless oil; IR ($CHCl_3$, cm^{-1}) 1458, 1337, 1148; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83−5.69 (m, 2 H), 5.16−5.07 (m, 4 H), 4.38 (s, 2 H), 3.39 (t, J = 7.5 Hz, 4 H), 2.37 (ddd, J = 7.6, 7.5, 6.9 Hz, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.2, 117.7, 47.9, 41.5, 33.2; HRMS (EI) m/z (M^+) calcd 283.0064, obsd 283.0083. Anal. Calcd for $C_9H_{16}BrNO_2S$: C, 38.31; H, 5.71. Found: C, 38.55; H, 5.79.

General Procedure for Radical Cyclizations. A solution of tri-*n*-butyltin hydride (1.5 mmol) and AIBN (0.1 mmol) in deoxygenated benzene (2.5 mL) was added over 3 h by means of a syringe pump to a refluxing solution of the substrate (1.0 mmol) in the same solvent (2.5 mL). Following completion of the addition, the reaction mixture was heated for an additional 3 h then directly concentrated in vacuo. The residue was

subsequently chromatographed on silica gel with hexanes/ethyl acetate (10:1 to 1:1 depending on polarity).

For **13**: 80% yield of **23**; colorless oil; IR ($CHCl_3$, cm^{-1}) 1644, 1456, 1420, 1237, 1140, 1032; ^1H NMR (300 MHz, $CDCl_3$) δ 5.87−5.73 (m, 1 H), 5.29−5.18 (m, 2 H), 3.68 (dd, J = 14.7, 6.2 Hz, 1 H), 3.66 (dd, J = 14.7, 6.6 Hz, 1 H), 3.36−3.28 (m, 2 H), 2.79−2.68 (m, 3 H), 1.18 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.5, 119.1, 53.9, 53.6, 47.0, 27.1, 18.6; HRMS (EI) m/z (M^+) calcd 175.0667, obsd 175.0672. Anal. Calcd for $C_7H_{13}NO_2S$: C, 47.98; H, 7.48. Found: C, 47.70; H, 7.53.

For **14**: 82% yield of **23**; identical in all respects to the above material.

For **16**: 85% yield of **23**; identical in all respects to the above material.

For **21**: 5% yield of **28** and 54% yield of **29**.

28: colorless oil; IR ($CHCl_3$, cm^{-1}) 1641, 1458, 1355, 1249, 1150; ^1H NMR (300 MHz, $CDCl_3$) δ 5.84−5.71 (m, 1 H), 5.13−5.05 (m, 2 H), 3.51 (dt, J = 2.4, 13.4 Hz, 1 H), 3.27−3.11 (m, 3 H), 3.06 (dd, J = 3.2, 12.9 Hz, 1 H), 2.56 (br t, J = 12.2 Hz, 1 H), 2.45−2.29 (m, 2 H), 1.70−1.59 (m, 1 H), 1.44−1.28 (m, 2 H), 1.06 (d, J = 5.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.8, 117.0, 54.8, 48.5, 46.7, 33.2, 31.2, 30.5, 21.3; HRMS (EI) m/z (M^+) calcd 203.0980, obsd 203.0982.

29: colorless oil; IR (CH_2Cl_2, cm^{-1}) 1641, 1453, 1414, 1326, 1244, 1135; ^1H NMR (300 MHz, $CDCl_3$) δ 5.86−5.72 (m, 1 H), 5.14−5.05 (m, 2 H), 3.30 (br t, J = 6.8 Hz, 4 H), 3.18 (br t, J = 6.0 Hz, 2 H), 2.35 (dd, J = 7.2, 14.4 Hz, 2 H), 1.95−1.82 (m, 4 H), 1.76−1.69 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.8, 117.2, 54.9, 48.2, 45.3, 33.7, 27.3, 25.5, 22.6; HRMS (EI) m/z (M^+) calcd 203.0980, obsd 203.0987.

For **17**: 51% yield of **31**; colorless oil; IR ($CHCl_3$, cm^{-1}) 1641, 1458, 1419, 1302, 1239, 1137; ^1H NMR (300 MHz, $CDCl_3$) δ 5.86−5.72 (m, 1 H), 5.15−5.05 (m, 2 H), 3.41−3.33 (m, 2 H), 3.20−3.11 (m, 1 H), 3.05−2.97 (m, 1 H), 2.84−2.69 (m, 3 H), 2.35 (m, 2 H), 1.21 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.8, 116.9, 54.2, 53.8, 43.8, 32.3, 27.2, 18.7; HRMS (EI) m/z (M^+) calcd 189.0824, obsd 189.0823.

For **18**: 59% yield of **33**; colorless oil; IR ($CHCl_3$, cm^{-1}) 1641, 1454, 1418, 1299, 1238, 1136; ^1H NMR (300 MHz, $CDCl_3$) δ 5.86−5.72 (m, 1 H), 5.07−4.96 (m, 2 H), 3.39−3.30 (m, 2 H), 3.13−3.03 (m, 1 H), 2.98−2.88 (m, 1 H), 2.81−2.69 (m, 3 H), 2.11 (br m, 2 H), 1.73−1.62 (m, 2 H), 1.22 (d J = 6.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.4, 115.4, 54.4, 53.9, 43.9, 30.8, 27.2, 27.0, 18.7; HRMS (EI) m/z (M^+) calcd 203.0980, obsd 203.0981.

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Supporting Information Available: Copies of the ^1H and ^{13}C NMR spectra of those compounds for which combustion analyses are lacking. This material is available free of charge via the Internet at http://pubs.acs.org.

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