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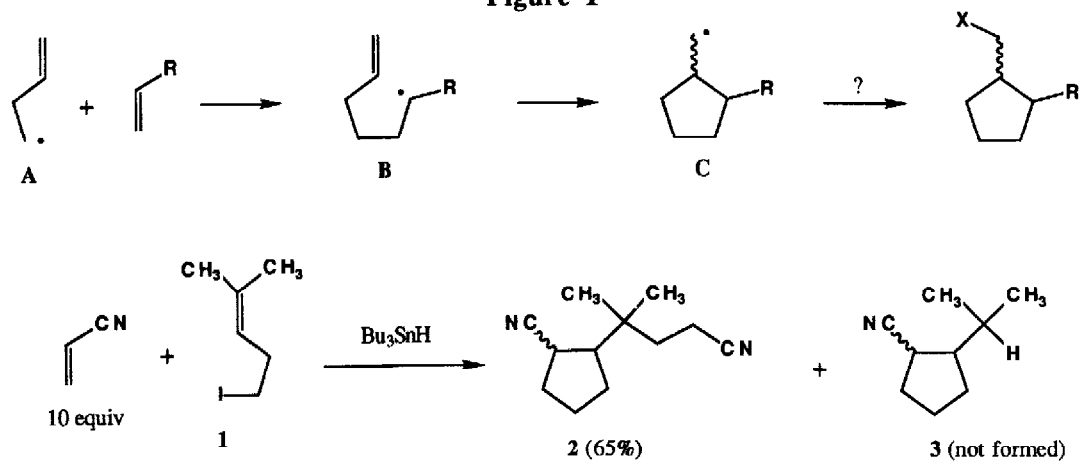
A Strategy for Radical Annulation Based on Allyl and Vinyl Stannanes

Dennis P. Curran*[1] and Paul A. van Elburg
Department of Chemistry, University of Pittsburgh, Pittsburgh, PA, 15260, USA

Abstract: *E-[(t-butyldimethylsilyl)methylene]cyclopentanes have been prepared by a new [3+2] radical annulation strategy starting from Z-1-t-butyldimethylsilyl-2-trimethylstannyl-4-iodo-1-butene and electron deficient alkenes.*

The sequencing of radical reactions to form several carbon–carbon bonds at once is a powerful strategy to quickly build complex molecules from simple precursors.[2] Radical annulation—the combination of an addition reaction and a cyclization reaction—is one of the most useful radical sequences. But it is also one of the most difficult to conduct. As illustrated in Figure 1, at least three radicals (**A**, **B**, **C**) must be generated and each must react selectively in the presence of the same pool of external reagents. Radical **B** is easily differentiated from **A** and **C** if its cyclization is faster than any bimolecular reaction. The differentiation of **A** and **C** is more difficult; if these two radicals have similar reactivity profiles, then they are destined to undergo the same reactions. For example, reduction of homoallylic iodide **1** in the presence of excess acrylonitrile (the Giese reaction) gives the "double adduct" **2** because both radical **A** and **C** have suffered the same fate (addition to acrylonitrile).[3] The "single adduct" **3** is not observed. The reaction conditions can be altered such that the intermediate radical **C** will be reduced faster than it adds to acrylonitrile, but then radical **C** will rarely form because reduction of **A** will be faster than formation of **B**. However, radicals **A** and **C** can sometimes be differentiated in the tin hydride method by substituent effects.[3a,4] Annulations based on iodine atom transfer also show promise.[5]

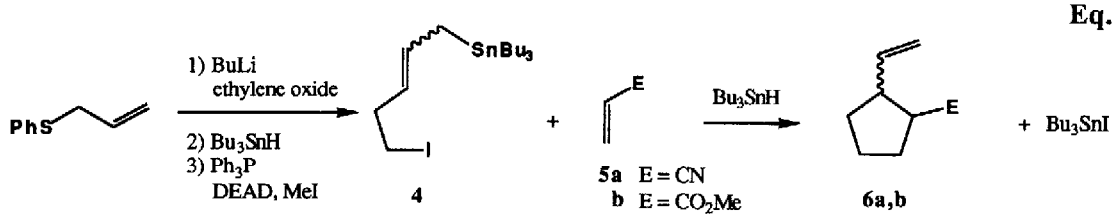
Figure 1



It was our premise that annulation reactions could be developed based on the known chemistry of allyl and vinyl stannanes.[2,6,7] If **C** were a β-stannyl radical, its fragmentation would be more rapid than any bimolecular reaction, thereby differentiating it from **A**.[8]

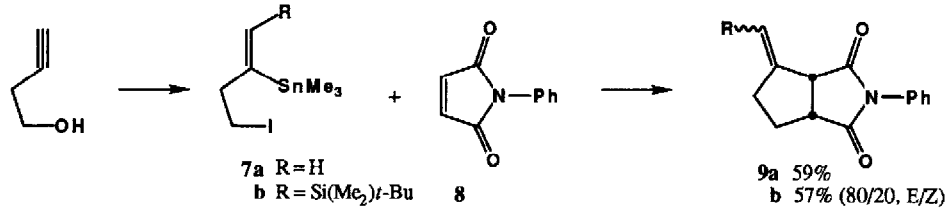
To test this idea, we first prepared allylic stannane **4** (75/25, E/Z) from allyl phenyl sulfide (Eq 1).[9] In principle, the combination of **4** with electron deficient alkenes is a chain reaction that requires only initiation. However, only small amounts of **6a,b** were produced when **4** was reacted in benzene with 1.2 equivalents of acrylonitrile (**5a**) or methyl acrylate (**5b**) under a variety of standard conditions (AIBN, heat; $Bu_3SnSnBu_3$, hv or heat). In contrast, when a solution of tributyltin hydride containing 10% AIBN was added slowly to a mixture of **4** and **5a** or **5b**, isolable quantities of **6a,b** were formed. We found that the reactions were incomplete when only small quantities (5-10%) of tin hydride were added so we adopted a procedure of adding one full equivalent of tin hydride. Even under these "optimum" conditions, isolated yields of **6a** and **6b** (1/1 mixtures of stereoisomers) were only 20-25% after chromatography. Part of the reason for the low yields may be due to the instability of starting iodide **4**; it decomposed to unidentified products when heated at 80 °C for 5 h. Preliminary experiments with modified reagents did not appear promising.[10]

Eq. 1



Better results were obtained with vinyl stannanes. Reagent **7a** was prepared by addition of trimethylstannyl cuprate to 1-butyn-4-ol (40%),[11] followed by Mitsunobu substitution (64%).[9c] Syringe pump addition of a solution of tributyltin hydride (1.5 equiv, with 10% AIBN) in benzene to **7a** and *N*-phenylmaleimide (2 equiv, 80 °C) gave **9a** in 59% isolated yield. As before, lower yields were obtained when catalytic quantities of tin hydride were added. Unfortunately, attempted reactions of **7a** with methyl acrylate or phenyl vinyl sulfone did not produce the corresponding annulated products.

Eq. 2



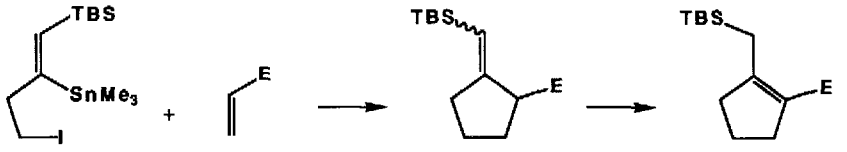
Based on known substituent effects in the cyclization of carbonyl-substituted radicals,[12] we speculated that these reactions might have failed because the intermediate adduct radicals (see B, Figure 1) might have undergone 6-endo rather than 5-exo cyclization. Intermediates resulting from 6-endo closure are α-stannyl radicals that cannot suffer β-elimination. Thus, an obvious chain transfer step is lacking. Based on this assumption (for which there is no experimental evidence), we prepared the *tert*-butyldimethylsilyl analog **7b**[13] by Pd(0)-catalyzed addition of $(t\text{-Bu})Me_2Si\text{–}SnMe_3$ to 1-butyn-4-ol (77%),[14] followed by Mitsunobu substitution.[9c] This Z-silylvinylstannane is a useful reagent.

Syringe pump addition of tin hydride to **7b** and *N*-phenylmaleimide (2 equiv) provided a separable mixture of **9b**E and **9b**Z (80/20) in 57% combined yield (see representative experimental procedure[15]). The major isomer was tentatively assigned as E based on chemical shift and coupling constant trends in the ^1H NMR spectra.[16] This corresponds to substitution of the tin with partial inversion. Because a previous cyclization of a vinyl stannane had occurred with a high level of

retention,[17] we felt obliged to provide a secure stereochemical assignment. An x-ray crystal structure of the major product showed that it was indeed **9b**E.[18]

The syringe pump addition of tributyltin hydride (0.7-2.0 equiv) to **7b** and a series of electron deficient alkenes gave the annulated products **10a-d** in 53-57% yield after chromatographic purification (Eq. 3). The E/Z selectivity ranged from good to excellent and in all cases the E-isomer predominated. The product **10c** was contaminated with a small amount of the conjugated allyl stannane **11c** (15%). Treatment of either **10b** or **10c** with DBU at 25 °C quickly (2 h, benzene) gave **11b** or **11c**. It is likely that either the vinyl or allyl silane products could be further functionalized by standard methods.

Eq. 3

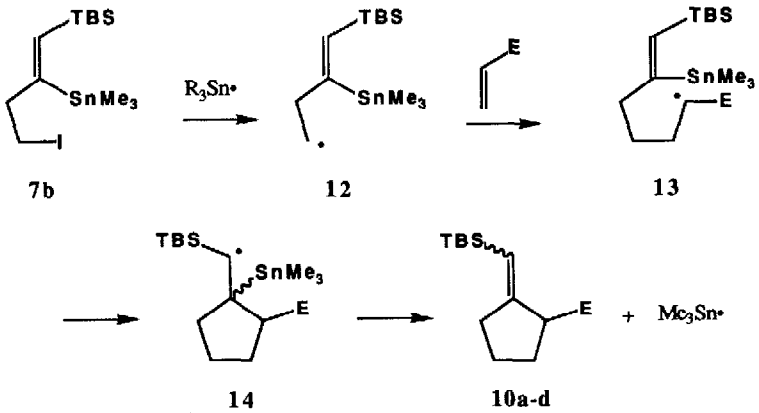


7b TBS = Si(Me)$_2$*t*-Bu **10a-d** **11b,c**

	E	%**10**	E/Z
a	CN	56%	89/11
b	CO_2Me	56%	98/2
c	COMe	53%	97/3
d	SO_2Ph	57%	97/3

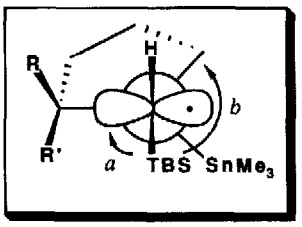
We propose the chain propagation sequence summarized in Eq. 4 to account for the formation of the annulated products. Abstraction of iodine from **7b** by $R_3Sn\bullet$ gives initial radical **12**. Addition of **12** to the alkene (to give **13**) is followed by 5-exo cyclization. Although cis and trans isomers of **14** can be formed, both should rapidly fragment with loss of $Bu_3Sn\bullet$ to give **10**E/Z.[19] This mechanism predicts that only catalytic quantities of tin hydride are required for initiation and we do not presently understand why large amounts are needed for optimum conversions.

Eq. 4



7b **12** **13** **14** **10a-d**

Figure 2



A qualitative understanding of the E-selectivity[20] can be derived from the model of Russell[6c] for related bimolecular substitutions. Figure 2 shows the postulated adduct prior to rotation and elimination of $Me_3Sn\bullet$. If R and R' are sufficiently small (for example, H),[17] then rotation in direction *a* occurs, $Me_3Sn\bullet$ is eliminated, and the olefin geometry is retained. If the interactions between the ring substituents (R,R') and the TBS group raise the barrier to rotation in direction *a* such that passing through eclipsed conformations becomes possible, then rotation in direction *b* is favored because it leads to a transition state for β-elimination that avoids interactions between TBS and R,R'.[19]

We believe that these results augur well for the development of related annulation reactions with other allyl and vinyl stannanes.[21]

References and Notes

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15. **Representative Experimental Procedure**: A solution of iodide **7b** (459 mg, 1.0 mmol) and *N*-phenylmaleimide (347 mg, 2.0 mmol) in benzene (2.9 mL) was heated at 85 °C and a solution of tributyltin hydride (808 μL, 3.0 mmol) and azo-*bis*-isobutyronitrile (AIBN) (16.5 mg, 0.1 mmol) in benzene (3.81 mL).was added by syringe pump over 6 h. The solvent was evaporated and the residue was dissolved in ether (3 mL) and titrated with a solution of iodine in ether until a yellow color persisted. The solvent was evaporated and the residue was purified by silica gel flash chromatography (petroleum ether/ether; 3/1): *E-isomer*: mp 114-115 °C (ethyl acetate/hexanes); ^{1}H NMR (C_6D_6) δ 7.37 (m, 2H), 7.10 (m, 2H), 6.97 (m, 1H), 6.11 (d, 1H, J = 1.5 Hz), 3.08 (d, 1H, J = 8.1 Hz,), 2.59 (dt, 1H, J = 8.1, 1.5 Hz), 2.18-1.99 (m, 3H), 1.50 (m, 1H), 0.90 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR δ 182.5 (s), 175.2 (s), 154.3 (s), 124.8 (d), 53.3 (d), 45.5 (d), 31.6 (t), 28.9 (t), 26.4 (q), 17.0 (s), –4.7 (q); MS *m/z*: 341 (M), 326, 310, 284, 73, 53; HRMS calcd. for $C_{19}H_{24}NO_2Si$ (M – CH_3): 326.1576; obs. 326.1576; Elemental analysis: Calcd for $C_{20}H_{27}NO_2Si$: C, 70.33; H, 7.97; N, 4.10. Found: C, 70.29, H, 7.68, N, 4.13. *Z-isomer*: ^{1}H NMR (C_6D_6) δ 7.37 (m, 2H), 7.10 (m, 2H), 6.98 (m, 1H), 5.95 (bs, 1H), 3.28 (d, 1H, J = 8.1 Hz), 2.52 (t, 1H, J = 8.1 Hz), 2.0-1.85 (m, 2H), 1.80 (m, 1H), 1.30 (m, 1H), 0.90 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H). ^{13}C NMR δ 179.2 (s), 175.4 (s), 154.1 (s), 124.3 (d), 49.0 (d), 46.1 (d), 36.5 (t), 28.5 (t), 26.7 (q), 16.2 (s), –4.6 (q), –5.0 (q); HRMS calcd. for $C_{19}H_{24}NO_2Si$ (M – CH_3): 326.1576; obs. 326.1576.
16. The vinyl proton appears at higher field in the Z isomer than the E. The allylic methyne appears at lower field in the Z-isomer and one of its two vicinal coupling constants is close to zero. See Ph. D. Theses of D. Kim (1988) and M.-H. Chen (1987), University of Pittsburgh.
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18. Full details of this crystal structure will be deposited in the Cambridge Crystallographic File.
19. We do not know the ratio of cis/trans isomers of **14** that is formed. As a consequence, we cannot comment on whether these isomers give the same or different E/Z ratios of the products **10**. The model in Figure 2 predicts that higher trans selectivity should result when the ester is in the R' position.
20. Control experiments with **9bE/Z** indicated that the stereoisomer ratio was kinetically controlled.

21. **Acknowledgements:** We thank Mr. Eric Bosch for important preliminary experiments and the National Institutes of Health (GM 33372) for funding.

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