Regio- and Stereochemical Control in Bis-functionalization−Cyclization: Use of Alleneyne Precursors for Carbocyclic and Heterocyclic Synthesis

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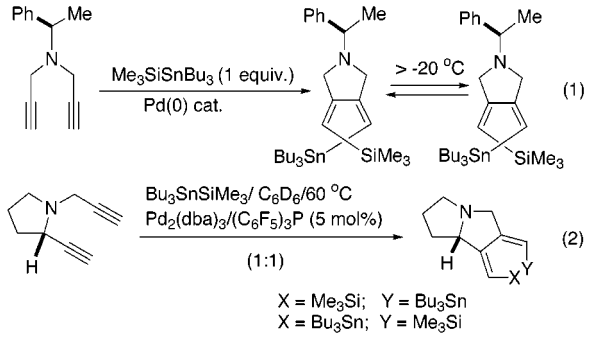
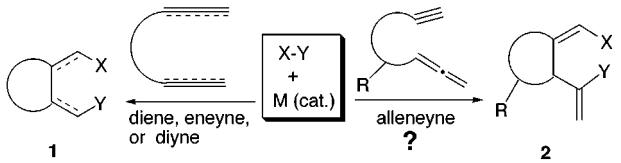
Catalytic synthesis of carbocyclic and heterocyclic compounds from acyclic olefinic and acetylenic precursors is a subject of great topical interest. A wide variety of substrates including eneynes, eneallenes, dienes, and diynes have been subjected to metal-catalyzed intramolecular cyclizations.[1] Many of these reactions are characterized by operationally simple procedures, high catalytic turnover and selectivity, and in several cases, exceptional functional group tolerance of the reagents. More recently, the value of such reactions have been enhanced further by the use of bifunctional (X−Y) reagents such as $R_3Si-SiR'_3$, $R_3Si-SnR'_3$, $R_3Si-BR'_2$, $R_3Sn-BR'_2$, as well as the more traditional trialkylsilicon- and trialkyltin- hydrides.[2] These reagents are incorporated into the reaction leading to highly functionalized end products (Scheme 1).

Last year we reported the cyclization of 1,6-diynes aided by trialkylsilyltrialkylstannanes ($R_3Si-SnR'_3$)[3] in the presence of Pd-(0) to give novel, helically chiral 1,2-dialkylidenecyclopentanes with an uncommon (*ZZ*)-geometry at the double bonds (eq 1).[4] This highly stereoselective reaction proceeds in good yields with no special care taken to avoid moisture and air, and is compatible with common functional groups such as ethers, esters, amides, carbonyl groups, and even tertiary amines. While the full synthetic potential of the product dienes remains to be explored, preliminary studies show that they undergo a number of selective transformations including proto-destannylation, Sn−halogen exchange, Stille coupling, and epoxidation of the vinylstannane.[5] Nevertheless, one limitation of this and *all* other related X−Y-mediated cyclizations that has become apparent is the lack of regioselectivity in some unsymmetrical substrates as illustrated in eq 2. The

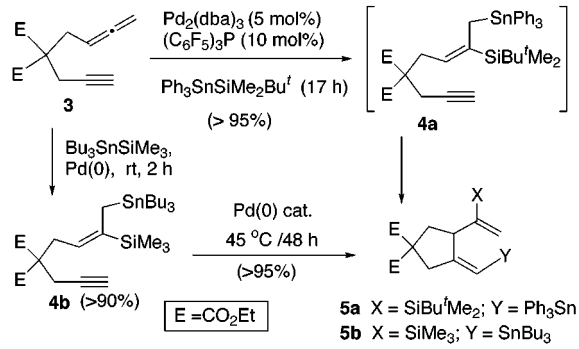


proline-derived diyne gave essentially a 1:1 mixture of regioisomeric products. We wondered whether by exploiting the different reactivities of allenes and acetylenes in Pd-catalyzed X−Y additions we could circumvent this problem.[6] Thus, cyclization

Scheme 1. Cyclizations Mediated by Bifunctional Reagents



Scheme 2. Silylstannylation/Cyclization of Allenyne



of an alleneyne would give a highly substituted alkylidenecyclopentane which maybe further elaborated through vinylsilane and vinylstannane chemistry (Scheme 1). We were encouraged by a timely study by Kang et al.[7] who reported that symmetric diallenes underwent Pd-catalyzed, stereoselective cyclization in the presence of $Bu_3SnSnBu_3$ and $Me_3SiSnBu_3$. In the meantime, our expectations on the allenyne cyclization have been borne out, and in this paper we report our initial findings on a highly chemo-, regio-, and stereoselective silylstannylation/cyclization reaction of these substrates.

The alleneyne **3**, in the presence of $Ph_3Sn-SiMe_2Bu^t$ (1.1 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol % in Pd) and $P(C_6F_5)_3$ (10 mol %) in C_6D_6 undergoes an exceptionally clean reaction (>95% yield of product by NMR) at room temperature to give the cyclic product **5a** in 80% isolated yield (Scheme 2). The lower *isolated* yield of the product is a measure of the instability of this relatively sensitive material which was isolated by column chromatography on silica gel using hexane containing 5% Et_3N.[8] The structure and configuration of **5a** were unambiguously

(1) For pertinent reviews see: Tamao, K.; Kobayashi, K.; Ito, Y. *Synlett* **1992**, 539. (b) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (c) Negishi, E.-i.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365. (d) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635. (e) Grubbs, R. H.; Chang, S. *Tetrahedron*, **1998**, *54*, 4413. (f) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1. (f) Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835. (g) Brummond, K. M.; Kent, J. L. *Tetrahedron*, **2000**, *56*, 3263.

(2) For recent review articles, see: (a) Suginome, M.; Ito, Y. *Chem. Rev.* **2000**, *100*, 3221. (b) Smith, N. D.; Mancuso, J.; Lautens, M. *Chem. Rev.* **2000**, *100*, 3257. For more recent representative publications that deal with R_3SiH and R_3SnH, see: (c) Ojima, I.; Lee, S.-Y. *J. Am. Chem. Soc.* **2000**, *122*, 2385 and references therein. (d) Kisanga, P.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 10017. (e) Lautens, M.; Mancuso, J. *Org. Lett.* **2000**, *2*, 671. (f) R_3Si-BR_2: Onozawa, S.; Hatanaka, Y.; Tanaka, M. *J. Chem. Soc., Chem. Commun.* **1997**, 1229. Suginome, M.; Matsuda, T.; Ito, Y. *Organometllics* **1998**, 5233. (g) R_3SnBR_2: Onozawa, S.; Hatanaka, Y.; Choi, N.; Tanaka, M. *Organometallics* **1997**, *16*, 5389. (h) $R_3SiSiR_3/R_3SnSnR_3/R_3SiSnR_3$: Obora, Y.; Tsuji, Y.; Kakehi, T.; Kobayashi, M.; Shinkai, Y.; Ebihara, M.; Kawamura, T. *J. Chem. Soc., Perkin Trans. 1* **1995**, 599. [SiSn]-mediated cyclization of eneynes: (i) Mori, M.; Hirose, T.; Wakamatsu, H.; Imakuni, N.; Sato, Y. *Organometallics* **2001**, *20*, 1907. See also, Radetich, B. Ph.D. Thesis, The Ohio State University, 2000.

(3) (a) Chenard, B. L.; Laganis, E. D.; Davidson, F.; RajanBabu, T. V. *J. Org. Chem.* **1985**, *50*, 3666. (b) Mitchell, T. N.; Killing, H.; Dicke, R.; Wickenkamp, R. *J. Chem. Soc., Chem. Commun.* **1985**, 354.

(4) Gréau, S.; Radetich, B.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2000**, *122*, 8579.

(5) Unpublished results of Warren, S.; Shin, S.

(6) (a) Addition of $R_3Si-SnR'_3$ and $R_3Sn-SnR'_3$ to allenes has been explored by Mitchell. See: Mitchell, T. N.; Schneider, U. *J. Organomet. Chem.* **1991**, *407*, 319. (b) Additions of $(OR)_2B-B(OR)_2$ to allenes have also been reported: Ishiyama, T.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1998**, *39*, 2357. (c) For a review of Pd-catalyzed reactions of allenes see: Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067.

(7) Kang, S.-K.; Baik, T.-G.; Kulak, A. N.; Ha, Y.-H.; Lim, Y.; Park, J. *J. Am. Chem. Soc.* **2000**, *122*, 11529.

(8) See Supporting Information for details.

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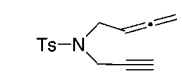
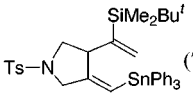
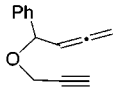
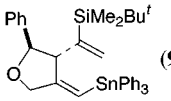
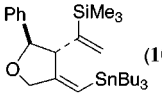
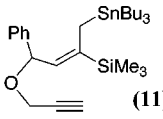
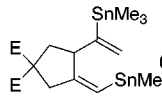
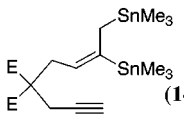
Table 1. Cyclization of Alleneynes Mediated by $R_3SiSnR'_3$ and R_3SnSnR_3

entry	substrate/X-Y/conditions[a]	product(s)[b]	yield[c]
1.	**3** /$Me_2Bu^tSiSnPh_3$/rt / 17 h (A)	**5a**	80 (>95%)
2.	**3**/$Me_3SiSnBu_3$/rt / 2 h (A)	**4b**	81 (>90%)[d]
3.	**3**/$Me_3SiSnBu_3$ /45 °C/48 h (A)	**5b**	71 (>95%)
4.	 **6**/$Me_2Bu^tSiSnPh_3$/rt / 24 h (A)	 (**7**)	41 (>90%)
5.	 **8**/$Me_2Bu^tSiSnPh_3$/rt / 16 h (B)	 (**9**)	61 (>80%)
6.	**8**/$Me_3SiSnBu_3$/80 °C / 5 h (B)	 (**10**)	72 (>85%)
7.	**8**/$Me_3SiSnBu_3$/rt/14 h (B)	 (**11**) + (**10**) [1:3]	(not isolated)
8.	**3**/Me_3Sn-$SnMe_3$/50 °C/48 h (A)	 (**13**)	46 (>90)
9.	**3**/Me_3Sn-$SnMe_3$/rt/2 h (A)	 (**14**)	46 (>90)

[a] A: 5 mol % $Pd_2(dba)_3$·$CHCl_3$ with 10 mol % $P(C_6F_5)_3$; B: 5 mol % $Pd(PhCN)_2Cl_2$ with 10 mol % $P(C_6F_5)_3$. [b] Isolated yields (yields determined by NMR in brackets). [c] Isolated material contained 8% **5b**.

established by NMR spectroscopy and elemental analysis. The identity of the SnC−*H* and the geometry of the double bond are clear from the coupling pattern (δ 6.40; s, $^2J_{Sn-H}$ = 74 Hz) and nOe difference spectrum.[8] Among the large number of monophosphine ligands that were screened for the reaction only P(3,5-Me_2−$C_6H_3)_3$ and $(C_6F_5)_3P$ gave any appreciable reaction after 12 h at room temperature (39 and 61%, respectively). The source of Pd, while not as critically important, showed a definite trend in reactivity when used in conjunction with $(C_6F_5)_3P$: $(PhCN)_2PdCl_2 \approx [Pd(allyl)Cl]_2/AgOTf > Pd_2(dba)_3$·$CHCl_3 \gg PdCl_2$. When the reaction was repeated with a less reactive silylstannane, Bu_3-$SnSiMe_3$, we were able to isolate an uncyclized adduct **4b** in excellent yield (81% isolated along with 8% **5b**) and stereochemical purity (Scheme 2).[9] On prolonged heating (45 °C, 48 h) the intermediate allylstannane **4b** is quantitatively converted into the cyclic product **5b**. Isolation of this key intermediate is indicative of the higher reactivity of the allene moiety (vis-à-vis the acetylene) and has clear mechanistic implications (vide infra). Presumably the corresponding allyltriphenylstannane **4a** is too reactive to accumulate in solution to any appreciable degree.

(9) The regioselectivity of addition of the silylstannanes under our modified reaction conditions appear to be different and, gratifyingly, better than originally reported by Mitchell et al.[6a] who used $(Ph_3P)_4Pd$ at 85 °C to effect the silylstannylation of allenes. For example, we find that addition of Me_2-$Bu^tSiSnPh_3$ and $Me_3SiSnBu_3$ to an *N*-allenyl-2-(*tert*-butyldimethylsiloxymethyl)oxazolidinone at room temperature leads to a single diastereomer in high yield. See Supporting Information for details.

Scheme 3. Possible Mechanism of Silylstannylation/Cycliation of an Allenyne

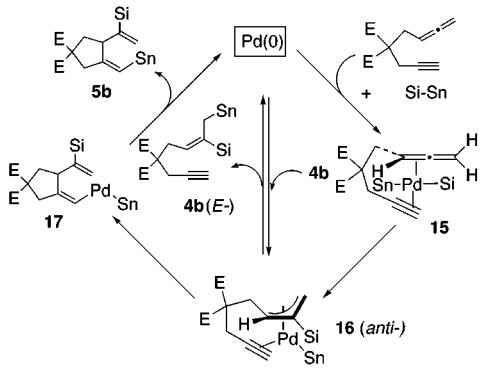


Table 1 shows the generality of the cyclization reaction. Reaction of Ph_3Sn−$SiMe_2Bu^t$ with *N*-tosylalleneyne **6** gives the cyclic product **7** in >90% yield at room temperature whereas the oxygenated derivative **8** gives the product **9** as a single diastereomer.[8] The less reactive trimethylsilyltributyl stannane takes 5 h at 80 °C to complete the cyclization of **8** to give the product **10**. At room temperature in the presence of $(PhCN)_2PdCl_2$ and $(C_6F_5)_3P$, **8** gives a mixture (1:3) of the allylstannane **11** and the cyclic product **10**.

The silyltin reagents are generally superior to other bisfunctionalization reagents in this type of cyclizations. For comparison, reactions of **3** and **8** with Me_3Sn−$SnMe_3$ and a boron−tin reagent Me_3Sn−B[−N(Me)CH_2CH_2(Me)N−] were attempted. Judged by "in situ" NMR analysis, the distannylation reaction proceed to give a good yield of **13**, albeit at a higher temperatures (entry 8).[8] Allenyne **8** gave a mixture of cyclic and acyclic products. The borostannylation is a relatively poor reaction, giving a similar adduct (<50% crude yield). Isolation of the Sn−Sn and Sn−B compounds presents significant problems, and upon chromatography severe losses are encountered.

A unified mechanism that accounts for the observed results is shown in Scheme 3. Bidentate coordination of the Pd^{2+} on the allene and acetylene (**15**) would lead to the more stable *anti* π-allyl Pd-complex **16**, which upon reductive elimination with formation of the less congested allylstannane and regeneration of Pd(0) would give the primary product **4b**. A more energetically demanding insertion of the acetylene into this π-allyl Pd complex takes place at a higher temperature, leading to the cyclic product **5b** via **17**.[10] In support of such a mechanism we have observed that isolated **4b** can be converted into **5b** using Pd(0) and $(C_6F_5)_3P$ at elevated temperatures.[11]

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Supporting Information Available: Spectroscopic and other analytical data for full characterization of all new compounds and NMR spectra (^1H, ^{13}C, COSY and nOe's) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA011281T

(10) (a) For a metal-catalyzed carbocyclization by intramolecular reactions of allylsilanes and allylstannanes with alkynes, see: Fernández-Rivas, C.; Méndez, M.; Echavarren, A. M. *J. Am. Chem. Soc.* **2000**, *122*, 1221. This reaction in which the trialkyltin moiety is lost is mechanistically different from latter stages of the silylstannylation/cyclization. (b) For intermolecular versions see: Shirakawa, E.; Yoshida, H.; Nakao, Y.; Hiyama, T. *Org. Lett.* **2000**, *2*, 2209 and references therein. A less likely alternate mechanism proceeding through an oxidative cyclization to form an intermediate palladacycle with Pd(IV) cannot be ruled out at this time.

(11) The Pd(0)-catalyzed isomerization of β-silyl-substituted allylstannanes observed by Mitchell[6a] could also involve a π-allyl-Pd intermediate.