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Silylstannylation of Highly Functionalized Acetylenes. Synthesis of Precursors for Annulations via Radical or Heck Reactions

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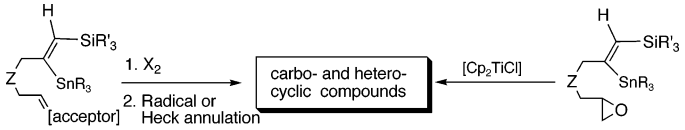
ABSTRACT

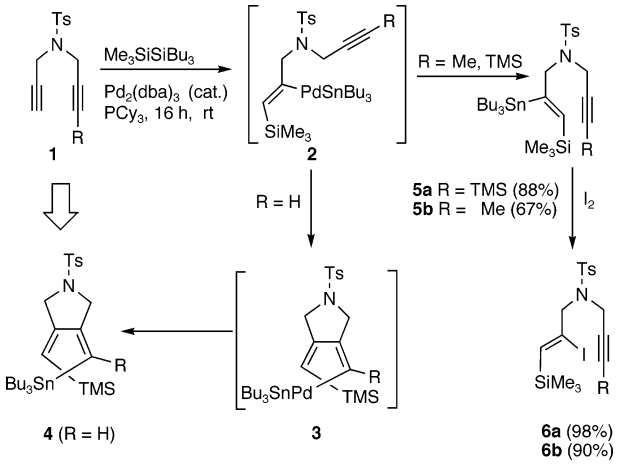


• acceptor: aldehyde, non-terminal acetylene, epoxide, simple or activated olefin
• silylstannyl olefins prepared from acetylenes by Pd-catalyzed reaction with R'_3SiSnR_3

Pd-catalyzed silylstannylation of acetylenes tolerates a variety of reactive functional groups (aldehydes, nonterminal acetylenes, epoxides, activated and unactivated olefins), providing easy access to precursors that can be converted into carbocyclic and heterocyclic compounds via free radical or Heck reactions. Examples of the synthesis of pyrrolidines, bicyclic β-lactams, hydrindanes, and tetrahydrofurans are described.

While trying to expand the scope of the trialkylsilyltrialkylstannane-mediated cyclization of 1,6-diynes,[1, 2] (Scheme 1, **1** → **4**), we have found that some individual steps of the reaction are remarkably selective for monosubstituted acetylenes. As illustrated in Scheme 1, neither the putative initial 1,2-silylpalladation (e.g., **1** → **2**) nor the subsequent carbopalladation (e.g., **2** → **3**) takes place at the more substituted acetylene (R = TMS or Me). Such chemoselectivity results in the formation of a (*Z*)-1,2-silylstannyl olefin **5** as the only product when one of the acetylenes is nonterminal. The reaction at the terminal acetylene proceeds with excellent regio- and stereoselectivity, leading to the olefin with a terminal SiR_3 group and an internal SnR_3 group. Instead of a nonterminal acetylene, the second functional group can also be an activated or unactivated olefin, a 1,3-diene, an aldehyde, or even an epoxide. Because of the presence of unsaturation on the appendage and the facility with which a C−Sn bond can be replaced by a C−X bond (e.g., **6a**, **6b**),

Scheme 1. Selectivity in the Silylstannylation of Acetylenes



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alternate strategies for cyclization of these adducts can now be envisioned. In this paper we report several examples of such applications of the silylstannyl olefins for the synthesis of highly functionalized carbocyclic and heterocyclic compounds. These include (a) cyclizations of vinyl radicals, (b) intramolecular Heck additions of vinyl iodides to acetylenes and olefins, and (c) additions of β-alkoxyradicals (generated from epoxides and Cp_2TiCl) to vinylstannanes.

Examples of the exquisite selectivity in the silylstannylation of substrates with terminal acetylenes are shown in Table 1. Typically the reaction is run in a hydrocarbon solvent such as benzene with a slight excess of the silylstannane in the presence of 5 mol % of a Pd(0) source such as $(Ph_3P)_4Pd$ or $Pd_2(dba)_3$ and a phosphine.[3] Depending on the substrate, temperatures between 25 and 80 °C are employed. Optimization of the reaction for a new substrate is best accomplished by mixing the reagents and the catalyst in a deuterated solvent and following the reaction by ^1H NMR. Conditions have been found where nonterminal acetylenes (entries 1 and 2), activated or unactivated olefins[4] (entries 3−8), 1,3-dienes (entry 7), epoxides (entry 9), and aldehydes[3] are also not affected. The proline-derived acetylenic alcohol derivative **13**, which is a potential source of bicyclic alkaloid intermediates, is readily converted into a silylstannyl olefin (entry 5). The corresponding allyl alcohol from which **13** was derived underwent the reaction, albeit in a lower yield (21%). Several epoxyacetylenes,[3] exemplified by **19a**,**b** (entry 9), gave the silylstannyl olefin in surprisingly good yields.

The vinyl-stannane substrates are useful intermediates for further synthesis. For example, the acetylenes **5a** and **5b** upon treatment with iodine in CH_2Cl_2 give very high yields of the vinyl iodides **6a** and **6b** *with complete retention* of stereochemistry at the double bond (Scheme 1). Treatment of the iodide **6b** with Bu_3SnH in refluxing benzene gives the (*Z*,*Z*)-bis-alkylidenecyclopentane **21b** in 48% yield (eq 1). An interesting application of this sequence for the

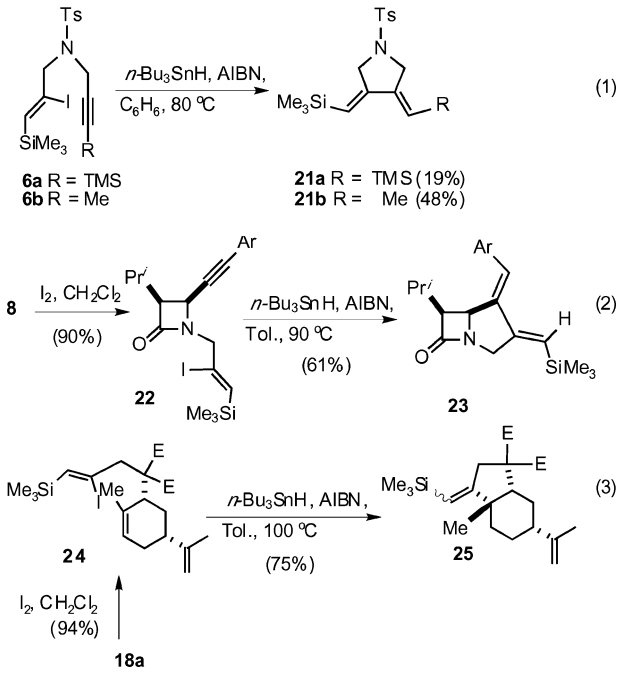


Table 1. Silylstannylation of Functionalized Acetylenes[a]

no.	substrate	product	y (%)
1.	**1a** R = SiMe **1b** R = Me	**5a** **5b**	**5 a** (88) **5 b** (67)
2.	**7**	**8**	54
3.	**9**	**10**	80
4.	**11**	**12**	90
5.	**13**	**14**	41
6.	**15**	**16**	73
7.			(60)[b]
8.	**17a** 1,3-cis **17b** 1,3-trans	**18a,b**	**18 a** (41) **18 b** (92)
9.	**19a** X = NTs **19b** X = $C(CO_2Et)_2$	**20a, b**	**20 a** (92) **20 b** (90)

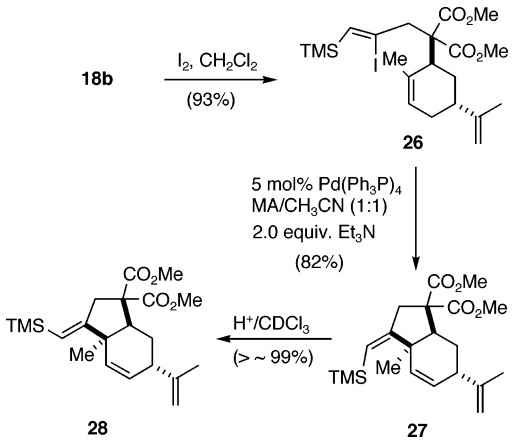
[a] See Scheme 1 and the text for a typical procedure. See Supporting Information for other examples, including aldehyde and acetylenic ester substrates, and specific experimental details. [b] Yield of two steps.

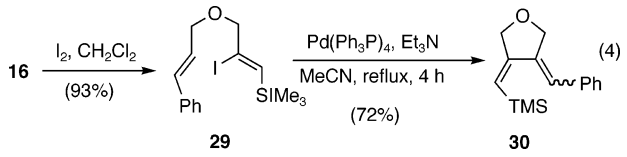
synthesis of a bicyclic β-lactam is shown in eq 2. Precursors such as **8** are easily synthesized via Hart's imine-ester enolate cycloaddition[5] followed by N-propargylation and silylstannylation. Treatment of **8** with iodine in CH_2Cl_2 followed by cyclization mediated by Bu_3SnH at 90 °C in toluene give the bicyclic β-lactam **23** in 61% yield.

Employing this strategy, readily available dimethyl 2-(3-propynyl)malonate can be used as a cyclopentane-annulation reagent. The two prototypical substrates shown in Table 1, entry 8 were readily prepared from a mixture of (±)-carveol mesylate and sodium dimethyl 2-(3-propynyl)malonate using a procedure similar to what has been reported by Trost.[6] The *cis*-adduct **17a** undergoes the silylstannylation (to **18a**) followed by iodination to give the vinyl iodide **24**, which when subjected to radical cyclization gives a mixture of alkylidenecyclopentanes, **25** (eq 3). Note that a highly congested ring junction with a quaternary carbon is produced in this key step in a very respectable 75% yield. Not surprisingly, a mixture of *Z*- and *E*-vinylsilanes is obtained in the reaction.[7] The configuration of the ring junction has been assigned as *cis* on the basis of ample precedents for the formation of bicyclo[4.3.0]-nonane skeletons under similar situations.[8]

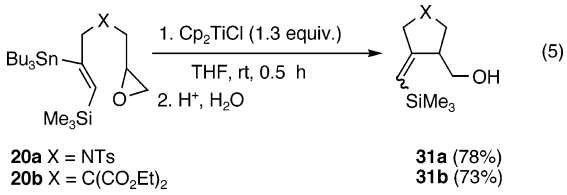
The *trans*-malonate adduct **17b**, upon silylstannylation followed by iodination, give a surprisingly high 86% yield (two steps) of the vinyl iodide **26.** Under Heck reaction conditions **26** gives 82% of a vinylsilane **27** with the formation of an endocyclic olefin. Unlike the radical reaction, the configuration of the vinylsilane (*Z*) is maintained in the Heck reaction. However, upon treatment with catalytic amounts of *p*-toluenesulfonic acid, the *Z*-vinylsilane **27** rearranges to a more stable *E*-vinylsilane **28** in nearly quantitative yield. A similar strategy can also be used for the synthesis of bis-alkylidenetetrahydrofurans as shown in eq 4. The vinyl iodide **29** was prepared starting from propargyl bromide and *trans*-cinnamyl alcohol in three steps and was subjected to intramolecular Heck reactions to give the product as a mixture of two isomers in a ratio of 9:1, with the (*Z*,*E*)-product predominating.[3,9]

Scheme 2. Cyclopentane Annulation via Heck Reaction





Titanium(III)-mediated epoxide opening as a method of generation of functionalized radicals has become a powerful tool for the synthesis of carbon−carbon bonds, homolytic reductions, and deoxygenations.[10] The vinylstannane adducts derived from the epoxy acetylenes (e.g., **20a**,**b)** undergo facile cyclization upon treatment with Cp_2TiCl in THF (eq 5).[11] The product was isolated as a mixture of *E* and *Z*-olefins (**31a** 1.0:0.2; **31b** 1.0:0.6).[12]



In summary, in this communication we demonstrate the remarkable functional group compatibility of the silylstannylation of acetylenes that permits the preparation of polyfunctional molecules that are difficult if not impossible to synthesize by conventional methods. Applications for the synthesis of highly functionalized carbocyclic and heterocyclic compounds through free radical or Heck cyclization protocols illustrate the myriad possibilities of using these building blocks for further synthesis.

(3) See Supporting Information for specific details of experimental conditions. A more complete table with other examples, including acetylenic aldehydes and propiolate esters, can also be found there.

(4) Some eneynes with terminal olefins do undergo competitive silylstannylative cyclization depending on the catalyst and reaction conditions. For example, see: Mori, M.; Hirose, T.; Wakamatsu, H.; Imakuni, N.; Sato, Y. *Organometallics* **2001**, *20*, 1907. See also: Lautens, M.; Mancuso, J. *Synlett* **2002**, 394. We found that 4,4′-dicarboethoxy-6-ene-1-yne under catalysis of $Pd_2(dba)_3/(C_6F_5)_3P$ leads to predominant silylstannylation-cyclization, whereas with $(Ph_3P)_4Pd$ simple addition to the terminal is observed. Radetich, B. Ph.D. Thesis, The Ohio State University, 1999. See Supporting Information.

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(7) The inversion barrier for a vinyl radical is very low (~2 kcal). For a leading references to a discussion of stereochemistry of vinyl radicals, see: (a) Bentrude, W. G. *Annu. Rev. Phys. Chem.* **1967**, *18*, 283. (b) Jenkins, P. R.; Symons, M. C. R.; Booth, S. E.; Swain, C. J. *Tetrahedron Lett.* **1992**, *33*, 3543. For early examples of vinyl radicals in organic synthesis, see: (c) Stork, G.; Mook, J. R. *J. Am. Chem. Soc.* **1983**, *105*, 3720. (d) Choi, J.-K.; Hart, D. J. *Tetrahedron* **1985**, *41*, 3959 and references therein.

(8) Stork, G.; Reynolds, M. E. *J. Am. Chem. Soc.* **1988**, *110*, 6911 and earlier papers in this series.

(9) A dienyl-propargyl ether derived from sorbyl alcohol and propargyl bromide also undergoes silylstannylation followed by iodination in overall 60% yield (entry 7, Table 1). See footnote 3.

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(11) For related C−C bond-forming reactions involving homolytic substitution via addition-fragmentation, see: (a) Baldwin, J. E.; Kelly, D. R.; Ziegler, C. B. *J. Chem. Soc., Chem. Commun.* **1984**, 133. (b) Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley, M. R. *Tetrahedron* **1985**, *41*, 4079. (c) Lowinger, T. B.; Weiler, L. *Can. J. Chem.* **1990**, *68*, 1636.

(12) Note that the *E* and *Z*-isomers of **31a** and **31b** have different vinylsilane configurations because the priorities of groups around the double bond change with the nature of X.

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Supporting Information Available: Experimental procedures for the synthesis of all new compounds and their full characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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