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Formation of Homoallyl Stannanes via Palladium-Catalyzed Stannylative Cyclization of Enynes

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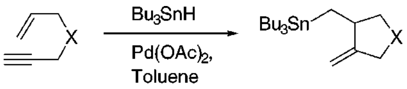
ABSTRACT



Treatment of 1,6-enynes with tri(*n*-butyl)tin hydride in the presence of a catalytic amount of palladium acetate leads to the formation of *exo*-methylenecyclopentanes bearing a tri(*n*-butyl)stannylmethyl moiety.

Organostannanes enjoy extensive use in organic synthesis due to the multitude of transformations they can undergo, of which one of the most important is tin−lithium exchange.[1,2] Recently, palladium-catalyzed carbon−carbon bond formation methods have been developed which use vinyl-, alkenyl-, and benzylstannanes as nucleophilic species, for coupling with various electrophiles under mild and neutral conditions.[3] Homoallyl stannanes can be used to generate cyclopropane systems by epoxidation of the olefin, followed by a facile 1,3-elimination.[4]

Several methodologies exist for the generation of vinyl-, allyl-, and alkylstannanes.[5] Recently, our group has investigated stannylative carbocyclization of 1,6-diynes, involving the use of tri(*n*-butyl)tin hydride and Pearlman's catalyst ($Pd(OH)_2/C$), leading to the formation of dialkylidenecyclopentanes with a terminal tributylstannyl moiety.[6] The methodology was extended to substrates bearing heteroatoms, allowing the formation of pyrrolidine and tetrahydrofuran systems. These structures are common motifs in many natural products.

Our current studies are focused on the reactions of 1,6-enynes. The hydrostannation of the diester **1** using Pearlman's catalyst in the presence of 1.5 equiv of tri(*n*-butyl)tin hydride led to the isolation of homoallyl stannane **2** albeit in poor yield (∼10%) (Scheme 1). Changing the catalyst to $PhCl_2(PhCN)_2$ gave better yields (∼50−60%). Changing the solvent had little effect, and toluene was selected as the solvent of choice (Table 1). To confirm the location of the tributylstannyl moiety (homoallylstannane versus vinylstannane), ozonolysis of **2** was carried out and the ^1H NMR spectra of the resulting ketone showed resonances attributed to the Bu_3Sn group.

Scheme 1

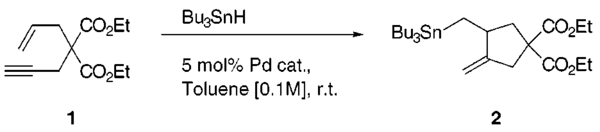


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Table 1. Hydrostannation/Cyclization of **1** in Various Solvents

solvent	$Pd(OAc)_2$ (mol %)	yield of **2** (%)[a]
1,2-dichloroethane	6	54
benzene	6	62
dichloromethane	7	62
diethyl ether	5	55
tetrahydrofuran	5	67 (60)
tetrahydrofuran (1 mmol)	5	78
toluene	6	52
toluene (1 mmol)	5	83

[a] Yields were determined by ^1H NMR using mesitylene as standard. Isolated yields are in parentheses. 0.25 mmol of substrate was used except where indicated.

Table 2. Hydrostannation/Cyclization of **1** with Various Palladium Catalysts

entry	catalyst	mol %	additive	yield (%)[a]
1	$Pd(OAc)_2$	6		75
2		8	BBEDA	54
3	$PdCl_2$	9		72
4	$Pd_2(dba)_3$	3		72
5		3	Ph_3As	49
6		3	Ph_3Sb	12
7	$PdCl_2(PhCN)_2$	6		58
8	$PdCl_2(MeCN)_2$	6		56
9	Pd(phen)Me(Cl)	6	$NaB(ArF)_4$	56
10	$[PdCl(\pi\text{-allyl})]_2$	5		55
11		6	$NaB(ArF)_4$	24
12	$PdCl_2(PPh_3)_2$	5		22
13	$Pd(PPh_3)_4$	5		20
14	$Pd(OH)_2/C$	8		13

[a] Yields were determined by ^1H NMR using mesitylene or tetramethyltin as standards. Scale: 0.25 mmol substrate. phen = 1,10-phenanthroline, $NaB(ArF)_4$ = sodium tetra(3,5-bis(trifluoromethyl))phenyl)borate.

The choice of catalyst was examined next (Table 2). Palladium(II) acetate (entry1), palladium(II) chloride (entry 3), and tris(dibenzylideneacetone)dipalladium(0) (entry 4) were found to be the most reactive catalysts for this reaction. However, the use of additives such as bis(benzylidene)-ethylenediamine (BBEDA), triphenylarsine, and triphenylstibine (entries 2, 5, and 6, respectively) in conjunction with these catalysts did not improve the yields. Nitrogen-based ligands (entries 7 and 8) were found to give moderate yields. Suprisingly, a cationic Pd complex which failed for the hydrosilylation/cyclization of 1,6-enynes in the study by Widenhoefer et al. was found to promote hydrostannation/cyclization (entry 9).[7,8] The π-allyl palladium chloride dimer gave a modest yield of product **2** (entry 10), but when rendered cationic, the yield was greatly reduced (entry 11).

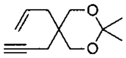
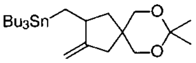
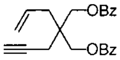
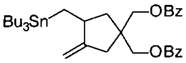
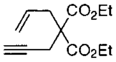
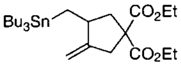
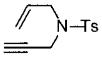
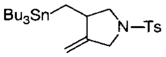
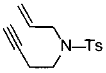
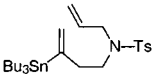
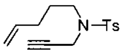
Phosphine-containing catalysts (entries 12 and 13) and Pearlman's catalyst (entry 14) were found to give poor yields.

The only related work is presented in a communication by Tanaka et al. where a single example of borylstannation/cyclization of diester **1** using $Pd(PPh_3)Cl_2$ led to the isolation of a carbocycle containing a borylmethylidene moeity in 82% yield.[9] Due to the different electronic character of our stannylating agent, phosphine-containing catalysts are inappropriate for our reaction and it is believed that the phosphine ligands occupy coordination sites on the Pd center whose vacancy is required for cyclization. Similar observations were made when diynes were treated with palladium and a phosphine ligand.[6]

Application of this methodology to other substrates was then attempted. Various enyne systems were constructed bearing modifications at the allylic/propargylic position (Table 3). Isolated yields were found to be approximately 10% lower than those estimated by ^1H NMR, presumably due to protodestannylation on silica gel.

Entries 1 and 2 illustrate that protected diols can readily undergo the reaction. The free diol caused degradation of the catalyst, allowing deposits of palladium black to form. Diester **1** (entry 3) was one of the best substrates, and nitrogen heterocycles could be created in moderate yield

Table 3. Hydrostannation/Cyclization of Various Enynes Using $Pd(OAc)_2$[a]

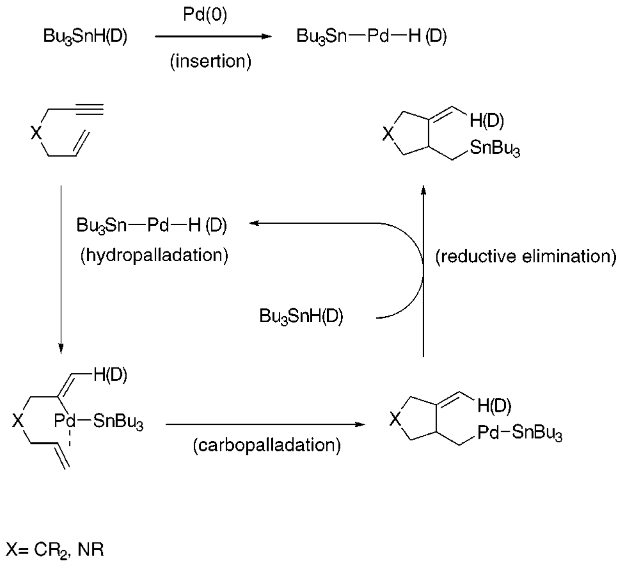
entry	substrate	mol %	product	yield
1		8		61%
2		10		50%
3		8		67%
4		8		41%
5		5		58%
6		5	2.8:1 internal:terminal	---

Conditions: 1.3 eq. Bu_3SnH in toluene [0.1M] added via syringe pump over 1.5h, followed by 2h stirring at room temperature. All products isolated by silica gel column chromatography.

(entry 4). A 1,7-enyne did not lead to ring formation but rather gave the internal addition product (entry 5). Similar results were seen for a 1,8-enyne (entry 6), but the ^{1}H NMR spectrum indicated a mixture of acyclic hydrostannated products, consisting predominantly of the internal addition product.

The reaction mechanism was probed using tri(*n*-butyl)tin deuteride and is believed to proceed as indicated in Scheme 2. Palladium(II) acetate undergoes reduction to palladium(0) by Bu_3SnH, which then oxidatively inserts into the tin–hydrogen bond of another molecule of hydride. Hydropalladation of the acetylenic moiety then occurs, followed by intramolecular carbopalladation of the double bond via a 5-*exo-trig* process. Reductive elimination then occurs to yield the cyclized product and Pd(0), allowing the cycle to repeat. Disappearance of the upfield *exo*-methylene proton signal was seen when tin deuteride was used (product of Table 3, entry 3, δ 4.9 present, δ 4.84 absent).

Scheme 2



The formation of the internal vinylstannane as major product for entries 5 and 6 of Table 3 may indicate that the presence of the remote alkene exerts a modest directing effect on the regioselectivity. It is known that the presence of a heteroatom at the propargylic position, as in entry 6, does promote formation of the internal addition product via chelation to the Pd center.[10] The carbopalladation step for the construction of six- and seven-membered ring sizes may be unfavorable due the size of the chelate formed when the olefin coordinates to the palladium. In these cases, reductive elimination of palladium(0) is the faster process, allowing isolation of acyclic vinylstannanes.

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Supporting Information Available: Detailed experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Pd(phen)Cl_2 was not effective as a catalyst for this reaction, giving only 3% cyclized product.

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