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Mechanistic Studies on the *O*-Directed Free-Radical Hydrostannation of Disubstituted Acetylenes with Ph_3SnH and Et_3B and on the Iodination of Allylically Oxygenated α-Triphenylstannylalkenes

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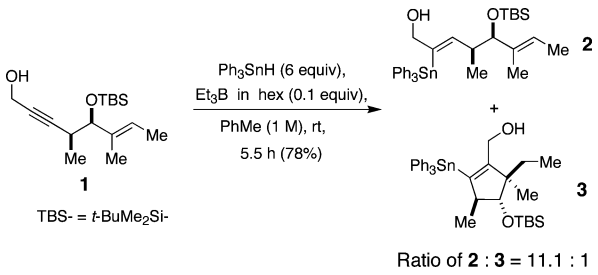
ABSTRACT



The free-radical hydrostannation of 1 with Ph_3SnH and catalytic Et_3B in PhMe has been mechanistically probed. At high Ph_3SnH concentrations, the *O*-directed hydrostannation pathway dominates, and 2 is formed with good selectivity (ca. 11.1:1). Substantially lower stannane/substrate concentrations increase the amount of tandem 5-*exo-trig* cyclization product 3 that is observed.

In this final paper of the series,[1] we shall discuss the mechanism of the *O*-directed free-radical hydrostannation reaction in light of recent experiments that we have performed with the propargylic alcohols **1** and **4** (Figure 1**)**.

One aspect of the hydrostannation mechanism that we were particularly keen to investigate was whether propargylically oxygenated alkyl acetylenes would undergo significant, but reversible, triphenylstannyl radical addition to the β-acetylenic carbon when subjected to the standard Ph_3SnH/cat. Et_3B hydrostannation conditions. We reasoned that if β-addition was significant in such systems, it should be quantifiable with the reporter molecules **1** and **4**, as these would generate α-vinyl radical intermediates with a capacity to cyclize via the 5-*exo-trig* pathway[2] (see **15** in Scheme 2). A reliable

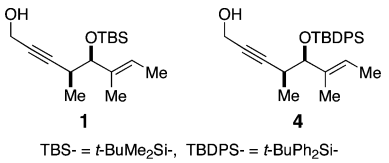


Figure 1. Free-radical hydrostannation probes **1** and **4**.

(1) For part 1, see: (a) Dimopoulos, P.; Athlan, A.; George, J.; Manaviazar, S.; Walters, M.; Lazarides, L.; Aliev, A. E.; Hale, K. J. *Org. Lett.* **2005**, *7*, 5369. For part 2, see: (b) Dimopoulos, P.; Athlan, A.; Manaviazar, S.; Hale, K. J. *Org. Lett.* **2005**, *7*, 5373.

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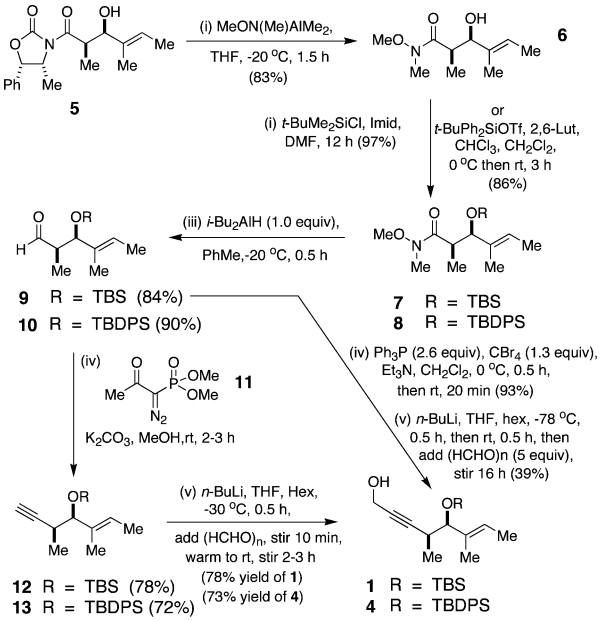
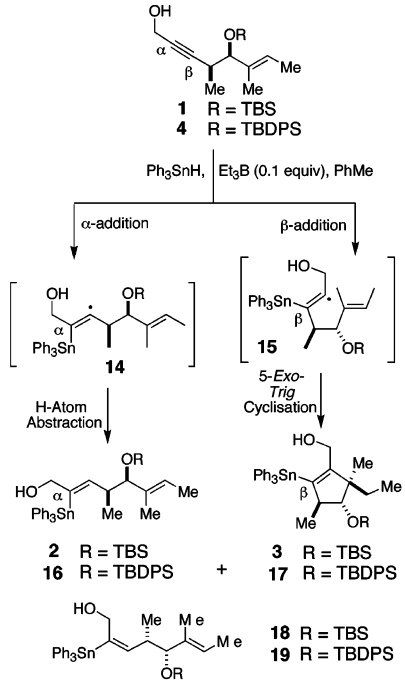
Scheme 1. Routes Used To Access Probes **1** and **4**



Scheme 2. Concentration Effects in the Free Radical Hydrostannation of **1** and **4** with Ph_3SnH and Catalytic Et_3B



Entry	Alkynol	*c* in PhMe	Ph_3SnH	Time	Products	Ratio[a]	% Yield
1	**1**	0.1 M	1.5 equiv	16 h	**2**:**3**	3.5:1[b,d]	67
2	**1**	0.1 M	4.0 equiv	5.5 h	**2**:**3**	4.5:1[b,d]	79
3	**1**	1.0 M	6.0 equiv	5.5 h	**2**:**3**	11.1:1[b,d]	78
4	**1**	0.01 M	3.0 equiv	24 h	**2**:**3**	1:1.7[b,d]	56
5	**4**	0.1 M	1.5 equiv	4 h	**16**:**17**	3.7:1[c,d]	66

a Ratio determined by 500 MHz ^{1}H NMR spectroscopy on the crude reaction mixture in $CDCl_3$.
b A very small amount of **18** appeared to be present in the crude mixture but was difficult to quantify.
c A very small amount of **19** appeared to be present in the crude mixture but was difficult to quantify.
d Products **18** and **19** have only had their structures tentatively assigned.

estimate of the amounts of cyclization vs hydrostannation products that were being generated from **1** and **4** at different stannane and substrate concentrations might potentially clarify the role of the propargylic *O*-atom in the *O*-directed free radical hydrostannation mechanism, and simultaneously give important new insights into the operational workings of these reactions.

A detailed study of **1** and **4** might also allow experimental conditions to be defined for performing the *O*-directed hydrostannation process on propargyloxy substrates with a substituted 3-butenyl grouping, *without* the occurrence of 5-*exo*-*trig* cyclization. The ability to control the hydrostannation outcome in such systems would not only enhance the overall utility of this reaction in organic synthesis, it would also potentially allow it to be used in the total synthesis of molecules such as allopumiliotoxin 334A,[3] A83586C,[4] stipiamide,[5] and halichomycin.[6]

With these considerations in mind, we synthesized the probe molecules **1** and **4** from the known aldol adduct **5**[7] by the routes shown in Scheme 1 (see the Supporting Information for further details and literature references). Initially, we subjected the propargylic alcohols **1** and **4** to our standard free radical hydrostannation conditions (i.e., 1.5 equiv of Ph_3SnH/0.1 equiv of Et_3B, and PhMe [*c* of **1** and **4** = 0.1 M] at rt for 16 and 4 h, respectively). In the case of **1** (Scheme 2, entry 1), compounds **2**/**3** were obtained in 67% yield and 3.5:1 ratio, alongside a tiny amount of **18**. For alkynol **4** (Scheme 2, entry 5), a comparable ratio of the products **16**/**17** (3.7:1) was obtained in almost identical yield (66%) alongside a trace amount of **19**. Similar results (4.5:1 of **2**:**3**) were observed when **1** was reacted with 4 equiv of Ph_3SnH and 0.1 equiv of Et_3B in PhMe (*c* of **1** = 0.1 M) for 5.5 h at rt (entry 2).

Importantly, however, when **1** was subjected to free-radical hydrostannation under much more concentrated conditions (i.e., 6 equiv of Ph_3SnH and 0.1 equiv of Et_3B in PhMe (*c* of **1** = 1 M) at rt for 5.5 h), the ratio of **2**/**3** changed substantially to 11.1:1 (entry 3). *Significantly, the method had now become preparatively useful for the synthesis of reasonably pure* α*-triphenylstannyl alkenes with a substituted 3-butenyl grouping*.

By way of contrast, when the same hydrostannation was performed under fairly dilute conditions, (i.e., 3 equiv of Ph_3SnH/0.1 equiv of Et_3B in PhMe [*c* of **1** in PhMe = 0.01 M] at rt for 24 h) a 1.7:1:0.6 ratio of **3**/**2**/**1** was obtained (Scheme 2, entry 4). Interestingly, compound **3** was now the predominant reaction product.

Given that high stannane concentrations markedly favored addition of the Ph_3Sn radical to the α-acetylenic carbon of

(2) Padwa, A.; Rashatasakhon, P.; Daut Ozdemir, A.; Willis, J. *J. Org. Chem.* **2005**, 70, 519.
(3) (a) For recent synthetic work and references on the pumiliotoxins see: Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* **2000**, *122*, 6950. (b) See also: Franklin, A.; Overman, L. E. *Chem Rev.* **1996**, *96*, 505.
(4) For our asymmetric total synthesis of the antitumor antibiotic A83586C, see: Hale, K. J.; Cai, J. *Chem. Commun.* **1997**, 2913.
(5) Stipiamide total synthesis: Andrus, M. B.; Lepore, S. D.; Turner, T. M., *J. Am. Chem. Soc.* **1997**, *119*, 12159.
(6) Halichomycin synthetic studies: Hale, K. J.; Dimopoulos, P.; Cheung, M. L. F.; Steed, J. W.; Levett, P. *Org. Lett.* **2002**, *4*, 897.

1, while low stannane concentrations marginally favored attack on the more electron-rich β-acetylenic carbon, this strongly pointed to high stannane concentrations *promoting* coordination between the stannane and the α-directing propargyl *O*-atom.

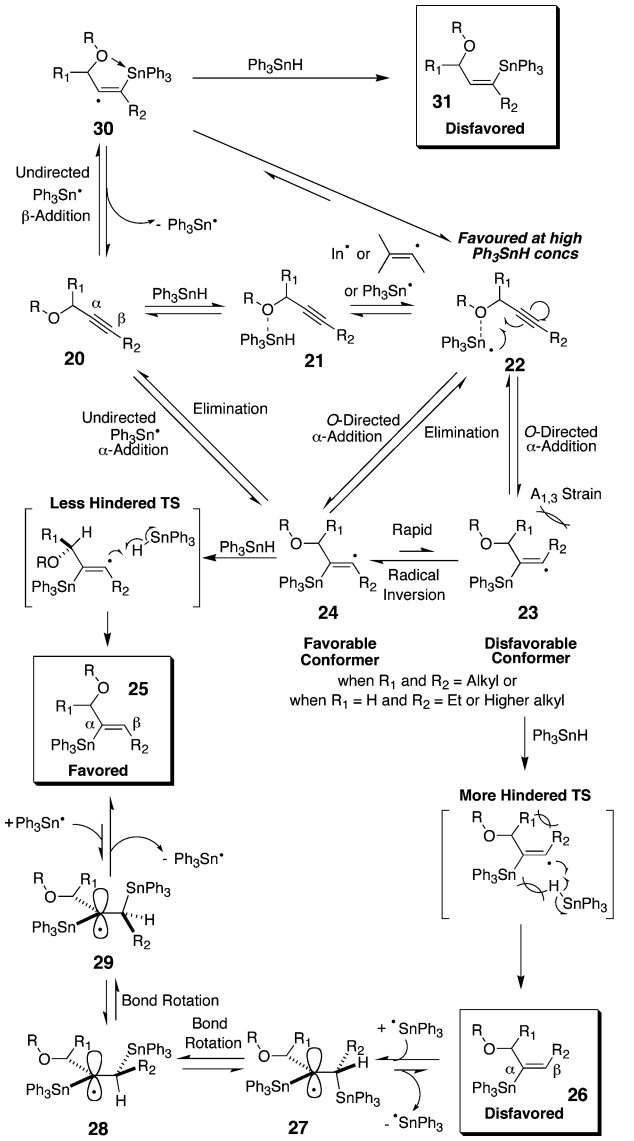
Since, under the "standard" hydrostannation conditions, most propargylically oxygenated alkyl acetylenes generally react with much higher levels of α/β regioselectivity than do **1** and **4** (see Scheme 2, entries 1 and 5), this naturally raised questions as to why these two alkynes should appear to deviate so markedly. It is our belief that alkynes **1** and **4** *do not* behave differently from other propargylically oxygenated alkyl acetylenes, with respect to the regiochemistry of $Ph_3Sn^{\bullet}$ addition, under the standard conditions. Rather, we contend that α- and β-triphenylstannylvinyl radical intermediates have a very significant tendency to rapidly dissociate back into either the starting alkyne and the Ph_3Sn radical, or an *O*-complexed Ph_3Sn radical (see intermediate **22** in Scheme 3), and that an extremely complex and reversible equilibrium[8,9] is operational at many stages of these reactions which, ultimately, favors accumulation of the *O*-directed α-triphenylstannyl alkene products.

In the case of **1** and **4**, because the 5-*exo*-*trig* vinyl radical cyclization of **15** (R = TBS or TBDPS) is quite facile (Scheme 2), it is possible to detect and intercept this set of fairly short-lived, and rapidly inverting, regioisomeric β-triphenylstannylvinyl radicals, before they can fully revert. The reporter molecules **1** and **4** thus enabled us to confirm that Ph_3Sn radicals are almost certainly adding to *both* acetylenic carbons of most propargylically oxygenated alkylacetylenes, under the standard experimental conditions we use, but with a distinct preference for the α-carbon.

While it is possible to invoke that a reversible *O*-directed equilibrium, between propargyloxystannyl radicals and intermediary vinyl radicals, is solely responsible for the excellent ratios of α/β-triphenylstannylalkene regioisomers that are observed in most reactions, we believe that such a mechanistic picture would not only be highly simplistic, it would also be rather illusory. Past work by Utimoto and Oshima[8] has demonstrated that a significantly enriched 9:1 mixture of (*Z*):(*E*)-1-triphenylstannyl-1-octene isomers can be readily converted into a 4:1 (*E*):(*Z*) mixture by the action of 0.2 equiv of Ph_3SnH and 0.1 equiv of Et_3B in hexane at rt for 12 h. Their results,[8] and those of others,[10] thus indicate that vinylstannane isomerization is almost certainly occurring in most (if not all) alkyne free-radical hydrostannation reactions.

In light of this combined data, we have now put forward a mechanistic scheme (Scheme 3) for the *O*-directed free-radical hydrostannation reaction of propargyloxy alkyl acetylenes with Ph_3SnH, which summarizes the main factors

Scheme 3. Some of the Mechanistic Processes Operating in the *O*-Directed Free-Radical Hydrostannation Mechanism



that we believe are contributing to the excellent levels of regio- and stereocontrol that are typically observed. In our newly proposed scheme, the combination of moderately enhanced Lewis acidity and greatly magnified steric effects in the stannane, as well as multiple reversible additions and eliminations of the complexed and uncomplexed triphenylstannyl radical, are all suggested to contribute to the final successful hydrostannation outcome.

We postulate that, under the "standard" hydrostannation conditions, complexation of the stannane is significant, and that *H-atom abstraction occurs more readily from the stannane of complex **21** than from Ph_3SnH itself.*[11,12] We also contend that **22** preferentially delivers its *O*-coordinated Ph_3Sn radical to the α-alkyne carbon to give a mixture of rapidly interconverting α-triphenylstannylvinyl radicals **23** and **24**, in which the preferred and more populated radical conformer is **24** due to adverse allylic ($A_{1,3}$) strain effects destabilizing **23**. Although one can easily imagine that **24** will benefit from

(7) Hale, K. J.; Bhatia, G. S.; Peak, S. A.; Manaviazar, S. *Tetrahedron Lett.* **1993**, *34*, 5343.
(8) Taniguchi, M.; Nozaki, K.; Miura, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 349.
(9) Marco-Contelles, J.; Mainetti, E.; Fensterbank, L.; Malacria, M. *Eur. J. Org. Chem.* **2003**, 1759.
(10) Leusink, A. J.; Budding, H. A.; Drenth, W. *J. Organomet. Chem.* **1968**, *11*, 541.

a hyperconjugative interaction between the sp^2 σ-radical and the back lobe of the C−Sn σ-bond, recent ab initio calculations on comparable β-silyl substituted vinyl radicals suggest that β-silyl hyperconjugative stabilization is negligible in such systems.[13] By analogy, therefore, it is probably correct to assume that hyperconjugative stabilization of **24** will also be minimal. It is now proposed that the exceedingly bulky Ph_3SnH preferentially donates its H-atom to the vinyl radical conformer **24** rather than **23**, since this will lead to a far less sterically crowded transition state than the alternative; this would, of course, preferentially deliver vinylstannane **25**.

It is further proposed that the majority of **26** that is formed will have a very strong tendency to be converted into **25** by the reversible addition of Ph_3Sn radicals to the β-olefinic carbon of **26**.[14] In this regard, molecular models of the transition state for β-addition suggest that it will be far less sterically crowded than that for α-addition; the β-addition pathway would also produce a much less sterically encumbered tertiary radical **27** that would be doubly stabilized by the α- and β-stannyl groups. By way of contrast, stannyl radical addition to the α-carbon of **26** would lead to a much more severely crowded transition state, and afford a less stable (but, nevertheless, hyperconjugatively stabilized) secondary carbon radical. Once generated, radical **27** has the choice of either dissociating back into **26** or undergoing immediate C−C bond rotation to place the two bulky Ph_3Sn substituents as far apart as possible, as in radical rotamer **28**; further bond rotation in the direction of rotamer **29** would then allow the β-C−Sn bond to hyperconjugatively stabilize the adjacent radical center. Elimination at this stage would produce **25** and place the R group *cis* to the α-Ph_3Sn group. In our view, this mechanistic picture most satisfactorily explains all of the observations made so far on this remarkable reaction.

At this juncture, we would now like to change direction and comment on the reason why allylically oxygenated α-triphenylstannylalkenes react successfully with I_2, while allylically oxygenated (*Z*)-β-triphenylstannylalkenes do not. To gain some insights into this behavior, we examined the X-ray crystal structures of **32**−**36** (see the Supporting Information). The five studies gave rise to 10 independent determinations of geometry at the four-coordinate Sn atoms.

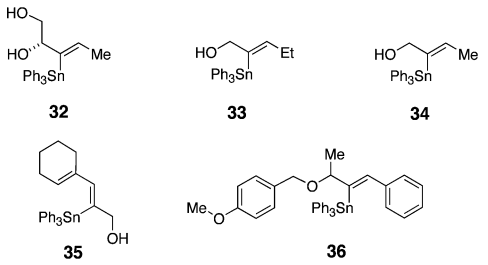


Figure 2. Vinylstannanes **32**−**36**.

The angles subtended at the metal fell within the range 101.75° to 125.27°, with both extremes being found within the crystal structure of **32**. The nonbonded Sn···O distances generally fell within a relatively narrow range (3.09−3.44 Å). The only two exceptions were the structures for **33** and **34**, where one molecule in the asymmetric unit had a "normal" short contact, while the second independent molecule adopted a different conformation with a much greater Sn···O separation (4.41 Å). Although most of these distances are less than the sum of the van der Waals radii of tin and oxygen (3.57 Å) they are much greater than a typical Sn−O covalent bond distance (2.20−2.25 Å). Since there are no significant distortions to the tetrahedral geometry of Sn, we have concluded that, in the solid at least, there is no evidence for valence expansion at the metal nor for a consequential selective weakening of any of the aryl C−Sn bonds within compounds **32**−**36**. This behavior contrasts with (*Z*)-disubstituted β-triarylstannylated allyl alcohols where the central Sn atom is always distorted trigonal bipyramidal with the apical aryl C−Sn bonds being significantly weakened and more readily cleaved by I_2. The lack of internal Sn···O coordination in allylically oxygenated α-triphenylstannylalkenes means that they behave like normal vinyltrialkylstannanes with respect to the metal−halogen exchange reaction; in other words, they are converted to vinyl iodides with retention of olefin geometry.

In closing, we believe that the mechanistic and structural insights that we have provided will aid chemists wishing to apply our methodology soon.

Acknowledgment. We thank the EPSRC (Project Grants GR/N20959/01 and GR/S27733/01), the University of London Central Research Fund, Novartis (Basel/USA), Merck (Harlow), and Pfizer (Sandwich) for their generous financial support and Profs. B.P. Roberts and A.G. Davies, FRS, of UCL for helpful discussions.

Supporting Information Available: Full experimental procedures and detailed spectral data, 500 MHz ^1H and 125 MHz ^{13}C spectra, and HRMS spectra for all new compounds are provided, along with X-ray crystallographic data and product ratio determinations in the hydrostannation reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The significantly enhanced reactivity of trigonal bipyramidal, heteroatom-complexed, tin hydrides towards Sn−H homolysis has already been documented in the literature for the organostannatrane hydride, $Me_2N(CH_2)_3(Me)_2SnH$. The latter stannane does not even require any external initiator to be added for it to mediate its free-radical reduction of 3-iodobenzoic acid to benzoic acid in H_2O at rt. For more details, see: Han, X.; Hartmann, G. A.; Brazzale, A.; Gaston, R. D. *Tetrahedron Lett*. **2001**, *42*, 5837.

(12) In light of this, one would expect that complexation of Ph_3SnH with the propargylic *O*-atom of **20** would likewise cause a significant elongation and weakening of the Sn−H bond in the resulting complex **21**; this would clearly facilitate H-atom abstraction from its stannyl component as is being proposed. It is also very reasonable to assume that *O*-coordinated triphenyltin radicals such as **22** will have extra longevity than uncoordinated Ph_3Sn radicals due to magnified steric hindrance around the radical center; again, this should favor the α-mode of addition.

(13) Lalitha, S.; Chandrasekhar, J. *Proc. Indian Acad. Sci. (Chem. Sci.)* **1994**, *106*, 259.

(14) This isomerization will be especially favorable when R_1 and R_2 are both alkyl groups due to significant $A_{1,3}$ strain being present within **26**.