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O-Directed Free-Radical Hydrostannations of Propargyl Ethers, Acetals, and Alcohols with Ph_3SnH and Et_3B

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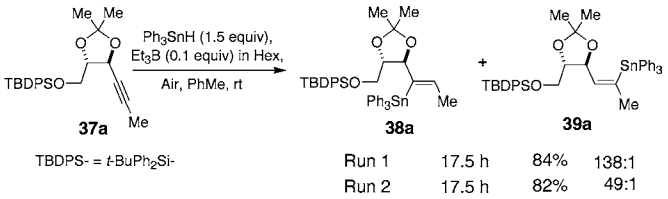
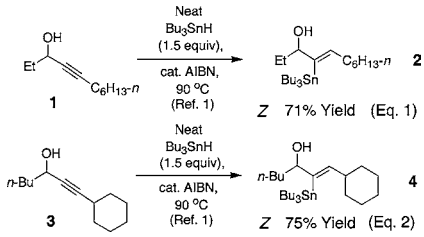
ABSTRACT



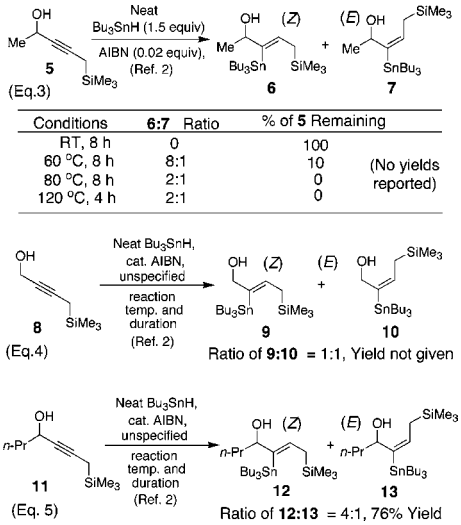
The *O*-directed hydrostannation of various propargyloxy substrates is reported with Ph_3SnH/Et_3B.

Although disubstituted alkyl propargyl alcohols are reported to undergo highly regio- and stereoselective, *O*-directed, free-radical hydrostannation reactions[1−4] with 0.36−1.5 equiv of *neat* Bu_3SnH and cat. AIBN (2,2′-azobisisobutyronitrile) at temperatures of 60−120 °C (see eqs 1 and 2[1]), there are



many substrates that perform poorly under these conditions (see, for example, eqs 3−5).[1−3]

The frequently encountered variability and/or poor practicality of much of the currently available technology[1−7] for the *O*-directed free-radical hydrostannation of substituted



alkynes recently prompted us to search for milder and more effective alternatives. After giving the problem some con-

(1) Konoike, T.; Araki, Y. *Tetrahedron Lett.* **1992**, *33*, 5093.
(2) Nativi, C.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 820.
(3) Ensley, H. E.; Buescher, R. R.; Lee, K. *J. Org. Chem.* **1982**, *47*, 404.
(4) (a) Benechie, M.; Skrydstrup, T.; Khuong-Huu, F. *Tetrahedron Lett.* **1991**, *32*, 7535. (b) Addi, K.; Skrydstrup, T.; Benechie, M.; Khuong-Huu, F. *Tetrahedron Lett.* **1993**, *34*, 6407. (c) Lautens, M.; Huboux, A. H. *Tetrahedron Lett.* **1990**, *31*, 3105. (d) Betzer, J.-F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997**, *62*, 7768.

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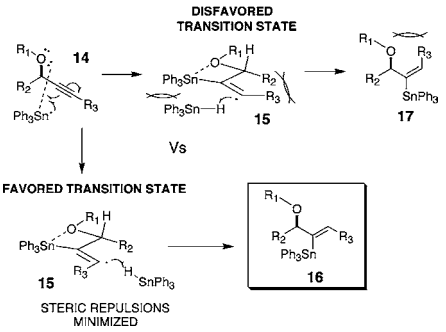
Scheme 1. Transition-State Considerations That Guided Development of the *O*-Directed Free-Radical Hydrostannation of Disubstituted Alkyl Acetylenes with Ph_3SnH/Et_3B

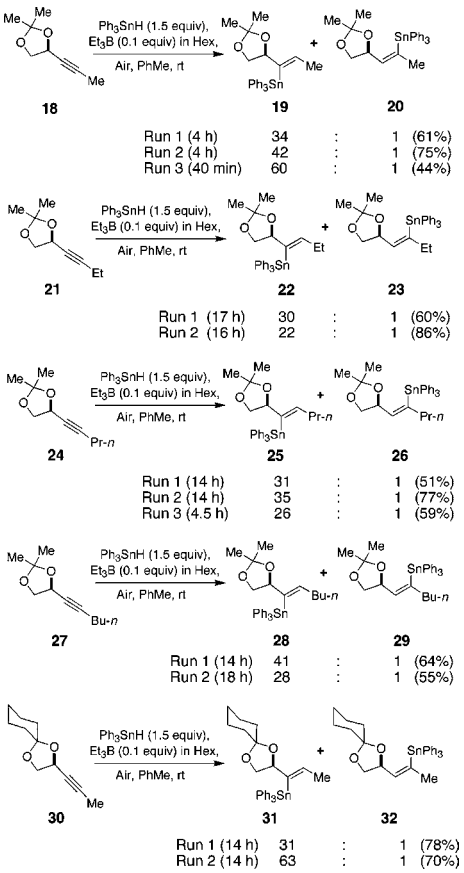


siderable thought, we eventually decided to examine the utility of Ph_3SnH and cat. Et_3B in PhMe at rt for this purpose, based on the following considerations.

Because the central tin atom in Ph_3SnH is connected to three electron-withdrawing phenyl groups, we believed that it would have enhanced Lewis acidity compared with Bu_3SnH and that it would therefore coordinate to the *O*-atom of propargylically oxygenated alkyl acetylenes much more effectively than the latter. We also believed that *O*-coordinated Ph_3SnH would more readily undergo H-atom abstraction than uncoordinated Ph_3SnH and that *O*-coordinated triphenylstannyl radicals would have a longer lifetime in solution compared with their uncoordinated counterparts, due to the Sn atom of the former species being significantly more hindered. We reasoned that by creating a much longer-lived *O*-coordinated tin-centered radical, we might potentially improve the prospects for delivering the tin unit to the α-acetylenic carbon of **14**. We further postulated that if Ph_3SnH was employed for hydrostannation (as opposed to Bu_3SnH), greatly magnified steric repulsive effects would operate in the vinyl radical H-atom abstraction step, owing to the bent nature of alkylvinyl radicals **15**[8] and the likelihood that such radicals would abstract hydrogen from the stannane via a transition state that would minimize steric repulsions between the bulky Ph_3Sn group of **15** and the incoming stannane, while simultaneously avoiding $A^{1,3}$ strain (Scheme 1). All told, we predicted that the transition state that would lead to **16** would be considerably more favored with Ph_3SnH than the corresponding one with Bu_3SnH, and as consequence, we postulated that higher regio- and stereoselectivity would result with the former stannane.

With this picture of the situation in mind, we applied the Ph_3SnH/cat. Et_3B hydrostannation process[9] to a wide range of alkylacetylene substrates **14** and now report a convenient

Scheme 2 *O*-Directed Free-Radical Hydrostannation of Alkyl Acetylenes Bearing a Terminal Propargyl 1,3-Dioxolane[a]



[a] N.B.: minor isomer structures are only assigned tentatively.

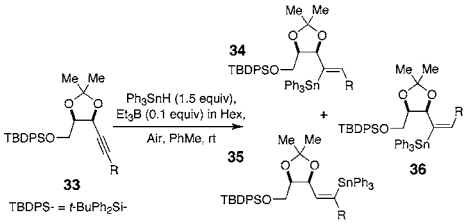
and highly reliable protocol for obtaining vinylstannanes of general structure **16** with excellent levels of regio- and stereocontrol, in good yield (Scheme 1). Our preferred procedure utilizes 1.5 equiv of commercially available Ph_3SnH and 0.1 equiv of Et_3B in PhMe at rt[9] and conducts the hydrostannation for anywhere between 3 and 72 h at 0.1 M concentration with respect to the starting disubstituted alkyne.

Initially, we examined the acetylenes **18**, **21**, **24**, **27**, and **30** (Scheme 2) in the Ph_3SnH/cat. Et_3B rt process. In every case, the anticipated vinylstannanes **19**, **22**, **25**, **28,** and **31** all emerged with selectivities that exceeded 22:1 (Scheme 2) and yields that ranged between 51 and 86%. The modest yields encountered in some runs are merely a reflection of the difficulties sometimes encountered in separating certain of these products from hexaphenylditin by SiO_2 flash chromatography. In all cases, the hydrostannation reactions were themselves very clean according to TLC analysis, and the starting alkyne was always fully consumed (Scheme 2).

In view of these successes, we decided to examine the scope and utility of our *O*-directed hydrostannation process in other propargylically oxygenated disubstituted alkyne systems where there was additional substitution *β*- to the acetylenic carbon (Scheme 3). In the *cis*-1,3-dioxolane systems that we studied (**33a**, **33b**, and **33c**), a net *anti*-addition of the stannane occurred to the alkylacetylene, with

(5) Liron, F.; Le Garrec, P.; Alami, M. *Synlett* **1999**, 246.
(6) Keck, G. E.; Wager, T. T.; Rodriguez, J. F. D. *J. Am. Chem. Soc.* **1999**, *121*, 5176.
(7) Dodero, V. I.; Koll. L. C.; Mandolesi, S. D.; Podesta, J. C. *J. Organomet. Chem.* **2002**, *650*, 173.
(8) The ESR data that is available on *simple* α-alkylvinyl radicals suggests that they adopt a rapidly equilibrating sp^2 bent structure. See, for example: (a) Rubin, H.; Fischer, H. *Helv. Chim. Acta* **1996**, *79*, 1670. (b) Fessenden, R. W. *J. Chem. Phys.* **1967**, *71*, 74.
(9) Nozaki, K.; Oshima, K.; Utimoto, K. *Tetrahedron* **1989**, *45*, 923.

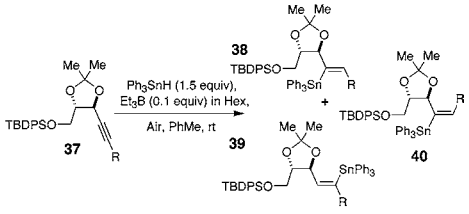
Scheme 3. Substituted Acetylene Substrates Bearing a Substituted Propargyl 1,3-Dioxolane[a]



Alkyne	Run	Time	% Yield	34:35
33a R = Me	Run 1	18 h	67%	ca. 53:1
	Run 2	16 h	88%	72:1
33b R = Et	Run 1	18 h	75%	26:1
	Run 2	18 h	77%	>16:1
33c R = *n*-Pr	Run 1	18 h	86%	41:1
	Run 2	18 h	72%	29:1

Alkyne	Run	Time	% Yield	34d:36
33d R = Ph	Run 1	3 h	88%	75:1
	Run 2	18 h	73%	60:1
	Run 3	18 h	68%	146:1

N.B. Minor isomer structures are only assigned tentatively.



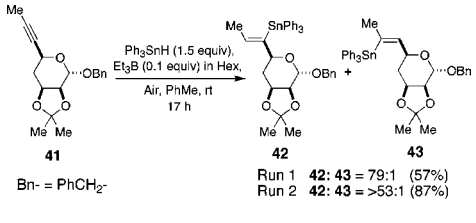
Alkyne	Run	Time	% Yield	38a:39a
37a R = Me	Run 1	17.5 h	84%	138:1
	Run 2	17.5 h	80%	49:1

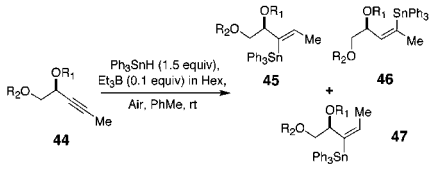
Alkyne	Run	Time	% Yield	38b:40
37b R = Ph	Run 1	16 h	72%	16:1
	Run 2	190 min	73%	>128:1

N.B. Minor isomer structures are only assigned tentatively.

[a] N.B.: minor isomer structures are only assigned tentatively.

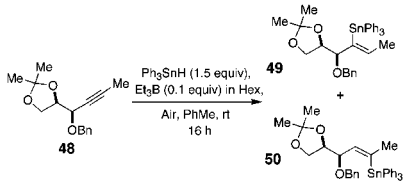
Scheme 4. Alkyl Acetylene Substrates with Pyranosidic Propargyloxy and Propargylic Ether Protecting Groups[a]





Alkyne	Time	% Yield	Products	Ratio	Run
44a R_1 = R_2 = TBDPS-	16 h	81%	**45a: 47a**	20:1	Run 1
	21 h	78%	**45a: 47a**	25:1	Run 2
44b R_1 = H, R_2 = TBDPS-	3 h	81%	**45b: 46b**	199:1	Run 1
	4 h	75%	**45b: 46b**	48:1	Run 2
44c R_1 = R_2 = H	18 h	45%	**45c: 46c**	103:1	Run 1
	18 h	69%	**45c: 46c**	73:1	Run 2

TBDPS = *t*-BuPh$_2$Si-



[a] N.B.: minor isomer structures are only assigned tentatively.

excellent levels of stereocontrol typically manifesting themselves. For the phenylacetylene **33d** even better results were obtained; in this instance, α-regiocontrol was total and stereoselectivity was again very high (>60:1). Alkyne **37a**, which had a *trans*-1,3-dioxolane ring positioned directly adjacent to the two alkyne carbons, also reacted to give the expected addition product **38a** as the primary reaction product; it was formed alongside **39a** in 80−84% yield and with >49:1 selectivity. The arylacetylenic acetal **37b** was also an excellent substrate for this reaction, it reacted in good yield and with high stereoselectivity.

Notwithstanding us having obtained some impressive results with a significant number of propargylically oxygenated arylacetylenes, we must emphasize that such substrates generally do not work as well as their alkyl acetylene counterparts in the *O*-directed Ph_3SnH/cat. Et_3B hydrostannation process.[10] Our work on aryl and heteroarylpropargyloxy substrates will be discussed in a more detailed full paper that will be written up shortly.

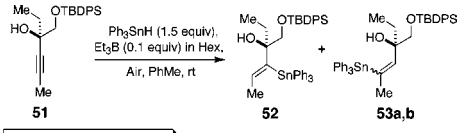
In an effort to gauge whether a pyranosidic propargylic-*O* could exert a substantial directing effect in this reaction, we subjected pyranoside **41** to our standard rt conditions (Scheme 4). To our great delight, the anticipated reaction product **42** predominated in the mixture of vinylstannanes that resulted; the latter was isolated in 57−87% yield and with >53:1 selectivity.

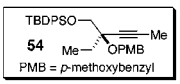
A particularly pleasing outcome was obtained when the di-*O*-TBDPS ether **44a** was hydrostannylated. It reacted efficiently under the standard rt conditions (Scheme 4), with all of the starting alkyne generally being consumed within 16−21 h, and the expected vinylstannane **45a** predominating in the *E*:*Z* mixture of alkenes that formed. Together, this mixture was isolated in 78−81% yield with a selectivity level that exceeded 20:1.

The observation that a bulky propargylic OTBDPS group could effectively direct the course of a free radical hydrostannation with Ph_3SnH under these very mild conditions is highly noteworthy and beautifully illustrates the enormous scope and potential of the Ph_3SnH/cat. Et_3B rt protocol for the hydrostannylation of oxygenated alkyl propargyl systems. Presumably, the long Si−O bond pushes the bulky silyl group away from the acetylenic α-carbon, allowing the propargyl *O*-atom to still efficiently direct the regio- and stereochemical course of the hydrostannation process.

(10) ESR investigations on α-styryl radicals suggest that they adopt an sp linear structure. See: ref 8a and the following earlier references: (a) Panek, E. J.; Kaiser, L. R.; Whitesides, G. M. *J. Am. Chem. Soc.* **1977**, *99*, 3708. (b) Neilson, G. W.; Symons, M. C. R. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1405. This difference in vinyl radical structure may go some way to explaining the poorer stereochemical outcome in certain instances with arylacetylene substrates.

Scheme 5. Tertiary Acetylenic Alcohol and Ether Substrates[a]





Run 1 19 h **52: 53** = 32:1 (30%)
Run 2 67 h **52: 53** = 19:1 (45%)

TBDPS = *t*-BuPh$_2$Si-

N.B. Minor isomer structures are only assigned tentatively

As one might expect, the much less sterically encumbered propargylic-*O* in **44b** gave even higher levels of stereo- and regiocontrol in this process (48−199:1 selectivity). Significantly, the corresponding 1,2-diol **44c** only hydrostannylated slowly, possibly due to the Ph_3SnH tightly chelating with the terminal 1,2-diol grouping. Although, this reaction proceeded very cleanly, starting alkyne did always remain after 18 h, on the two occasions it was examined. Notwithstanding **44c** not always being fully consumed, a 45−69% yield of **45c** was nevertheless obtained with >73:1 selectivity.

Other commonly used ether protecting groups that can readily serve as efficient regio- and stereochemical directors include benzyl (Bn) and *p*-methoxybenzyl (PMB) ethers. In this regard, the *O*-benzylated alkyne **48** performed admirably in its orchestration of the desired hydrostannation event, it affording a 44:1 and 59:1 mixture of the two vinylstannanes **49** and **50** (Scheme 4).

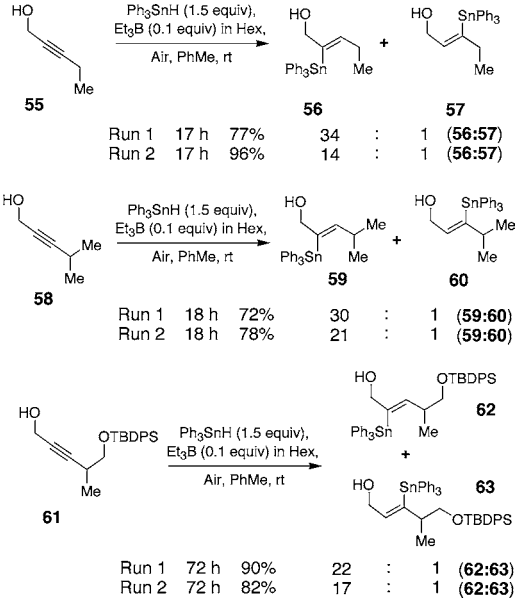
Our experience with tertiary propargyloxy systems has not been especially good; the reactions are typically very hard to drive to completion. Although the tertiary alkynol **51** reacted cleanly under the standard rt conditions to give vinylstannane **52** as the major reaction product (Scheme 5), it could never be isolated in more than 30−45% yield. Alkyne **54** also reacted very slowly but, in this instance, an inseparable mixture of vinylstannanes and starting **54** was obtained in ca. 1:1 ratio.

Other alkylpropargyloxy systems that we have hydrostannylated successfully include **55**, **58**, and **61** (Scheme 6).

With regard to the conversion of alkylpropargyloxy systems such as **14** into alkylvinyltriphenylstannanes **16** (Scheme 1), a general guideline can now be adumbrated. For high stereo- and regiocontrol to be predictably observed in this process, the R_3 group must be either an ethyl or a higher alkyl substituent when R_2 = H. Likewise, if R_3 = Me, the R_2 group must be either an alkyl or an alkyloxy substituent for good results generally to be obtained.

Direct comparison of the rt Bu_3SnH/cat. Et_3B method with its Ph_3SnH/cat. Et_3B counterpart, on several of the alkynes reported herein, has revealed that the Ph_3SnH system is uniformly superior in every respect for effecting the *O*-directed free radical hydrostannation reaction. Not only does the Ph_3SnH/cat. Et_3B partnership more readily convert propargylically oxygenated disubstituted alkynes into vinylstannanes of general structure **16**, it also delivers them with improved stereo- and regiocontrol. In our experience, when the Bu_3SnH/cat. Et_3B system is employed, large excesses of reagent and prolonged heating are often necessary to get a satisfactory hydrostannation rate, conversion, and yield, and such conditions typically erode the levels of stereo- and regiocontrol one finally attains.

Scheme 6. Primary Propargylic Alcohol Alkyl Acetylene Substrates in the Ph_3SnH/Et_3B Room-Temperature Hydrostannation Process[a]



[a] N.B.: minor isomer structures are only assigned tentatively.

It is our belief that Ph_3SnH and cat. Et_3B in PhMe at rt currently represents the best and most convenient reagent combine available for effecting the highly regio- and stereocontrolled *O*-directed hydrostannation of propargylically oxygenated alkyl acetylene substrates under free radical conditions. Although a significant number of arylpropargyloxy systems have also proven good substrates for the Ph_3SnH/cat. Et_3B process, our cumulative data on this class has revealed that they can on occasion give a less certain outcome.

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Supporting Information Available: Full experimental procedures and detailed spectral data, a range of 500 MHz ^{1}H and 125 MHz ^{13}C spectra, and IR and HRMS spectra for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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