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Synthetic Methods

2,2′-Azobis(2-methylpropionitrile)-Mediated Alkyne Hydrostannylation: Reaction Mechanism**

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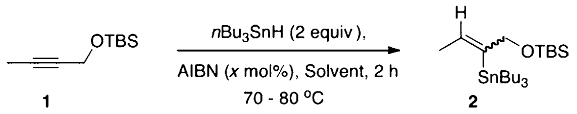
The hydrostannylation of alkynes to produce vinylstannanes of high regio- and stereochemical fidelity is a process of high importance in synthetic chemistry.[1,2] Consequently, the mechanism of free-radical-mediated hydrostannylation has been intensively studied since it was first reported in 1968 by Leusink.[1] All proposed hypotheses include one common feature: the process involves radical intermediates exclusively.[3] On the surface, this is reasonable because the reaction is initiated by rather 2,2′-azobis(2-methylpropionitrile) (AIBN) or Et_3B, both of which are well-established radical initiators.[2,3] Unfortunately, this underlying central belief, upon which all understanding is built for this important transformation, appears not to be correct.

It is known that molecular oxygen (O_2) initiates autoxidation with Et_3B to liberate the radicals which are necessary to facilitate tin radical formation, and then enter chain propagation.[2–4] What has not been known until now is that O_2 is also necessary for the same transformation when AIBN is used as the radical initiator (see below). That reactions with Et_3B are run in air by necessity to commence the radical chain (through autoxidation of Et_3B) has masked the need for O_2 in alkyne hydrostannylation beyond initiation.[2–4] In the case of AIBN-promoted transformations, it would have been reasonable to assume that the standard Schlenk technique employed when running these reactions would eliminate all air, and again would deflect mechanistic consideration away from any potential role of O_2. However, despite best efforts, it is very difficult to prevent trace amounts of O_2 from getting into reactions when they are conducted outside of a glove box. It was not until we were enticed by results that we could not explain (see below) to question whether O_2 was involved in radical-mediated hydrostannylation. When rigorously O_2-free conditions are used with AIBN, the reaction fails to proceed, whereas the addition of even trace O_2 back into these same reactions drives hydrostannylation to completion. Herein, we propose a new mechanism for the hydrostannylation of alkynes, in particular synthetically useful propargylic alcohols and their derivatives, and it includes the crucial role of O_2. In doing so we have shed new light on the profound regio- and stereoselectivity demonstrated in this central hydrometallation protocol.

Recently, we reported that polar solvents accelerate Et_3B-mediated hydrostannylation of propargylic alcohols and their derivatives.[4d] When we varied the solvent using AIBN as the mediator, the reaction proceeded to 100% conversion in THF, 1,4-dioxane, NMP, and DMPU, while poorer conversion were obtained in benzene and toluene, which are commonly used solvents for hydrostannylation (Table 1). These results cast doubt on mechanisms proposing that AIBN- and Et_3B-mediated alkyne hydrostannylation involves solely radical intermediates. We considered two main possibilities to rationalize the polar solvent effect seen with these radical-involved processes. These hydrostannylations could involve cationic intermediates whose formation would be favored by polar solvents, or molecular oxygen (O_2) is involved and it miscibility or diffusion is promoted in solvents of increasing polarity.[5]

Table 1: Solvent effect on AIBN-mediated hydrostannylation of **1**.



Entry	Solvent	AIBN (mol%)	**2** Conv. [%][a]
1	benzene	2.5	100
2	benzene	0.5	40
3	toluene	0.5	50
4	THF	0.5	100
5	1,4-dioxane	0.5	100
6	NMP	0.5	100
7	DMPU	0.5	100

[a] Percent conversion was determined by ^1H NMR spectroscopy of the crude reaction mixture. DMPU = 1,3-dimethyltetrahydro-2-pyrimidone, NMP = *N*-methyl-2-pyrrolidone.

To probe any possible effect of O_2 on AIBN-mediated hydrostannylation, the alkyne **1** (made fresh) was degassed in previously freeze-pump-thawed solvent then degassed and water-free AIBN was added inside an argon-filled glove box. The O_2-free reaction mixture was heated. Strikingly, the rigorous exclusion of O_2 saw hydrostannylation drop to only 5% conversion with the unreacted starting alkyne accounting for the mass balance (Scheme 1a). The same reaction conducted without degassing any of the reagents proceeded rapidly to give **2** in 100% conversion (see the Supporting

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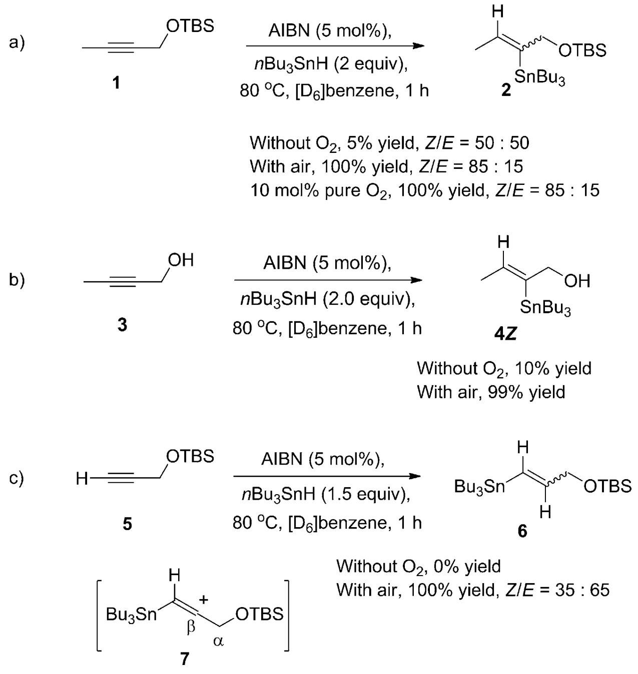
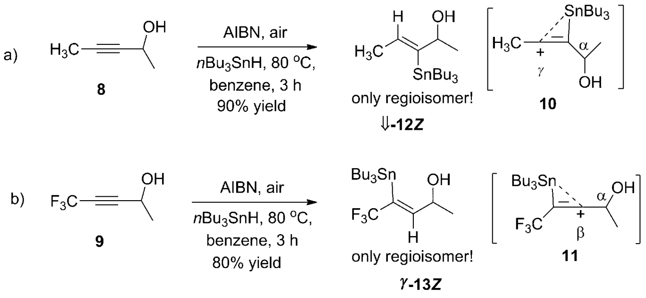


Scheme 1. Molecular oxygen effect on the AIBN-mediated hydrostannylations of **1**, **3**, and **5**.

Information for spectra of crude reaction mixture). To confirm oxygen as the component of air that is responsible for promoting this transformation, we again rigorously excluded all air from one experiment and then carefully added pure O_2 (10 mol % based on the alkyne) to the reaction and it proceeded to completion (Scheme 1 a). These results confirm the necessity of O_2 and implies that only a catalytic amount is needed for hydrostannylation to proceed to completion. Similarly, low conversion (10 %) of the free propargylic alcohol **3** was observed in the absence of O_2, whereas full conversion into **4** occurred in air (Scheme 1 b). Most shockingly, the AIBN-mediated hydrostannylation of the terminal propargylic ether **5** did not proceed at all to **6** in the absence of O_2 (Scheme 1 c).[2,6] To see if this effect is unique to AIBN in alkyne hydrostannylation, the radical mediators *p*-methoxybenzene thiol and *tert*-butylbenzoperoxoate were examined and also found to be similarly O_2 dependent (see the Supporting Information). Further, if the radical initiator is omitted, hydrostannylation does not proceed, hence the generation of a tin radical by the mediators is crucial to the overall addition process, regardless of the role of oxygen.

Following conventional pure radical mechanisms in the literature, few would argue against suggestions that the radical intermediate arising from tin radical addition to a ground-state terminal alkyne would favor terminal placement of the tin moiety for both steric and electronic reasons (i.e., generating a secondary radical as opposed to a primary one).[2,6] However, since the addition only proceeded in the presence of O_2, and was faster in polar solvents, perhaps the rational is in fact not based on steric or radical stability, but on cation stability. In this case, the cation will primarily localize on the β-carbon atom because the α-methylene can better stabilize an adjacent cation than the terminal hydrogen atom (**7**; Scheme 1 c)

If our rationale for the stability of cationic intermediates is operative, then it suggests that the regioselectivity of hydrostannylation can be reversed by changing the electronics of the δ substituent. To explore this concept, we carried out the hydrostannylation of the propargylic alcohols **8** and **9** (Scheme 2). Strikingly, as a mechanism involving cationic intermediates would predict, the regiochemical outcomes of the hydrostannylations of **8** and **9** were fully reversed! While the electron-donating *δ*-CH_3 group can better stabilize an adjacent cation relative to the α-CH_2 group which has an oxygen substituent β to it (see **10**), the electron-withdrawing *δ*-CF_3 group more strongly disfavors adjacent cation formation, thus leading instead to **11**. The three-center nature of the intermediates **10** and **11** originated from our computational assessment of the reaction surface of this transformation, and is discussed in detail (see below).[7] On the basis of the tin radical oxo-coordination hypothesis,[3] which has been used for decades to rationalize regiochemical outcomes in radical-mediated hydrostannylation of internal propargylic alcohols, both reactions in Scheme 2 should have given the same regiochemical outcome, but they did not. Thus, an electronic effect involving cationic intermediates can adequately explain this stark reversed regioselectivity.



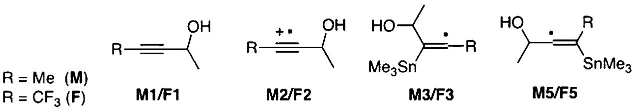
Scheme 2. Reversed regioselectivity in the reaction of **8** and **9**.

The ^{119}Sn NMR spectrum of a 1:1 mixture of $n\mathrm{Bu_3SnH}$ and AIBN in degassed [D$_6$]benzene heated at 80 °C showed the formation of $Bu_3SnSnBu_3$ ($\delta = -79$ ppm) whose formation can only be explained by the presence of $n\mathrm{Bu_3Sn^{\bullet}}$ (see the Supporting Information).[8] Additionally, AIBN-mediated deiodination of alkyl iodide with $n\mathrm{Bu_3SnH}$, ran under identical reaction conditions as the hydrostannylation experiments in this study, proceeded smoothly in the absence of O_2 (see the Supporting Information). Also of note, the hydrostannylation of all the above-mentioned alkynes only proceeded in the presence of O_2 in the dark, thus, excluding any effect of light. Finally, isomerization of the kinetically formed *Z* isomer by $n\mathrm{Bu_3Sn^{\bullet}}$ to the corresponding thermodynamic *E* isomer (e.g., (*Z*)-**2** to (*E*)-**2**) occurs in the absence of O_2 (see the Supporting Information). Taken together, this suggests that oxygen's involvement relates to the alkynes, or their resultant vinyl radical intermediates, and not anything related to the radical initiators.

We reasoned that oxygen's role, which is central in all of this, is most likely as a redox shuttle[9] which can be involved at one of two possible points in the addition process, either before[10] or after tin radical addition. While single-electron transfer (SET) from alkynes to O_2 to form radical cations and superoxide $O_2^{\bullet -}$ is reported in the literature, the process is highly endothermic and only truly practical under metal catalysis.[10] As shown in Table 2, computational studies reveal that it is much more facile to remove an electron from the vinyl radical species **M3**, **M5**, **F3**, and **F5** (e.g, **M3**, 4.79 eV) than from the closed shell alkynes **M1** and **F1** (e.g, **M1**, 8.50 eV) in the gas phase. When the PCM solvation model was included,[11] oxidation is favored significantly in THF (e.g, **M3**, 0.55 eV) over benzene (e.g, **M3**, 2.05 eV), and is consistent with the faster rate which we observe in THF relative to benzene.[4d,12] Thus, while suggested in the literature, alkyne oxidation to the radical cations **M2/F2** is unlikely and rather SET occurs from the vinyl radicals to O_2 to form highly reactive vinyl cations **M4/F4**.

Table 2: DFT energies [eV] required for redox processes.

Redox process	Gas phase	Benzene	THF
$M1+O_2 \rightarrow M2+O_2^{\bullet -}$	8.50	5.61	4.04
$M3+O_2 \rightarrow M4+O_2^{\bullet -}$	4.79	2.05	0.55
$M5+O_2 \rightarrow M4+O_2^{\bullet -}$	4.70	1.96	0.45
$F1+O_2 \rightarrow F2+O_2^{\bullet -}$	9.62	6.61	4.95
$F3+O_2 \rightarrow F4+O_2^{\bullet -}$	5.57	2.81	1.28
$F5+O_2 \rightarrow F4+O_2^{\bullet -}$	5.73	2.98	1.46
$Me_3SnH+O_2^{\bullet -} \rightarrow Me_3SnH^{\bullet -}+O_2$	1.16	2.15	2.65
$Me_3Sn^{+}+O_2^{\bullet -} \rightarrow Me_3Sn^{\bullet}+O_2$	−5.80	−2.74	−1.02



To support the selectivities associated with the reactions and provide new mechanisms, more DFT calculations were performed (free energies, 25 °C, 1 M substrates). First, we examined the currently accepted all-radical mechanism and the potential energy surface depicts the addition of tin radical to the alkyne **M1/F1** (Figure 1) where $R=CH_3$ (**M** surface) or CF_3 (**F** surface). The key feature for regioselectivity is traversing the highest transition state (TS) on going from **M1/F1** to **M6/F6** or **M11/F11**. For $R=CH_3$, **M9** is 3.2 kcal mol^{-1} lower than **M10**, thus leading to the experimentally observed product **M6**. In contarst, for $R=CF_3$ there are two rate-limiting TSs, **F7** and **F8**, which are similar in energy (8.3 and 7.9 kcal mol^{-1}, respectively), thus a mechanism involving only radical intermediates would predict a roughly equal mixture of the two regioisomeric products. It should be noted that calculations including a solvation model were performed on the potential energy surfaces depicted in Figures 1 and 2 but the predicted selectivities were unchanged from the gas phase estimates.[13]

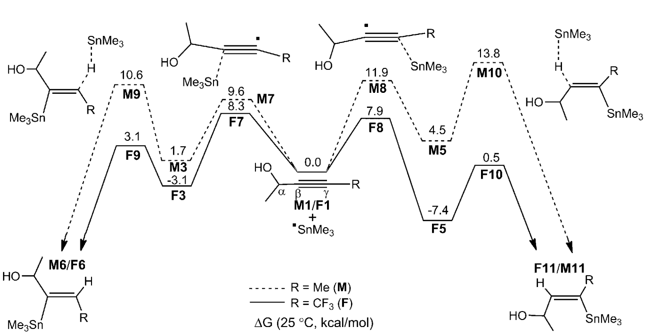


Figure 1. DFT potential energy surface of pure radical mechanism. Free energies (kcal mol^{-1}) are relative to the tin radical and the respective alkynes.

However, where oxidation occurs at the vinyl radical stage, direct tin radical addition to the alkyne **M1/F1** provides a regioisomeric mixture of vinyl radicals. Computationally, one can mimic SET to O_2 from the vinyl radical intermediates by removing an electron and re-optimizing the geometries (Figure 2). Interestingly, **M3** and **M5** both optimize to the same vinyl cation, **M4**, while **F3** and **F5** both form only **F4**. The optimized cationic complexes are three-centred, stabilized species where the tin atom interacts with both a principal alkyne carbon atom and the adjacent carbocation in **M4** and **F4**. Most importantly, the tin atom leans toward different alkyne carbon atoms in the two cases as the Sn–C bond is shorter for the β position (2.65 Å) in the methyl species (**M4**) and the γ position (2.82 Å) for the trifluoromethyl compound (**F4**). The partial charges, + 0.06 at the γ position of **M4** and + 0.08 at the β position of **F4**, reflect this difference and are consistent with the charge distribution shown qualitatively in Scheme 2. A regioselective hydride transfer from Me_3SnH to the reactive cationic **M4** and **F4** will then quantitatively give the kinetic products, **M6** and **F11**, respectively, and Me_3Sn^{+}. The three-center transition-state model also explains why the kinetic product is always the antiaddition product, which would be analogous to alkyne bromination.[14] The hydride delivery transition states reveal that **F13**, which leads to **F11**, is 3.4 kcal mol^{-1} lower in energy than **F12** while **M12**, which leads to **M6**, is 3.7 kcal mol^{-1} lower in energy than **M13**. The hydride-transfer step appears to be both the rate- and selectivity-determining step for this novel mechanism, which is consistent with our kinetic isotope effect data (K_H/K_D) of

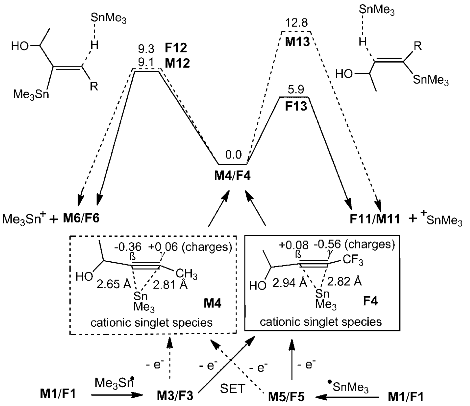


Figure 2. DFT potential energy surface of radical/SET mechanism. Free energies Δ*G* (25 °C, kcal mol^{-1}) are relative to the respective cations (**M4/F4**) and tin hydride.

2.33.[4d] Since a typical Sn-H stretching frequency is approximately 1800 cm^{-1}, it is expected that a primary isotope effect would occur with a smaller K_H/K_D than the breaking of a typical C–H bond. An electron transfer from $O_2^{\bullet-}$ to Me_3Sn^+ will then generate $Me_3Sn^\bullet$ and the O_2 catalyst. The $O_2^{\bullet-}$ reduction of Me_3Sn^+ to $Me_3Sn^\bullet$ was also found to be highly exothermic and favorable (−1.02 eV in THF, Table 2).

The difference in the two processes (pure radical and SET cationic) is now clear. For the methyl alkyne, both processes lead to the experimentally observed regioisomer **M6**. However, for the trifluoromethyl alkyne, the pure radical process predicts a mixture of regioisomers while the cationic process predicts only the observed regioisomer **F11**, and accounts for the role of O_2 as redox shuffle. The correct stereoselectivity is also predicted and the full potential energy surface describing this selectivity is provided in the Supporting Information.

Based on the experimental and computational studies above, the most plausible mechanism of radical-mediated alkyne hydrostannylation is depicted in Figure 3. In this mechanism, the initial tin radical addition to **9** need not be regioselective and will give rise to a regioisomeric mixture of vinyl radicals (**14** and **15**). A SET from both **14** and **15** to O_2 will coalesce to form the same three-centered vinyl cation **11** and $O_2^{\bullet-}$. A regioselective hydride addition from nBu$_3$SnH to the cationic β-carbon atom of **11** will ultimately give the kinetic product γ-**13Z** and nBu$_3$Sn$^+$, which is rapidly reduced by $O_2^{\bullet-}$ to nBu$_3$Sn$^\bullet$, thus completing the catalytic cycle.[15] Deuterium-labeling studies with nBu$_3$SnD unambiguously confirmed the tin reagent as the source of the hydrogen atom in the vinylstannane product (see the Supporting Information).

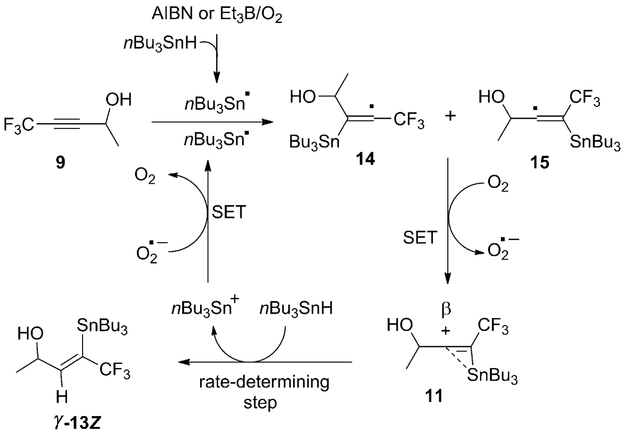
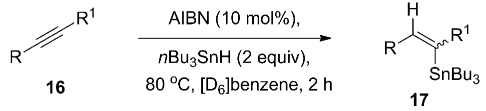


Figure 3. Possible mechanism of radical-mediated hydrostannylation of internal propargylic alcohols and their derivatives by O_2 SET oxidation of vinyl radical.

Finally, to investigate whether the effect of O_2 on AIBN-mediated hydrostannylation was unique to propargylic alcohols, we examined some simple alkyl and aryl alkynes (**16**; Table 3). Interestingly, no hydrostannylated products were observed for both terminal and internal alkynes in the absence of O_2. Remarkably, in all cases excellent conversions to the respective products were obtained in the presence of O_2, thus confirming that this effect is not unique to alkynes flanked by an oxygen-based functional group.

Table 3: Molecular oxygen effect on the AIBN-mediated hydrostannylation of simple alkynes **16**.



Entry	R	R^1	Yield [%][a,b]	
			Without O_2	With Air
1	C_6H_{13}	H	< 5	90 (E/Z = 90:10)
2	C_2H_5	C_2H_5	< 5	95 (Z/E > 99:1)
3	Ph	H	0	100 (E/Z > 99:1)
4	Ph	C_2H_5	0	100 (Z/E > 99:1)

[a] Isomeric ratios were determined by ^{1}H NMR spectroscopy on the crude reaction mixture. [b] A greater than 99:1 means no other isomer detected.

A combination of detailed control experiments and DFT studies has revealed two long-held, but related misconceptions about radical-mediated alkynes hydrostannylation. In the absence of O_2 this transformation does not proceed whereas it completes readily and reproducibly in the presence of O_2 with high regio- and stereoselectivity. The necessity for O_2 indicates that the hydrostannylation does not proceed by a pure radical process, as has been long thought. All experiments, including the polar solvent studies, strongly suggest that cationic intermediates are involved and that O_2 is serving as a redox catalyst in this process.[9,10] The localization of the resulting cationic character on the two sp-carbon atoms, as dictated by the substituent at the δ-carbon atom, plays the key role in controlling the regiochemical outcome of the addition. We have provided a new mechanism involving catalytic O_2 in this hydrostannylation study, and it would hold when employing any radical initiator (e.g., AIBN, Et$_3$B, etc.). The vinyl radical oxidation mechanism accounts for all aspects of selectivity in the addition and presents barriers that are well within reach on the reaction surface. This discovery strongly impacts synthetic and mechanistic chemistry and could cause other well-established molecular-oxygen-free reactions to be reevaluated.

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[13] Solvation data for structures are included in the Supporting Information. With a solvation model, the radical selectivity is unchanged for R = CF_3 (**F7** vs. **F8**) and slightly decreased for R = CH_3 from 3.2 kcal mol^{-1} (gas phase) to 2.8 kcal mol^{-1} (THF) (**M9** vs. **M10**). For the cationic surface, the selectivity systematically favors TS **13**. Thus for R = CF_3, the 3.4 kcal mol^{-1} (gas phase) difference favoring of **F13** has increased to 3.9 kcal mol^{-1} (THF) whereas on the R = CH_3 surface, the 3.7 kcal mol^{-1} selectivity favoring **M12** has been reduced to 2.1 kcal mol^{-1} in THF.

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[15] A SET reduction of tin hydride to tin hydride radical anion, which could generate tin radical upon hydride transfer as shown below, was considered by computational studies and found to be quite endothermic and, as a consequence, unlikely (2.65 eV in THF, Table 2).