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Pronounced Solvent Effect on the Hydrostannylation of Propargylic Alcohol Derivatives with nBu$_3$SnH/Et$_3$B at Room Temperature

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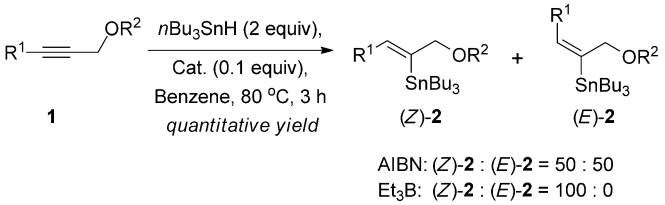
Alkenylstannanes have been used in a wide array of transformations including Stille–Migita cross-coupling, metal–halogen exchange, and transmetallation reactions.[1] One of the most efficacious approaches to alkenylstannanes is the direct hydrometallation of alkynes. Stereo-defined alkenylstannanes have been prepared from both internal and terminal alkynes by using Pd-catalysed [nBu$_3$SnH-Pd^0],[2] Cu-mediated [nBu$_3$Sn(R)CuCNLi$_2$][3], and radical protocols with either AIBN [nBu$_3$SnH-AIBN], or Et$_3$B/O$_2$ [nBu$_3$SnH-Et$_3$B/O$_2$ or Ph$_3$SnH-Et$_3$B/O$_2$] as mediators (AIBN = azobisisobutyronitrile).[4] Of course, of equal merit is the ability to prepare alkenylstannanes of a single regiochemistry, which is especially challenging when the alkyne precursor is internal. Here, propargylic alcohols and their derivatives have shown a strong preference to place the tin moiety on the proximal carbon of the alkyne (i.e., β to oxygen).[4a,d–f] Taken together, the ability to carry out radical hydrostannylation under very mild conditions with high regio- and stereochemical fidelity across a wide variety of substrates is important and necessitates a solid mechanistic understanding of the process.

While the Et$_3$B/O$_2$-mediated hydrostannylation of propargylic alcohols and their derivatives using nBu$_3$SnH proceeds well at 80 °C, the transformation is poor at room temperature requiring three days to reach completion and a large excess of tin hydride (at least 5.0 equiv).[4] Furthermore, hindered substrates react much slower in the solvents that are typically used for this transformation (e.g., benzene, toluene). We have reported that hydrostannylation with nBu$_3$SnH (2.0 equiv)/Et$_3$B at 80 °C proceeds with excellent stereoselectively (*trans* addition to produce the *Z* isomer) within 3 h (Scheme 1).[5] However, the transformation must be monitored carefully for beyond 3 h reaction time, isomerisation to the *E* isomer begins. Conversely, hydrostannylation with Ph$_3$SnH (1.5–2.0 equiv) is known to proceed well at room temperature in benzene or toluene.[4d–f] However, poor reproducibility with regard to regioselectivity and yield, coupled with difficulty in product isolation relative to



Scheme 1. Hydrostannylation of **1** using Et$_3$B/O$_2$ as mediators.[5]

nBu$_3$Sn derivatives, makes the use of Ph$_3$SnH impractical and less attractive.[2e] Furthermore, while stereospecific tin/halogen exchange of the tributylstannyl moiety proceeds reliably to give the alkenylhalide, sides reactions in phenylhalogen exchange plague the corresponding triphenylstannyl moiety.[4f] Consequently, the development of a hydrostannylation method using nBu$_3$SnH that proceeds efficiently under mild and environmentally friendly conditions is a priority.

Free-radical-mediated hydrostannylation is invariably reported in benzene or toluene, primarily for solvent compatibility reasons. When the rate of hydrostannylation with nBu$_3$SnH was followed in benzene, it is clear that the reaction is very slow (Figure 1). This cannot be an issue of radical initiation, as the autoxidation of Et$_3$B is instantaneous in the presence of trace oxygen, even at or below 0 °C.[4b] Despite the general belief that radical processes should not show a significant rate change in more polar solvents, there is precedent for significant increases (and decreases) in rate, when a more polar solvent is substituted for those conventionally used in radical reactions (e.g., CCl$_4$, benzene, alkanes).[6] Changing the solvent to THF resulted in a remarkable increase in the rate of hydrostannylation using nBu$_3$SnH (Figure 1). The ability to carry out the reaction at room temperature in THF offers several advantages. The stereoselectivity of the radical addition can be better controlled, since the isomerisation of the kinetically formed *Z* product to the thermodynamic *E* product is promoted at higher temperature.[4a] Furthermore, given that hydrostannylation is conducted on a large scale in industry,[7] the replacement of benzene for THF and a vast reduction in the equivalents of tin reagent required will impact significantly on safety and the environment.

In light of this result, the transformation was further optimised and other polar solvents evaluated (Table 1). Increasing the amount of Et$_3$B from 0.2 to 0.5 equivalents improved

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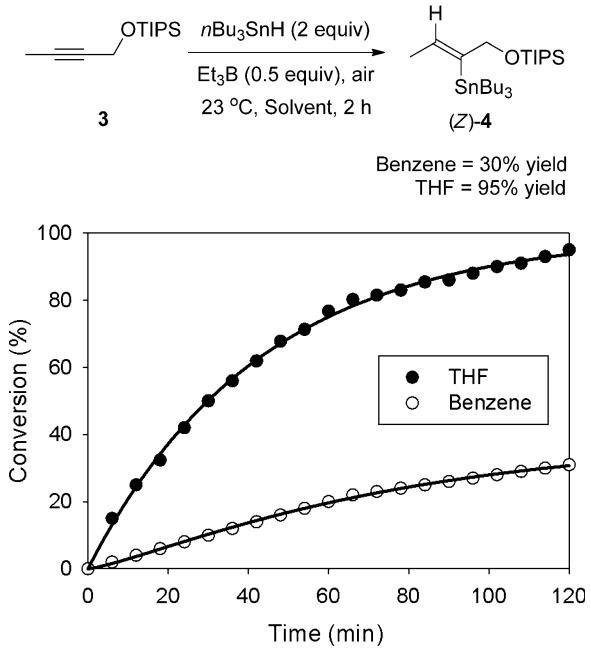
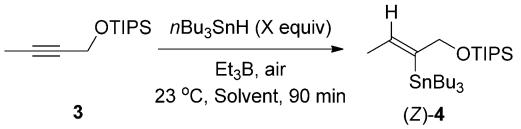


Figure 1. The rate of hydrostannylation of **3** using Et_3B/O_2.

Table 1. Et_3B/O_2-mediated nBu_3SnH addition to **3** in polar solvents.[a]



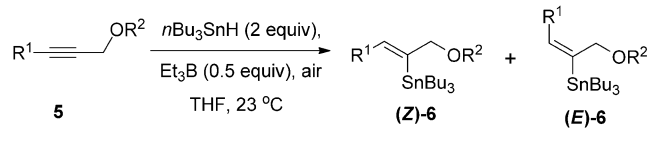
Entry	Solvent	Et_3B [equiv]	nBu_3SnH [equiv]	Conversion of (*Z*)-**4** [%][b]
1	benzene	0.2	1.5	5
2	THF	0.2	1.5	22
3	THF	0.5	1.5	60
4	THF	0.5	2	82[d]
5	acetone	0.5	2	50
6	DMF	0.5	2	80
7	$THF + H_2O$[c]	0.5	2	75
8	DMI	0.5	22	86[d]
9	DMPU	0.5	2	87[d]
10	NC—H	0.5	2	78

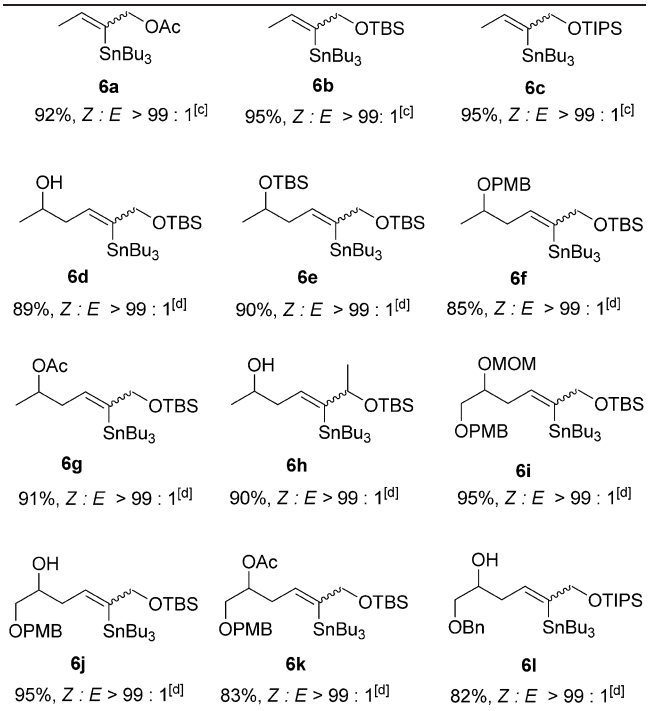
[a] Reactions were quenched at 90 min by passing them through a pad of silica gel. [b] Percent conversion was determined by ^1H NMR spectroscopy of the crude mixture. [c] Five equivalents of water were added to the reaction solution in anhydrous THF. [d] The reaction went to full conversion within 3 h.

conversion (entries 2 and 3), as did increasing the number of equivalents of nBu_3SnH from 1.5 to 2.0 (entries 3 and 4). While the conversion was lower in acetone (entry 5), satisfactory conversion was obtained in DMF (entry 6). Importantly, the presence of water has little effect on hydrostannylation (entry 7). Interestingly, the reaction gave the best conversion in the highly polar solvents 1,3-dimethyl-2-imidazolidinone (DMI) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU; entries 8 and 9). The reaction also proceeded satisfactorily in isobutyronitrile as the solvent (entry 10). In general, polar solvents accelerate hydrostannylation, leading to greater percent conversion. It is very important to note that a limited amount of molecular oxygen is required for the hydrostannylation of propargylic alcohol derivatives reported here to proceed, irrespective of the solvent and radical initiator employed. If too much oxygen is present, hydrostannylation fails to proceed (vide infra). While the reactions carried out in DMI and DMPU gave slightly higher yields than in THF, they are often difficult to remove during workup, thus we moved forward using THF.

To probe the generality of the nBu_3SnH/Et_3B/THF/room temperature protocol, we embarked on a scope study that included different functional groups (Table 2) and found that a variety of substituents on the propargylic alcohol were readily tolerated (e.g., OAc: , OTBS, and TIPS: **6a–c**). Also impressive, the secondary propargylic silyl ether (**5h**), which did not hydrostannylate well in benzene at 80 °C, was

Table 2. Scope studies for Et_3B/O_2-mediated hydrostannylation in THF at room temperature.[a,b]





[a] Isomeric ratios were determined by ^1H NMR spectroscopy of the crude reaction mixture. [b] Yields were determined after purification by silica gel chromatography. For selectivities reported at >99:1, we do not see any of the *E* isomer. [c] Alkyne (0.5 M in THF) and Et_3B (0.5 equiv), nBu_3SnH (2 equiv), 3 h. [d] Alkyne (0.5 M in THF), nBu_3SnH (2 equiv), Et_3B (1.0 equiv), 12–18 h.

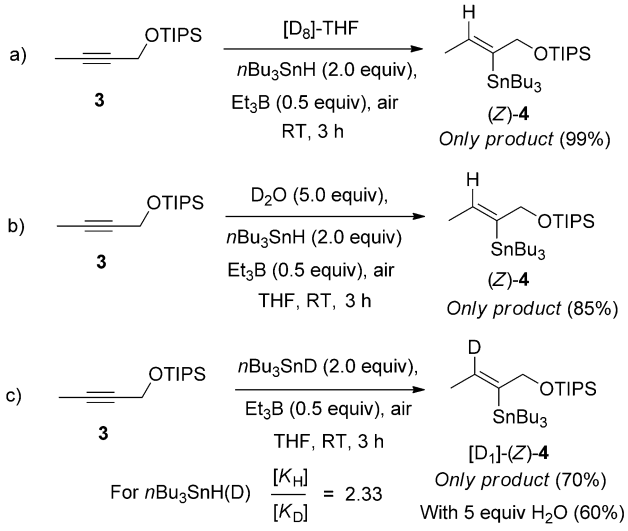
readily hydrostannylated in THF at room temperature to give **6h**. Excellent yields and absolute regio- and stereocontrol were achieved for all cases.

Our group,[5] and others,[8] have examined the autoxidation of Et_3B in benzene and reported that with sufficient oxygen the first and second autoxidations are rapid at room temperature, while the third is slow. We have also demonstrated for the first time that each of these autoxidation products [$Et_2B(OEt)$, $EtB(OEt)_2$ and $B(OEt)_3$] can individually mediate hydrostannylation of propargylic alcohol derivatives in air, albeit at very different rates.[5b] In the presence of oxygen, the first autoxidation product, $Et_2B(OEt)$, mediates hydrostannylation faster than the second, $EtB(OEt)_2$, which is much faster than $B(OEt)_3$. When the autoxidation of Et_3B (100 μL, 1 M in hexane) was conducted in [D_8]THF (0.5 mL) in this study, the first autoxidation to $Et_2B(OEt)$ was again rapid, but now the second autoxidation to $EtB(OEt)_2$ is significantly slower (approximately 4 h to be fully formed compared with about 5 min in benzene).[9] When the reaction of **3** with nBu$_3$SnH was closely monitored and deemed to be just complete, the ^{11}B NMR spectrum of the mixture revealed that $EtB(OEt)_2$ was the only boron species present. Considering the lifetime of the autoxidation products, overlaid with the rates of the reaction in both solvent systems, it would appear that in benzene $EtB(OEt)_2$ is the active species, while in THF it is primarily $Et_2B(OEt)$. Here, it is likely that the oxygen atom of THF and the other polar solvents are stabilising the boron centre thus extending the lifetime of the more active oxidation products in solution (i.e., $Et_2B(OEt)$ is longer lived in polar solvents than apolar solvents), which causes the rate acceleration. Although it was difficult for us to synthesise pure $Et_2B(OEt)$ and use directly for the hydrostannylation, using commercially available and pure $Et_2B(OMe)$ led to identical results as Et_3B in THF. In addition to the above, it is conceivable that the higher diffusion/miscibility of molecular oxygen in polar solvents is playing a crucial-secondary role, respectively.

Our hydrostannylation protocol with Et_3B involves sealing the reaction flask in air immediately following the addition of the last reagent, which means that the oxygen present in the flask is consumed and not replenished as autoxidation proceeds. When a large supply of oxygen was used in the reaction (using an oxygen-filled balloon) at, or above room temperature, the reaction did not proceed at all in any solvent. This is an indication of a rapid autoxidation to the less reactive boron species in the presence of excess oxygen. The solvent dependency of autoxidation coupled with the apparent specificity of which boron species is actually present and therefore presumably promotes the transformation in a particular solvent, suggests a delicate balance between the concentrations of Et_3B and O_2. That is, enough O_2 is required to reach the necessary species to drive the transformation in a particular solvent. However, if there is abundant O_2, autoxidation proceeds too far to yield a nonproductive species. So, having the right balance of Et_3B and O_2 is paramount.

In order to confirm a radical mechanism for Et_3B/O_2-mediated hydrostannylation, galvinoxyl (a known radical scavenger)[4,10] was added to the reaction mixture in benzene after the autoxidation process was allowed to proceed for 10 min, so as to ensure the formation of the active radical promoter, and no addition took place. Further, the reaction between nBu$_3$SnH and Et_3B/O_2 (1:1) in both benzene and THF was followed by ^{119}Sn NMR spectroscopy. The spectra showed the formation of nBu$_3$SnSnBu$_3$ (−79 ppm), which occurs by the combination of two tin radicals.[4,11] The ^{119}Sn NMR spectrum of the reaction of nBu$_3$SnH and AIBN (1:1) in C_6D_6, which presumably could only be radical mediated, also showed a prominent peak for nBu$_3$SnSnBu$_3$ at −79 ppm.[11]

Since the α-hydrogen of THF is susceptible to radical abstraction,[12] we carried out the hydrostannylation of **3** in [D_8]THF to track any hydrogen-atom transfer from the solvent, but only the undeuterated product ((***Z***)-**4**) was obtained (Scheme 2a). It has been proposed that H_2O can act



Scheme 2. Deuterium labelling studies for the hydrostannylation of **3**.

as a hydrogen donor in reactions mediated by Et_3B/O_2.[13] Since the THF protocol that we have developed proceeds in the presence of water (Table 1, entry 7), five equivalents of D_2O were added to the reaction mixture to see if adventitious water could serve as the hydrogen donor. Again there was no deuterium label in the product (Scheme 2b). We feel that this result also casts doubt on proposals that R_2BOOH and R_2BOH can be the hydrogen donor in these reactions. It has been shown by NMR spectroscopy that these protons are fully exchangeable in D_2O and yet there is zero deuterium transfer to the product.[13,14] Finally, we performed the hydrostannylation with nBu$_3$SnD and the alkenylstannane showed 100% deuterium incorporation ([D_1]-(*Z*)-**4;** Scheme 2c). The identical outcome was obtained when the reaction was conducted with H_2O present.

When we compared the rate of the reaction shown in Scheme 2c with its non-deuterated counterpart, the transformation was found to have a primary kinetic isotope effect (KIE) of 2.33.[11] Presuming that radical initiation is spontaneous, this points to the second step of radical chain propagation as being rate-limiting (Figure 2). Although the rate-

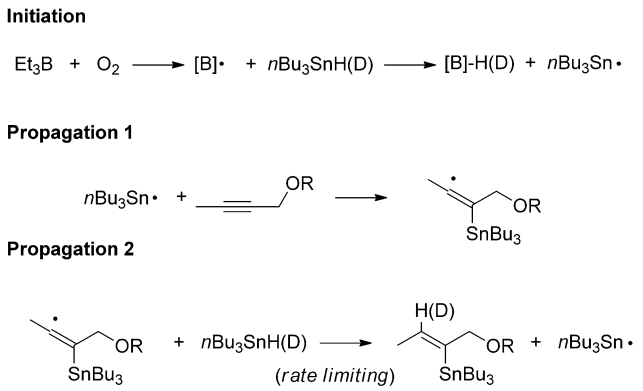


Figure 2. Putative alkyne hydrostannylation mechanism with Et_3B/O_2.[2a,e,f]

determining and selectivity-determining steps are not necessarily the same, a high transition-state barrier would help explain why there is such a pronounced kinetic stereoselectivity for the *Z* olefin, which would be determined in this step.

In conclusion, we have shed new light on the reactivity of Et_3B/O_2-mediated alkyne hydrostannylations using nBu$_3$SnH as the hydride source. Most importantly, we have developed new conditions for hydrostannylation at room temperature in THF, eliminating the need for benzene that carries with it significant health and environmental concerns.[15] We have also unveiled a rate-accelerating effect of polar solvents in hydrostannylation and demonstrated nBu$_3$SnH as the sole source of H• in step 3 of the radical-chain process. We believe that this step is rate-limiting in addition to being the selectivity-determining step in the process.

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Keywords: autoxidation · hydrostannylation · radicals · solvent effects · stereoselective · triethylborane

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