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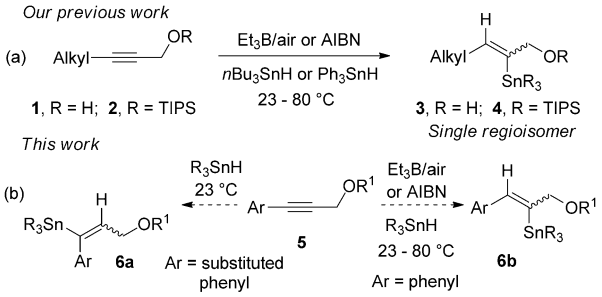
On the Hydrostannylation of Aryl Propargylic Alcohols and Their Derivatives: Remarkable Differences in Both Regio- and Stereoselectivity in Radical- and Nonradical-Mediated Transformations

Martins S. Oderinde,[a] Robert D. J. Froese,[b] and Michael G. Organ*[a]

Abstract: Herein, we describe a highly regio- and stereoselective radical-mediated and molecular-oxygen (O_2)-dependent hydrostannylation of phenyl propargylic alcohols and their derivatives. There is a significant steric effect on the stereoselectivity of the tin-radical addition. Further, the uncatalyzed regio- and stereoselective hydrostannylation of aryl propargylic alcohols with nBu$_3$SnH and Ph$_3$SnH is also described and occurs with near titration kinetics. Although the uncatalyzed addition with nBu$_3$SnH gave a remarkable γ-regioselectivity irrespective of the electronic nature of the aryl moiety, addition with Ph$_3$SnH appears to be driven by the electronic nature of the aryl alkynes.

Hydrometalation is one of the most important sub-classes of addition reactions involving alkenes, allenes, and alkynes.[1] Alkyne hydroboration, hydrozirconation, and hydrostannylation are central transformations within this sub-class.[1] Of the organometallic products from these reactions, vinylstannanes are arguably the most versatile due to the diverse array of reactions that they are capable to undergo (e.g., cross-coupling, metal–metal exchange, metal–halogen exchange).[2–3] Consequently, the ability to control the regio- and stereochemical aspects of alkyne hydrostannylation is of great interest, particularly with internal alkynes that give rise to increasingly complex, and thus valuable products.[4]

The stereoselectivity in hydrostannylation is largely predictable depending on whether it is transition metal catalyzed, which proceeds stereospecifically by *syn* addition of the tin hydride across the triple bond, or radical mediated that provides the *trans* addition product kinetically, although isomerization to the *syn* product can occur over time if there is a thermodynamic driving force.[5] However, the ability to control the regioselectivity of the addition has been the most challenging aspect of all hydrometalation reactions.[1,4] Although transition-metal-catalyzed hydrometalation reactions have shown poor to good regiocontrol, better selectivity has been achieved with radical-mediated hydrostannylation providing that a suitable directing force is present, such as is the case with alkyl propargylic alcohols and their derivatives (Scheme 1 a).[4–6]



Scheme 1. Regioselective radical-mediated hydrostannylation of propargylic alcohols and their derivatives.

We have studied the radical-mediated hydrostannylation of alkyl propargylic alcohols and their derivatives and found certain aspects of the reaction very intriguing.[6] For example, we reported that the regiochemical outcomes of hydrostannylation was unchanged when the hydroxyl group was adorned with bulky groups, such as triisopropylsilyl (TIPS), which casts doubt on proposals that suggest tin radical (or tin hydride) coordination to the oxygen atom in the transition state controls regioselectivity.[5]

In an effort to better understand alkyne hydrostannylation, we investigated the reaction of aryl propargylic alcohols and their derivatives. The products of such addition would be highly valued, and the steric and electronic nuances of the aryl systems can be systematically varied to provide key mechanistic understanding (Scheme 1 b). Surprisingly, we could not find any prior reports of radical-mediated hydrostannylation of aryl propargylic alcohols in the literature, and our initial reactions may provide some understanding for why these substrates have not been reported. Herein, we report on the radical-mediated and uncatalyzed hydrostannylation of aryl propargylic alcohols and their derivatives.

Unlike their alkyl counterparts (Scheme 1 a), the hydrostannylation of the free propargylic alcohol **7 a** gave a mixture of regio- and stereoisomers in low yield with either nBu$_3$SnH or

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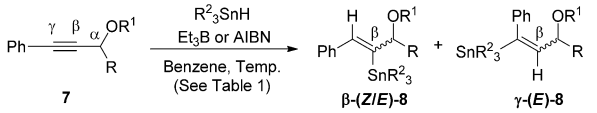
Ph_3SnH (Table 1, entries 1 and 2). Although we have demonstrated that Et_3B leads to better stereoselectivity during the hydrostannylation of **1** and **2**,[6] both Et_3B and Azobisisobutyronitrile (AIBN) were unselective in the hydrostannylation of **7a** (entries 1 and 3). Remarkably, the reaction gave absolute regiocontrol for the proximal **β-8b** without any of the distal **γ-8b** regioisomer in full conversion by using no more than 1.2 equivalents of nBu_3SnH, albeit with little stereocontrol when the alcohol was protected as an acetyl (Ac) group **7b** (Table 1, entry 4). Lowering the temperature from 80 to 23 °C had no effect on the stereoselectivity of the addition, although the reaction did go to completion (Table 1, entry 5). The ability to carry out the hydrostannylation of aryl propargylic moieties at RT by using nBu_3SnH in benzene showed the higher reactivity of aryl propargylic moiety over its alkyl counterpart.[5–6]

Interestingly, increasing the size of the protecting group from acetyl to *tert*-butyldimethylsilyl (TBS, **7c**) slightly improved the *Z* selectivity (i.e., *trans* addition) of the reaction (Table 1, entry 6). This selectivity was further enhanced when the bulk was increased to *tert*-butyldiphenylsilyl (TBDPS, **7d**, entry 7). Finally, when the triisopropylsilyl (TIPS) ether derivative (**7e**) was employed, absolute regio- and stereocontrol for **β-(*Z*)-8e** was attained (entry 8).

Armed with the knowledge that increased bulk on the propargylic oxygen atom improves the regio- and stereoselectivity of this radical-mediated hydrostannylation, we embarked on scope studies that included primary, secondary, and tertiary phenyl propargylic alcohols and their derivatives (Table 2). For primary substrates, the use of nBu_3SnH showed better stereoselectivity than Ph_3SnH (e.g., **8e** vs. **f**). Similarly, substituting the hydrogen atom of some secondary propargylic alcohols with *tert*-butyldimethylsilane (TBS) improved their stereoselectivity (e.g., **8g** vs. **h** and **8i** vs. **j**). We also found that substituents on the oxygen were not necessary for high selectivity when substituents were present at the α-position (**8k**–**n**). However, this change was accompanied by a reduced reaction rate at 23 °C, in which case the reactions were carried out at 80 °C by using AIBN with no adverse effect on regio- and stereoselectivity. In all cases, good to excellent yields with remarkable regio- and stereocontrol were obtained. We rationalized the trend in the above-described results on the basis of steric effects. As the bulk of the oxygen substituent increased from Ac to TIPS, there is a significant decrease in the rate of the tin radical addition onto the starting alkyne. More importantly, addition of a second radical onto the kinetically formed **β-(*Z*)-8** isomer was suppressed thus eliminating isomerization to the **β-(*E*)-8** isomer.[6a] With secondary and tertiary alcohols, an increase in bulk at the α-carbon also showed similar steric effects on selectivity.

For mechanistic considerations, we conducted the hydrostannylation of **7e** by using AIBN (5 mol%) in the presence (reagents not degassed) and absence (fully degassed reagents and the transformation was conducted inside of an argon-filled glovebox) of O_2 (Scheme 2). Interestingly, although the reaction conducted in the presence of O_2 (air) gave 100% conversion to product within one hour, the one conducted inside the glovebox with the rigorous exclusion of O_2 gave only 5%

Table 1. Radical-mediated hydrostannylation of phenyl propargylic alcohols and their derivatives.[a]

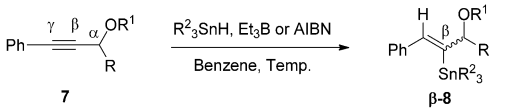


7 β-(*Z*/*E*)-8 γ-(*E*)-8

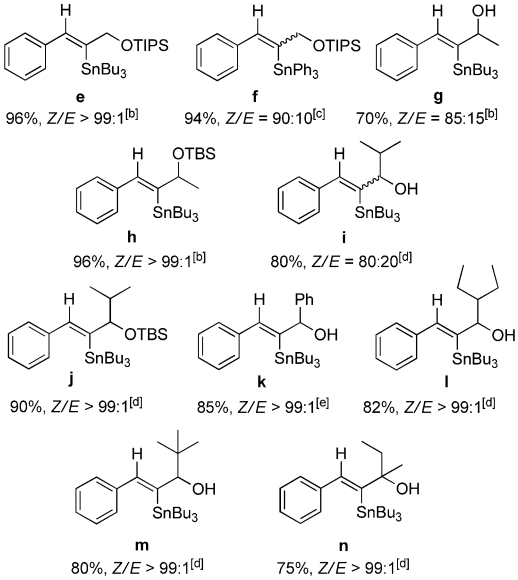
Entry	R	R^1	*T* [°C]	β-(*Z*)-8/ β-(*E*)-8	Conv. of β [%][b]	Conv. of γ-(*E*)-8 [%]
1 (**a**)	H	H	80	35:65	40[c]	30
2 (**a**)	H	H	23	30:70	35[d]	40
3 (**a**)	H	H	80	30:70	35[e]	20
4 (**b**)	H	Ac	80	55:45	100[c]	–
5 (**b**)	H	Ac	23	55:45	100[c]	–
6 (**c**)	H	TBS	23	66:34	100 (97)[c]	–
7 (**d**)	H	TBDPS	23	80:20	100[c]	–
8 (**e**)	H	TIPS	23	99:1	100 (96)[c]	–

[a] Percent conversion and isomer ratios were determined by ^1H NMR spectroscopy of the crude reaction mixture; >99:1 means that the other isomer was not detected. [b] Isolated yield in parenthesis. [c] Alkyne (0.5 M in benzene), nBu_3SnH (1.2 equiv), Et_3B (0.5 equiv), 2 h. [d] Ph_3SnH (2.0 equiv) was used, 1 h. [e] Alkyne (0.5 M in benzene), nBu_3SnH (1.2 equiv), AIBN (0.1 equiv), 2 h.

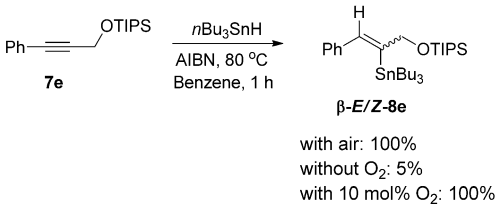
Table 2. Scope studies of radical-mediated hydrostannylation of phenyl propargylic alcohols and silyl ethers.[a]



7 β-8



[a] Isomeric ratios were determined by ^1H NMR spectroscopy of the crude reaction mixture; >99:1 means that the other isomer was not detected by ^1H NMR spectroscopy. [b] Alkyne (0.5 M in benzene), nBu_3SnH (1.2 equiv), Et_3B (0.5 equiv), 23 °C, 2 h. [c] Alkyne (0.5 M in benzene), Ph_3SnH (1.2 equiv), Et_3B (0.5 equiv), 23 °C, 1 h. [d] Alkyne (0.5 M in benzene), nBu_3SnH (2.0 equiv), AIBN (0.1 equiv), 80 °C, 3 h. [e] Alkyne (0.5 M in benzene), nBu_3SnH (1.2 equiv), AIBN (0.1 equiv), 80 °C, 2 h.



Scheme 2. Effect of molecular oxygen on hydrostannylation.

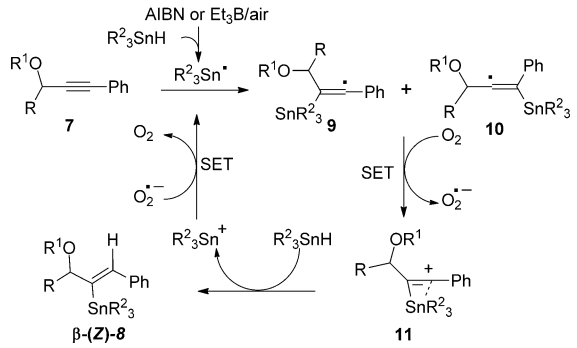


Figure 1. Proposed mechanism of radical-mediated hydrostannylation of phenyl propargylic alcohols in the presence of O_2.

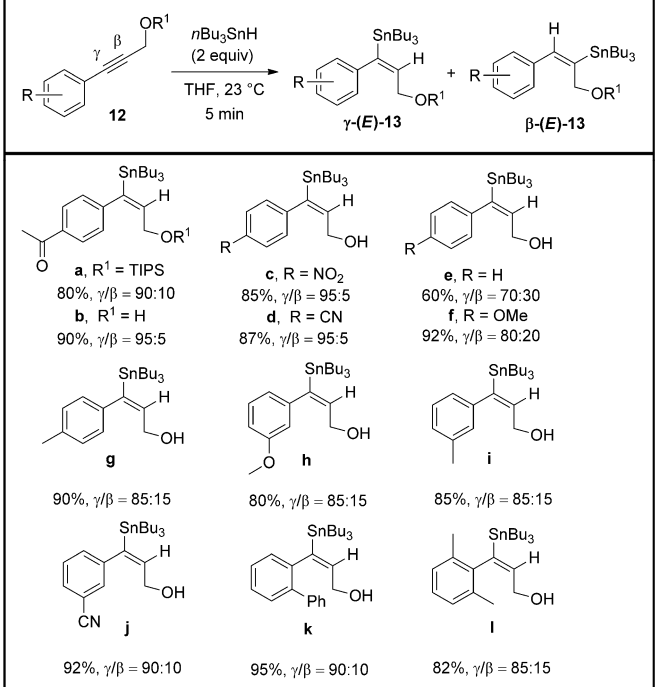
of conversion to product. As shown in Scheme 2, only a catalytic amount of O_2 (10 mol%, purity > 99.999%) is necessary for radical-chain propagation.

To account for these results, we propose the mechanism shown in Figure 1, which is consistent with our previous mechanistic studies on alkyl propargylic alcohols and that was supported by DFT studies.[7] Contrary to current belief in the hydrostannylation field, initial tin-radical addition to **7** need not be regioselective to give rise to a single isomer of the hydrometalated alkene product. In fact, there may be little or no selectivity in the initial tin-radical addition to give rise to an isomeric mixture of vinyl radicals **9** and **10**. A single-electron transfer (SET) from either **9** and **10** to O_2 will coalesce to form a more reactive benzylic/vinyl cation **11** and superoxide ($O_2^{\cdot-}$).[8] Regioselective hydride transfer from nBu$_3$SnH to the polarized three-centered cation **11** will ultimately give the kinetic product **β-(*Z*)-8** and nBu$_3$Sn$^+$, which is subsequently rapidly reduced by $O_2^{\cdot-}$ to regenerate nBu$_3$Sn$^{\cdot}$ and O_2 thus completing the catalytic cycle.[7] Non-O_2-dependent isomerization of the (*Z*)-isomer with nBu$_3$Sn$^{\cdot}$ would give rise to the (*E*)-isomer.[5,7]

Puzzled by the origin of **γ-*(E)*-**product in Table 1, entries 1–3, we conducted the hydrostannylations of substituted aryl propargylic alcohols and their silyl ethers in the absence of radical mediators, transition metals,[4] or oxygen by simply adding nBu$_3$SnH to O_2-free solutions of the alkynes and, shockingly, the hydrostannylation rapidly gave products at RT (Table 3).[9] Herein, not only the regiochemistry of the addition was completely reversed from the radical-mediated transformation, so was the stereoselectivity (i.e., now exclusive *syn* addition). We also found that the regioselectivities were significantly enhanced towards the major isomer in THF than benzene, in which the reactions proceed at a slower rate. The regiochemical outcome of the additions was only slightly influenced by the electronic nature of the substituents on the aromatic ring. For example, although the uncatalyzed hydrostannylation of aryl propargylic alcohols **12a–d** containing electron-withdrawing substituents (R = *p*-CH$_3$(CO), *p*-NO$_2$ and *p*-CN) gave γ-regioisomers **13a–d** in good yields (γ/β ≈ 95:5), the selectivity for the γ-regioisomer only slightly decreased when the *para*-position was unsubstituted **13e** (γ/β ≈ 70:30) or contained electron-donating groups (R = *p*-OMe and *p*-Me, **13f** and **13g**, γ/β = 80:20 and 85:15, respectively). Intriguingly, moving the substituents from the *para* site to either the *ortho* or *meta*- positions did not affect the high selectivity for the γ-regioisomer (**13h–k**).[9] Perhaps most impressive is the fact that even *ortho,ortho*-disubstituted aryl rings (**13l**) failed to diminish the high regioselectivity for what would appear to be the more sterically congested regioisomer.

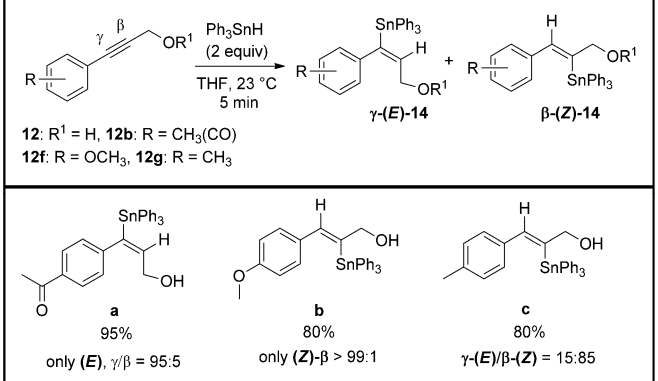
The regiochemical outcomes when Ph$_3$SnH was used instead of nBu$_3$SnH in these non-radical-mediated additions are in stark contrast (Table 4). Although the hydride of Ph$_3$SnH was added to the β carbon of **12b**, which has a *para*-electron-withdrawing group, to give **14a**, it added to the γ carbons of **12f** and **g** with *para*-electron-rich groups to give **14b** and **c**, respectively. Interestingly, *Z*-stereochemical outcomes were obtained for the β-vinyltriphenylstannanes **14b** and **c**. Assuming that the initial tin hydride additions in Table 3 and 4 proceed

Table 3. Scope studies of uncatalyzed hydrostannylation of aryl propargylic alcohols and silyl ethers with nBu$_3$SnH.[a,b,c]



[a] Isomeric ratios were determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [b] The regioisomers were easily separated by silica-gel chromatography giving rise to isomerically pure products in all cases. [c] Alkyne (0.5 M in THF), nBu$_3$SnH (2 equiv), 5 min.

Table 4. Scope studies of uncatalyzed hydrostannylation of aryl propargylic alcohols with Ph_3SnH.[a,b]



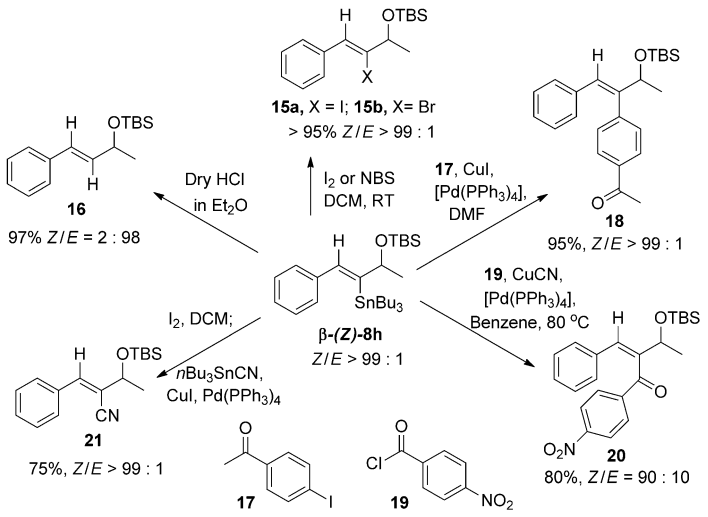
[a] Isomeric ratios were determined by ^{1}H NMR spectroscopy of the crude reaction mixture; >99:1 means that the other isomer was not detected by ^{1}H NMR spectroscopy. [b] Alkyne (0.5 M in THF), Ph_3SnH (2 equiv), 5 min.

by a stereospecific *syn*-addition,[10] the *Z* stereochemistries of **14b** and **c** can only be explained by rapid *E* to *Z*-isomerization, because any of the β-(*E*) isomer has been never observed, although it remains unclear how this process proceeds in the presumed absence of radicals. No such isomerization was observed with β-vinyltributylstannanes as for those shown in Table 3.

The fact that very similar substrates follow different hydrostannylation mechanisms is striking and noteworthy. From Table 1, simple phenylpropargyl alcohol appears to undergo the *trans* radical-mediated addition at a similar rate as the direct (uncatalyzed) *syn* hydrostannylation (Table 1, entries 1–3). Yet when different groups are placed on the oxygen moiety, this pathway is completely shut down despite still giving high conversion to the radical-addition product **β8** (entries 4–8). This was further demonstrated in Scheme 2, in which the reaction without O_2 did not give any *syn* hydrostannylation product despite that only traces of **β-*E*/*Z*-8e** were formed after 1 h. More striking is that the placement of seemingly any substituent at any position on the phenyl ring dramatically enhances direct hydrostannylation, which completes very rapidly at RT (Table 3). Indeed, when we submitted substrates **12b** and **f** to the radical-reaction conditions given in Table 2, only the *syn* hydrostannylation products **13** were produced; none of the *anti* addition product resembling **8** were ever observed. Thus, the direct hydrostannylation mechanism with aryl propargyl alcohol derivatives does not appear to be under electronic control imparted by the aryl ring, at least when using tributylstannane. The reactivity pattern being displayed between the two operating mechanisms in this hydrometalation study appears to be without precedent.

The high reactivity of the direct hydrostannylation warrants further comment. Additions involving the substrates in Table 3 are exothermic and in reality are just titrations. This encouraged us to revisit tolane hydrostannylation studies in the literature.[11] These Pd-catalyzed results that showed similar regiochemistry to those described in our study, that is, tin placement closest to the substituted aryl ring (even *ortho*-substituted) when simple phenyl was at the other end of the alkyne. We wondered if these reactions were, in fact, not catalyzed by Pd at all given the very high reactivity that has been observed with the aryl propargylic system in our study. Interestingly, when we used 1-(2-methylphenyl)-2-phenylacetylene under the conditions presented in Table 3, no reaction occurred, although it did go to completion when the Pd catalyst was added, as was described by Alami and co-workers[11a] and Gevorgyan and co-workers.[11b] Clearly, there is something unique about the aryl propargylic alcohol system that leads to this high reactivity.

Finally, we carried out six diverse stereospecific transformations on **β-(*Z*)-8h** to illustrate the value of the hydrostannylation methodology developed in this report (Scheme 3). Both the tin/iodide and tin/bromide exchange reactions of **β-(*Z*)-8h** by using I_2 and *N*-bromosuccinimide (NBS), respectively, proceeded quantitatively to give (*Z*)-**15a** and (*Z*)-**15b** selectivity. Likewise, the protodestannylation of **β-(*Z*)-8h** with HCl in Et_2O gave the disubstituted internal alkene **(*E*)-16** (*Z*/*E* 2:98) in high



Scheme 3. Stereospecific transformations of **β-(*Z*)-8h**. DCM = dichloromethane.

recovery. Pd-catalyzed cross-crossing of **β-(*Z*)-8h** with aryliodide **17** in the presence of CuI co-catalyst[10] gave (*Z*)-**18** without any isomerization of the double bond. Similarly, the Pd-catalyzed cross-coupling of **β-(*Z*)-8h** with acid chloride **19** in the presence of CuCN co-catalyst gave (*Z*)-**20** as the major isomer. Finally, the telescoped, two-step stereospecific conversation of **β-(*Z*)-8h** to vinylcyanide (*Z*)-**21** proceeded uneventfully giving another versatile building block for further elaboration.

In conclusion, we have carried out the first studies on the radical-mediated hydrostannylation of aryl propargylic alcohols and their derivatives. Increasing the bulk on the propargylic oxygen atom or at the α-carbon has two important roles. First,

it ensures complete regioselective placement of the tin distal to the phenyl ring, and second, it slows or completely prevents the isomerization of the kinetically formed (*Z*)-isomer. All experiments, including the dramatic effect of O_2, strongly suggest that a radical/cationic pathway is involved in the hydrostannylation of phenyl propargyl moieties and that O_2 is serving as a redox catalyst in this process.[7,8]

We have also described the first uncatalyzed hydrostannylation protocols of aryl-substituted propargylic alcohols with nBu$_3$SnH and Ph$_3$SnH. Although the uncatalyzed addition with nBu$_3$SnH proceeded with γ-regioselectivity irrespective of the electronic or steric nature of the aryl substituent, additions with Ph$_3$SnH demonstrated what appears to be an electronic bias. This direct *syn* hydrostannylation is strongly promoted by the presence of substituents on the aromatic ring, a result that we cannot understand yet, despite studying the system by computation methods. When these substituted arylalkynes are presented with a choice of undergoing radical-mediated addition, or simple direct *syn* hydrometalation, only the product of non-radical addition is obtained illustrating just how fast these non-catalyzed additions are. As was demonstrated, the hydrostannylation protocols of aryl propargylic alcohols described herein will be of value for the straightforward preparation of functionalized building blocks and complex target molecules in organic and medicinal chemistry.

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Keywords: hydrostannylation · radicals · regioselectivity · stereoselectivity · vinylstannane

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[1] For reviews see: a) B. M. Trost, Z. T. Ball, *Synthesis* **2005**, *6*, 853; b) N. D. Smith, J. Mancuso, M. Lautens, *Chem. Rev.* **2000**, *100*, 3257.
[2] a) D. Milstein, J. K. Stille, *J. Am. Chem. Soc.* **1979**, *101*, 4992; b) D. A. Evans, W. C. Black, *J. Am. Chem. Soc.* **1993**, *115*, 4497; c) J. R. Behling, K. A. Babiak, J. S. Ng, A. L. Campbell, R. Moretti, M. Koerner, B. H. Lipshutz, *J. Am. Chem. Soc.* **1988**, *110*, 2641.
[3] a) W. P. Neumann, *The Organic Chemistry of Tin*, Wiley, New York, **1970**; b) K. W. Kells, J. M. Chong, *J. Am. Chem. Soc.* **2004**, *126*, 15666.
[4] a) J. P. Betzer, F. Delaloge, B. Muller, A. Pancrazi, J. Prunet, *J. Org. Chem.* **1997**, *62*, 7768; b) H. X. Zhang, F. Guibé, G. Balavoine, *J. Org. Chem.* **1990**, *55*, 1857.
[5] a) M. Taddei, C. Nativi, *J. Org. Chem.* **1988**, *53*, 820; b) P. Dimopoulos, J. George, D. A. Tocher, S. Manaviazar, K. Hale, *Org. Lett.* **2005**, *7*, 5377; c) K. Nozaki, K. Oshima, K. Utimoto, *Tetrahedron Lett.* **1989**, *45*, 923; d) K. Nozaki, K. Oshima, K. Utimoto, *J. Am. Chem. Soc.* **1987**, *109*, 2547.
[6] a) M. S. Oderinde, H. N. Hunter, M. G. Organ, *Chem. Eur. J.* **2012**, *18*, 10817; b) M. S. Oderinde, H. N. Hunter, R. D. J. Froese, M. G. Organ, *Chem. Eur. J.* **2012**, *18*, 10821; c) M. S. Oderinde, M. G. Organ, *Angew. Chem.* **2012**, *124*, 9972 – 9975; *Angew. Chem. Int. Ed.* **2012**, *51*, 9834 – 9837; d) M. S. Oderinde, M. G. Organ, *Chem. Eur. J.* **2013**, *19*, 2615.
[7] M. S. Oderinde, R. D. J. Froese, M. G. Organ, *Angew. Chem.* **2013**, *125*, 11544; *Angew. Chem. Int. Ed.* **2013**, *52*, 11334.
[8] a) S. Zhu, A. Das, L. Bui, H. Zhou, D. P. Curran, M. Rueping, *J. Am. Chem. Soc.* **2013**, *135*, 1823; b) D. P. Kranz, A. G. Griesbeck, R. Alle, R. Perez-Ruiz, J. M. Neudorfl, K. Meerholz, H.-G. Schmalz, *Angew. Chem.* **2012**, *124*, 6102; *Angew. Chem. Int. Ed.* **2012**, *51*, 6000.
[9] The inclusion of 2 – 50 mol% of either Pd(PPh$_3$)$_2$Cl$_2$ or Ni(PPh$_3$)$_2$Cl$_2$ did not affect the reactivity or regiochemical outcomes of the addition. See; F. Liron, P. Le Garrec, M. Alami, *Synlett* **1999**, *2*, 246.
[10] J. Chae, T. Konno, M. Kanda, T. Ishihara, H. Yamanaka, *J. Fluorine Chem.* **2003**, *120*, 185.
[11] a) A. Hamze, P. Le Menez, O. Provot, E. Morvan, J.-D. Brion, M. Alami, *Tetrahedron* **2010**, *66*, 8698 – 8706; b) M. Rubin, A. Trofimov, V. Gevorgyan, *J. Am. Chem. Soc.* **2005**, *127*, 10243 – 10249.

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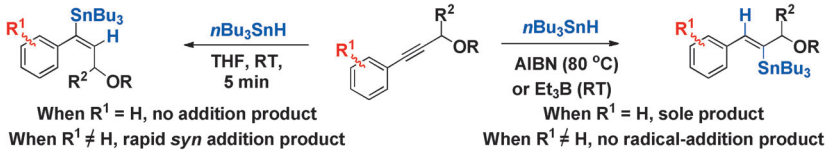

Electronic nature: The presence of seemingly any substituent on the ring of aryl propargyl alcohols led to extremely rapid hydrostannylation of the triple bond with tributyltin hydride. The addition is stereospecific (*syn*) and highly regioselective to place the tin moiety next to the aryl ring. This is in stark contrast to the radical-mediated hydrostannylation of simple phenyl propargyl alcohols that lead to both the opposite regio- and stereoselectivity (see scheme; AIBN=2,2′-azobisisobutyronitrile).