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A One-Pot Allylation–Hydrostannation Sequence with Recycling of the Intermediate Tin Waste

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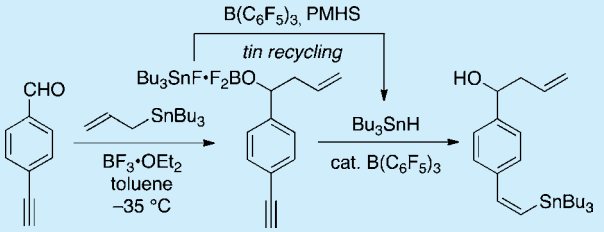
Supporting Information

ABSTRACT: A one-pot allylation and hydrostannation of alkynals where the tin byproduct formed in the first step of the reaction is recycled and used in the second step of the sequence is presented. Specifically, a $BF_3{\cdot}OEt_2$-promoted allylstannation of the aldehyde moiety in the alkynal is followed by the introduction of polymethylhydrosiloxane (PMHS) and catalytic $B(C_6F_5)_3$, which convert the tin byproduct of the allylation into Bu_3SnH, which then hydrostannates the alkyne in the molecule. ^{119}Sn and ^{11}B NMR data suggest an organotin fluoride species is formed during the allylation step and involved in the tin recycling step.



Previously, we reported *in situ* reductions of organotin halides and oxides by PMHS to afford organotin hydrides that can be employed in various hydrostannation protocols, including one-pot hydrostannation/Stille sequences catalytic in tin.[1] These successes drove us to consider other one-pot processes where the tin byproducts of an early step could be recycled and used in subsequent chemistry. We identified allylations as a reaction type that lends itself to such a one-pot sequence.

Allylation reactions of allylstannanes and aldehydes can take place under thermal,[2] high pressure,[3] Lewis acidic,[4] or transition-metal-catalyzed[5] conditions. The homoallylic alcohol products of such reactions can be converted to β-hydroxyaldehydes,[6] δ-lactones,[7] epoxides, or other oxygen-bearing compounds.[8] They can also be used in ring-closing metathesis[9] and cross-coupling reactions.[10]

An application of allylation chemistry that caught our attention was Nicolaou and co-workers'[11] syntheses of palmerolide A analogues where an aldehyde allylation was followed by an alkyne hydrostannation. This report prompted us to consider development of an allylation–hydrostannation protocol where the tin waste of the allylation step would be converted to an organotin hydride that would then be used in an ensuing hydrostannation reaction. Such a combined process would minimize tin handling and reduce the overall amount of tin reagents employed in syntheses as compared to these two steps performed separately.[12,13]

To develop the proposed allylation–hydrostannation protocol, knowledge of the nature of the tin byproducts of the allylation step is essential. Toward this end, Yamamoto and co-workers reported that palladium (or platinum)-catalyzed condensation of allylstannanes with aldehydes proceeds via intermediacy of stannyl ethers.[5] On the other hand, Baba and co-workers documented that allylations of aldehydes with allyltributylstannane and a catalytic amount of Bu_2SnCl_2 afford Bu_3SnCl as a waste product.[14] We anticipated that with proper choice of reducing agents either of these tin intermediates/byproducts could be reduced *in situ* to Bu_3SnH.[15]

In practice, though, neither of these methods proved amenable to one-pot allylation–hydrostannation performed with **1**, **2a**, and **3**. In such cases, the allylation of **1** went smoothly, resulting in **4** (Yamamoto's protocol) or the benzoyl derivative of **4** (Baba's protocol); however, *in situ* organotin hydride formation and subsequent hydrostannation of **3** by the action of PMHS, PMHS/TBAF, or Et_3SiH as the reducing agent with Pd or Pt as the hydrostannation catalyst failed. Given the incompatibility of the Yamamoto/Baba methods with our one-pot concept, we explored $BF_3{\cdot}OEt_2$-mediated allylations,[16] even though the tin intermediates that form in these reactions are not well characterized.[17a−e] In addition to the uncertain nature of the tin byproducts, we recognized that developing a one-pot allylation–hydrostannation sequence would be hampered by the inability of common hydrostannation catalysts, e.g., $PdCl_2(PPh_3)_2$[15b] or $MoBI_3$,[18] to survive in the presence of $BF_3{\cdot}OEt_2$. Rather than fighting against the Lewis acidic nature of $BF_3{\cdot}OEt_2$, we decided to exploit it by employing a Lewis acid mediated hydrostannation in the second step of our proposed sequence. Thus, $B(C_6F_5)_3$ was chosen as the hydrostannation catalyst.[15a,19] Et_3SiH was initially used as the hydride source per Yamamoto's *in situ* generation of Bu_3SnH for $B(C_6F_5)_3$-catalyzed hydrostannations.[15a]

Gratifyingly, with 10 mol % of $B(C_6F_5)_3$ and 1 equiv of Et_3SiH as the reducing agent, formation of 56% homoallylic alcohol **4** and 32% *z*-vinylstannane **5** was observed in the reaction using DCM as solvent (Table 1, entry 1). After significant optimization, we determined that 1.05 equiv of $BF_3{\cdot}OEt_2$ in conjunction with 20 mol % of $B(C_6F_5)_3$ and 2 equiv of

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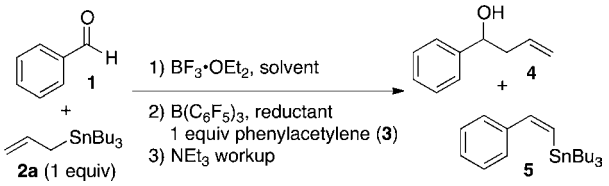
Table 1. Optimization of One-Pot Allylation−Hydrostannation Sequence



entry	$BF_3{\cdot}OEt_2$ (equiv)	solvent	temp (°C)	$B(C_6F_5)_3$ (mol %)	reductant[b] (equiv)	yield 4[c] (%)	yield 5[c] (%)
1	2	DCM	0	10	**A** (1)	56	32
2	2	DCM	0	20	**A** (1)	60	55
3	2	toluene	0	20	**A** (1)	72	65
4	2	toluene	0	100	**A** (1)	12	0
5	2	toluene	0	20	**A** (1.5)	63	85
6	2	toluene	0	0	**A** (1.5)	71	8
7	2	toluene	0	20	**A** (2)	46	76
8	2	toluene	0	30	**A** (1.5)	62	35
9	2	toluene	0	20	**B** (1) + **C** (cat.)	75	62
10	2	toluene	0	20	**B** (2) + **C** (cat.)	71	86
11	2	toluene	0	20	**B** (3) + **C** (cat.)	38	52
12	2	toluene	−35	20	**B** (2) + **C** (cat.)	73	92
13	3	toluene	−35	20	**B** (2)	61	99
14[a]	1.05	toluene	−35	20	**B** (2)	74	93
15[a]	1.05	toluene	−35	20	**B** (2)	78	100

[a]Entries 1−14 were quenched with 2.2 equiv of Et_3N, and entry 15 was quenched with 1.4 equiv of Et_3N. [b]**A** = Et_3SiH, **B** = PMHS, **C** = TBAF. [c]Determined using $Me_3SiOSiMe_3$ as internal standard.

PMHS in toluene at −35 °C followed by quenching the reaction with 1.4 equiv of NEt_3 furnished the highest combined yield of homoallylic alcohol **4** (78%) and vinylstannane **5** (100%) (Table 1). Compound **4** and **5** were isolated in 71% and 99% yield, respectively. Curiously, the hydrostannation result appears to stand in contrast with Yamamoto and co-workers' finding that reactions of $B(C_6F_5)_3$ tend to be inhibited by the presence of PMHS.[15a]

Having achieved a one-pot allylation−hydrostannation protocol where the aldehyde and alkyne moieties were separate, we sought to demonstrate the effectiveness of this protocol on alkynals **6**−**13** (Table 2). Aromatic alkynals **7**, **8**, **10**, and **11** were synthesized from commercially available bromo- or iodo-substituted aromatic aldehydes via Sonogashira coupling with TMS-acetylene followed by K_2CO_3 desilylation.[20] Aliphatic alkynals **12** and **13** were synthesized from the corresponding alkynols via Swern oxidation.[20]

Most of these alkynals responded favorably to the reaction conditions, producing allylation−hydrostannation products in the same reaction pot in fair yields (Table 2). Even though the allylation step of the reaction was fast for all the substrates examined (15−60 min except for entry 9), both sterics and electronics governed the fate of the hydrostannation step.

While hydrostannation of 4-ethynylbenzaldehyde (**6**) was the fastest (1 h) (Table 2, entry 1), the same reaction became increasingly slower when the ethynyl group moved closer to the aldehyde moiety (14 h for **7** and 1 d for **9**). An electron-withdrawing group was tolerated in the reaction (entry 3), albeit requiring a 3 d hydrostannation time. The presence of an electron-donating group inhibited the hydrostannation step (entry 5) as did an *o*-methyl (entry 6). For aliphatic alkynals (**12** and **13**), the second step of the reaction was the slowest (3 d) and yields were lower compared to most of their aromatic counterparts that successfully underwent allylation−hydrostannation. Finally, crotylation of **6** with (*E*)-crotylstannane (**2b**) (entry 9) was slower than the allylation (1.5 h vs 15 min). In all cases, (*Z*)-vinylstannanes were the exclusive or predominant product as reported earlier.[19]

To account for the moderate final product yields in the one-pot reactions and to compare their efficiency against a stepwise protocol, we carried out allylation and hydrostannation of an alkynal in two separate steps. The allylation product from reaction of 4-ethynylbenzaldehyde (**6**) and allylstannane (**2a**) in the presence of $BF_3{\cdot}OEt_2$ was purified and subjected to $B(C_6F_5)_3$-catalyzed hydrostannation with freshly prepared Bu_3SnH without PMHS. The yield of the hydrostannation product eroded (35%) in the stepwise protocol, *and* a 1.4/1 mixture of (*Z*)- and (*E*)-stannanes was produced along with 46% of the starting alkynol.[20] Notably, 71% of this alkynol was recovered when exposed to 20 mol % of $B(C_6F_5)_3$ and 2 equiv of PMHS and only trace amounts of (*Z*)-stannane was observed when freshly prepared Bu_3SnH was added to this mixture. These results indicate that degradation of the alkynol under our conditions does not fully explain the moderate yields of the final products. However, when allylation−hydrostannation product **14** was subjected to a reaction with 1 equiv of allylstannane (**2a**), 1.05 equiv of $BF_3{\cdot}OEt_2$, 20 mol % of $B(C_6F_5)_3$, and 2 equiv of PMHS and the resulting mixture was chromatographed, only 40% **14** was recovered along with protiodestannylated material and other unidentified impurities. This degradation of the final product in the reaction mixture is consistent with the moderate yields of the allylation−hydrostannation products in our one-pot protocol.

In order to show a synthetic application of our one-pot allylation−hydrostannation protocol, we treated compound **17** with I_2 to afford the corresponding vinyl iodide **22**. An unoptimized Pd-catalyzed intramolecular Heck cyclization of crude **22** afforded **23** in 35% yield over two steps (Scheme 1).

As stated earlier, the tin intermediates that form in $BF_3{\cdot}OEt_2$ reactions of allyltributyltin and aldehydes have not been well characterized.[17a−e] Denmark and co-workers have found direct evidence for interaction between the Lewis acid and the allylic

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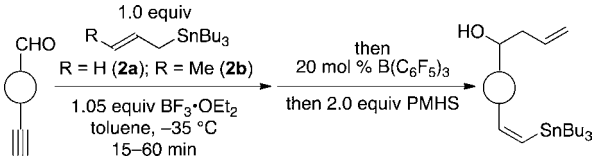
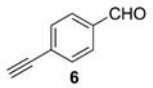
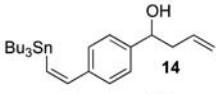
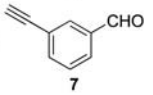
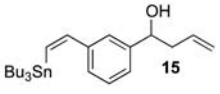
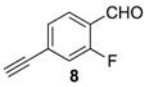
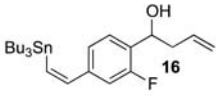
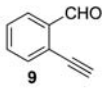
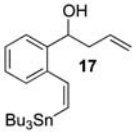
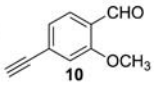
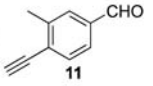
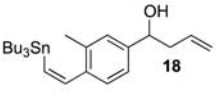
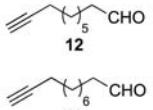
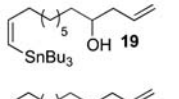
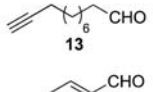
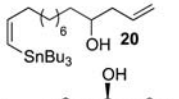
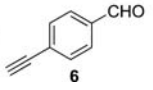
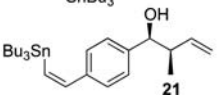
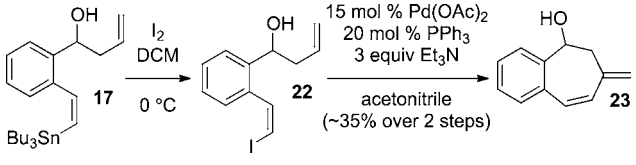
Table 2. One-Pot Allylation–Hydrostannation of Alkynals



entry	alkynal	stannylating agent	product	yield (%)[a]
1		2a		51
2		2a		48
3		2a		50
4		2a		57
5[b]		2a	—	—
6		2a		<7
7		2a		41
8		2a		41
9[c]		2b		38

[a]Yields shown are a two-run average. [b]Allylation–hydrostannation product was not observed. [c]90 min allylation reaction time, *erythro*/*threo* =7/1 based on NMR of crude material; product degradation occurred.

Scheme 1. Synthetic Application of One-Pot Allylation–Hydrostannation



stannane in the presence of the substrate aldehyde and that boryl ethers were the sole products of the allylation reaction and not stannyl ethers.[17b] To the best of our knowledge, there are no reports on $BF_3{\cdot}OEt_2$-mediated allylations being followed by ^{119}Sn and ^{11}B NMR, although such studies have been described for $SnCl_4$[17f] and solvent-mediated[17g] allylstannations.

In an attempt to provide at least some insight into the fate of the tin in $BF_3{\cdot}OEt_2$-mediated allylations and throughout our own allylation–hydrostannation sequence, we monitored the allylation–hydrostannation reaction of **1**, **2a**, and **3** by ^{119}Sn and ^{11}B NMR.[21] In the absence of $BF_3{\cdot}OEt_2$, ^{119}Sn NMR of the reaction mixture of the aldehyde and stannane showed only the characteristic peak for allyltributylstannane (~18 ppm).[22] When $BF_3{\cdot}OEt_2$ was added, a doublet at ~156 ppm (**Intermediate I**) (Figure 1) slowly grew in as the peak at

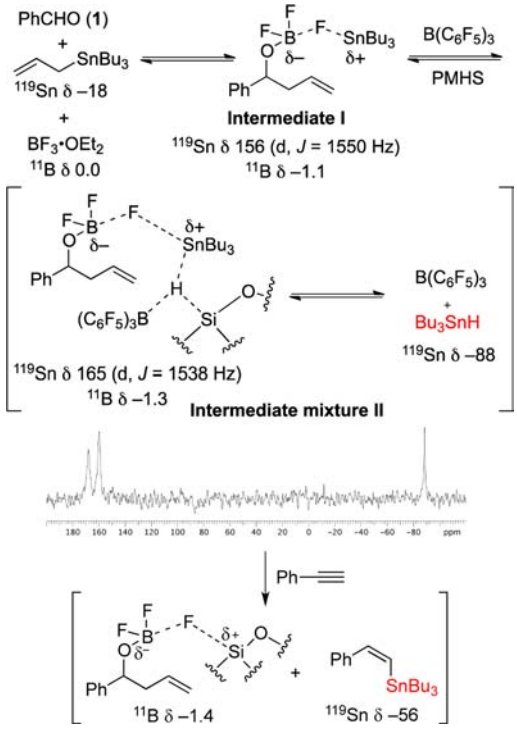


Figure 1. Mechanistic rationale of one-pot allylation–hydrostannation protocol.

~18 ppm diminished. The chemical shift and large coupling constant (J = 1550 Hz) observed for this doublet is consistent with a Sn–F species.[23] The ^{11}B NMR spectrum of **Intermediate I** showed peaks at 0.21 and −1.11 ppm, the latter corresponding to a boryl ether. When $B(C_6F_5)_3$ and PMHS were added to this mixture, the doublet in the ^{119}Sn spectrum shifted to 165 ppm (J = 1538 Hz) and a new peak at −88 ppm was visible corresponding to tributyltin hydride (**Intermediate mixture II**).[22] It should be noted that **Intermediates I** and **II** may not be discrete complexes. Organotin fluorides are rarely monomeric in solution, existing instead as polymeric structures. The relatively broad ^{119}Sn NMR peaks observed for **Intermediates I** and **II** (150–250 Hz line widths vs 5–20 Hz for the discrete vinyltins) suggest that they too may exist as aggregates.

To confirm that the splitting of the peak at 165 ppm in the ^{119}Sn NMR spectrum was due to fluorine, we performed a fluorine-decoupled ^{119}Sn NMR experiment of the mixture. Selective ^{19}F decoupling on the region around −194 ppm resulted in a collapse of the doublet, thereby confirming that the splitting was due to ^{19}F scalar coupling.[20] At this point, ^{11}B NMR showed the presence of another boryl ether at −1.33 ppm. Finally, upon addition of phenylacetylene (**3**), the tributyltin hydride and tin-doublet peaks disappeared and a peak corresponding to vinylstannane **5** appeared at −56 ppm in the ^{119}Sn NMR spectrum. ^{11}B NMR of the mixture revealed resonances at 0.13 and −1.40 ppm, the latter being consistent with presence of another boryl ether.

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Based on our NMR evidence, the following mechanistic rationale is proposed: The aldehyde reacts with allylstannane in the presence of $BF_3{\cdot}OEt_2$ to form a boryl ether and the positive (or partially positive) Sn−F intermediate.[24] PMHS, activated by $B(C_6F_5)_3$,[25] reduces this Sn−F intermediate into tributyltin hydride. Tributyltin hydride then enters the $B(C_6F_5)_3$ catalytic cycle to produce the corresponding vinylstannanes.[19] The NMR data for the Sn−F species indicated that it is not Bu_3SnF, which appears as a triplet at δ −10 ppm with J = 1350 Hz in hexane,[26] or a $Bu_3SnF{\cdot}$ $B(C_6F_5)_3$ adduct, which appears at −18 ppm in toluene.[20] To further eliminate the possibility of Bu_3SnF involvement, hydrostannation of phenylacetylene (**3**) was performed with premade tributyltin fluoride (1 equiv), $B(C_6F_5)_3$ (20 mol %), and PMHS (2 equiv). (*Z*)- and (*E*)-vinylstannanes were produced in almost equal amounts with a combined yield of 11%. The unselective product formation and low yield obtained further support the unlikelihood of Bu_3SnF being reduced to Bu_3SnH in our one-pot protocol.

In summary, we have developed a one-pot allylation−hydrostannation sequence of alkynals where tin waste from the allylation step is successfully recycled for use in the hydrostannation reaction. The unique reagent mix of this one-pot protocol selectively affords (*Z*)-stannanes unlike the *E*/*Z* generating stepwise reaction protocol. The allylation−hydrostannation product of the reaction can be manipulated to more complex molecules. Monitoring the reaction with ^{119}Sn and ^{11}B NMR revealed that a Sn−F intermediate is formed during the $BF_3{\cdot}OEt_2$-mediated reaction between the aldehyde and allyltributylstannane. That Sn−F intermediate is reduced to Bu_3SnH by $B(C_6F_5)_3$-activated PMHS. $B(C_6F_5)_3$ also acts as a catalyst for the subsequent hydrostannation.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and product characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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