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Regioselective hydrostannation of activated alkynes catalyzed by in situ generated copper hydride

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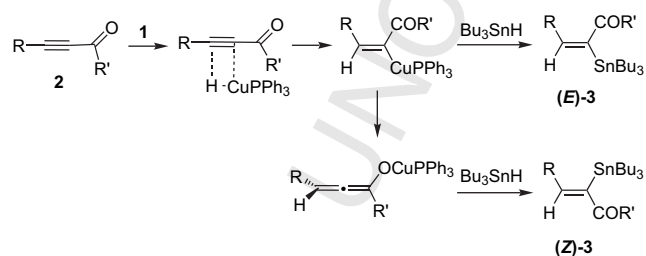
Abstract—The hydrostannation of activated alkynes proceed in good yields and high regioselectivities catalyzed by CuCl, in the presence of potassium *tert*-butoxide, triphenylphosphine, and tributylstannane, by generating copper hydride in situ.

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1. Introduction

The Stille coupling is one of the most extensively utilized palladium-catalyzed carbon–carbon bond forming reactions, and numerous examples of its application in the syntheses of natural products are found.¹ The application of the Stille vinylation reaction is dependent on the availability of vinylstannanes as precursors. Hydrostannation of alkynes is presently the most common way to gain access to vinylstannanes, with palladium complexes being the dominant catalyst for this reaction.

In this connection, we had previously reported on the use of copper as an alternative transition metal catalyst for hydrostannation in the form of hydrido(triphenylphosphine)-copper(I) hydride hexamer, [(Ph₃P)CuH]₆ (**1**),² known popularly as Stryker's reagent.^{3,4} The hydrostannation appears to be initiated by the copper hydride undergoing hydrocupration with an activated alkyne substrate (Scheme 1). Transmetalation of the vinylcopper with tin produces the vinylstannane.



Scheme 1. Hydrostannation catalyzed by **1**.

Keywords: Hydrostannation; Reductions; Stannanes; Catalysis; Regioselectivity.

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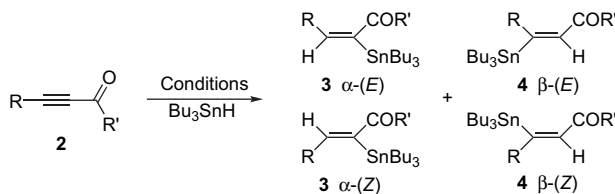
The overall reduction delivers hydride at the electrophilic β-position, resulting in only α-stannylated vinylstannanes with comparable or superior regioselectivity than that obtained in palladium-catalyzed hydrostannations.⁵ This improved selectivity is important and has significant practical advantages, since isomeric vinylstannanes are often hard to separate chromatographically and succumbs to decomposition over time on silica gel.

Although this hydrostannation is more regioselective and economical than palladium for hydrostannation of activated alkynes, it uses discreet copper hydride **1** as catalyst, which needs to be purchased or synthesized in the laboratory.⁶ Thus an alternative protocol using a more common and convenient source of copper for hydrostannation, which still achieves high regioselectivity would be practical and desirable.

2. Results and discussion

Recently we found that copper(I) chloride, with potassium *tert*-butoxide and triphenylphosphine, all of which can be weighed in open air without the aid of a dry box,⁷ directly promotes hydrostannation in the presence of tributylstannane, thus obviating the need to separately prepare, isolate, and purify **1**.

Copper chloride with only KO*t*-Bu or with Ph₃P alone does not promote the hydrostannation. This improved hydrostannation procedure presumably generates the required copper hydride in situ, since CuCl, KO*t*-Bu, and Ph₃P in the presence of hydrogen or hydrosilane are the starting materials for the preparation of **1**. In this improved hydrostannation protocol, the addition of hydrosilane is not required as tin hydride serves both as the reductant as well as the stannylating agent.⁸ The reddish brown color of the reaction mixture generated upon mixing of these reagents bears resemblance to the color of **1**.

Table 1. Hydrostannation of activated alkynes

Entry	Substrate	R	R'	Conditions ^a		
				A: Yield ^b (3:4)	B: Yield ^b (3:4)	C: Yield (3:4)
1	2a	Et	OEt	78% (>20:1) ^c ; E	81% (>20:1) ^c ; E	92% (15:1) ^c ; E
2	2b	TBSOCH ₂	OEt	74% (>20:1) ^c ; E	83% ^d (>20:1) ^c ; E	84% (91:9) ^f ; E
3	2c	<i>n</i> -Bu	OEt	71% (>20:1) ^c ; E	75% ^d (>20:1) ^c ; E	83% (3:1) ^g
4	2d	<i>n</i> -C ₆ H ₁₃	OMe	71% (>20:1) ^c ; E	70% ^d (>20:1) ^c ; E	75% (4:1) ^d
5	2e	<i>n</i> -C ₆ H ₁₃	OEt	78% (>20:1) ^c ; E	71% (>20:1) ^c ; E	
6	2f	<i>n</i> -C ₆ H ₁₃	<i>Oi</i> -Bu	79% (>20:1) ^c ; E	77% ^d (>20:1) ^c ; E	83% (2:1) ^d
7	2g	Ph	OEt	74% (>20:1) ^c ; E/Z=3.1:1 ⁱ	65% (>20:1) ^c ; E/Z=2.4: 1 ⁱ	71% (9:1) ^f ; E
8	2h	Ar ^h	OMe	73% (>20:1) ^c ; E/Z=4.7:1 ⁱ	73% (>20:1) ^c ; E/Z=3.8:1 ⁱ	83% (2.8:1) ^j ; E
9	2i	Et	Me	61% (>20:1) ^c ; Z	55% ^d (>20:1) ^c ; Z	58%; Z ^k
10	2j	<i>n</i> -C ₆ H ₁₃	Me	55% (>20:1) ^c ; Z	48% ^d (>20:1) ^c ; Z	≥61% (not isolated); E ^g
11	2k	<i>n</i> -Bu	Me	73% (>20:1) ^c ; Z	77% (>20:1) ^c ; Z	
12	2l	<i>n</i> -Bu	Et	68% (>20:1) ^c ; E/Z=1:20 ⁱ	69% ^d (>20:1) ^c E/Z=1:7.3	
13	2m	<i>n</i> -Bu	<i>t</i> -Bu	64% (>20:1) ^c ; E/Z=1:4 ⁱ	61% ^d (>20:1) ^c ; E/Z=1:4	

^a Conditions A: 10% CuCl, 10% KO^{*t*}-Bu, 15% Ph₃P, 1.5 equiv Bu₃SnH, PhMe; conditions B: 10% **1**, 1.5 equiv Bu₃SnH, PhMe; conditions C: 10% Pd(PPh₃)₄, 1.5 equiv Bu₃SnH.

^b Isolated yields after chromatography.

^c Only regioisomer **3** observed by ¹H NMR of the crude product mixture.

^d Ref. 2a.

^e Ref. 9a.

^f Ref. 9b.

^g Ref. 9c.

^h Ar=5-benzo[1,3]dioxo-.

ⁱ Ratio of *E/Z* isomers determined from ¹H NMR of the crude product mixture.

^j Ref. 9d.

^k Ref. 9e.

The reaction conditions for hydrostannation were explored for **2a** using 10% CuCl, 10% KO^{*t*}-Bu while varying the amount of Ph₃P (Table 1). At 10, 15, 20, and 30 mol % Ph₃P, the yields of **3a** obtained were 65%, 78%, 71%, and 52%, respectively, after about 30 min of reaction. The lower yield at 30 mol % Ph₃P is due to a slower rate of reaction, resulting in incomplete reaction of **2a** after 30 min, while conversions were complete at 10, 15, and 20 mol % Ph₃P.

Using these optimized conditions, the hydrostannation of various alkynes catalyzed by 10% CuCl/10% KO^{*t*}-Bu/15% Ph₃P (conditions A), by 10% **1** (conditions B), and by catalytic palladium (conditions C) were compared (Table 1). Notably, the results of the present hydrostannation catalyzed by the in situ generated copper hydride (conditions A) provide vinylstannanes with similar yields and regioselectivities to hydrostannation catalyzed by **1** (conditions B). Exclusive α -stannation was observed for all acetylenic substrates without exception, showing again similar or superior regioselectivity compared to palladium-catalyzed hydrostannation (conditions C), although the latter reaction system is clearly more reactive and the corresponding reaction time is shorter. Under conditions A, some destannylation was observed as a side reaction.

Entries 1–8 (Table 1) show the results of the hydrostannation of acetylenic esters. α -Stannation in all cases was exclusive in the copper-catalyzed hydrostannation to give vinylstannanes **3a–h**, and this stands in contrast to the palladium-

catalyzed reaction, where β -stannylated vinylstannanes **4a–h** in yields varying from 6–33% were produced as mixtures with **3a–h**.

Aryl-substituted alkynes have not been previously examined in the hydrostannation catalyzed by **1** and thus alkynoates **2g** and **2h** are included in the present study. It was found that, while copper-catalyzed hydrostannation of **2g** still generated exclusively α -stannated vinylstannane **3g**, it was obtained as a 3:1 mixture of *syn*- and *anti*-hydrostannated (*E*)-**3g** and (*Z*)-**3g** (entry 7). Similarly, both (*E*)-**3h** and (*Z*)-**3h** were obtained from the reaction of **2h** (entry 8). The two modes of addition presumably resulted from initially a *syn* hydrometallation, followed by an isomerization of the vinyl organometallic via a putative allenolate to the *anti*-hydrometallated product (Scheme 1). Apparently, in both of the copper-catalyzed hydrostannation reactions, this isomerization is facilitated by aryl groups in conjugation (R=Ph, 5-benzo[1,3]dioxo-). In the palladium-catalyzed hydrostannation of acetylenic esters, although mixtures arising from non-regioselective stannylation were obtained, isomerization resulting in *syn*- and *anti*-hydrometallated products was not observed.

Entries 9–13 (Table 1) show the hydrostannation of acetylenic ketones. Acceptable yields of α -stannated vinyl ketones **3** were obtained despite the sensitivity of these compounds to protodestannylation.¹⁰ For methyl acetylenic ketones **2i–k** (R'=Me), both copper and palladium catalyzed-hydrostannation resulted in full isomerization to give exclusively the

anti-hydrometallated product (*Z*)-**3i–k**. Other ketones showed incomplete isomerization, although (*Z*)-**3** was the major vinylstannane in all cases. The degree of isomerization appears to be inversely correlated to increasing steric bulk about the ketone (entries 11–13). Comparing the results of the two copper-catalyzed hydrostannations, conditions A tended to result in more isomerization to (*Z*)-**3** than conditions B (entry 12).

3. Conclusion

We have described an improved protocol for copper-catalyzed hydrostannation using copper hydride generated in situ from CuCl, KO*t*-Bu, Ph₃P, and tin hydride reacting as the reductant as well as the stannylating agent. The advantages of this method over the previous hydrostannation catalyzed by Stryker's reagent is that **1** does not need to be synthesized separately, and all the precursors could be handled without a dry box, making this an operationally more convenient way to execute the copper-catalyzed hydrostannation, yet delivering the same highly regioselective α -stannation products. Under these reaction conditions, alkynoates undergo regioselective *syn* hydrostannation, except for aryl-substituted alkynoates, which undergo some isomerization to yield both *syn* and *anti* hydrostannation products. Alkynones are regioselectively α -stannated to yield predominantly the products of *anti* hydrostannation. This methodology represents a more economical and selective alternative to palladium-catalyzed hydrostannation, especially for larger scale reactions.

4. Experimental

4.1. General

¹H and ¹³C NMR spectra were recorded in CDCl₃ with tetramethylsilane as an internal standard at ambient temperature on a Bruker DPX 300 or Avance 400 FT spectrometer operating at 300 MHz or 400 MHz for ¹H and 75 MHz or 100 MHz, respectively, for ¹³C. All spectra were calibrated at δ 7.26 or δ 0.00 ppm for ¹H and δ 77.03 for ¹³C. Both *J* (¹¹⁷SnH) and *J* (¹¹⁹SnH), and *J* (¹¹⁷SnC) and *J* (¹¹⁹SnC) values have been reported when the ¹¹⁷Sn and ¹¹⁹Sn satellite peaks are clearly distinct. Otherwise the indicated value of *J*_{SnH} and *J*_{SnC} must be considered as an approximate mean value of *J* (¹¹⁷SnH) and *J* (¹¹⁹SnH) due to overlap of the satellite peaks. IR absorption spectra were recorded as a solution in CH₂Cl₂ on a Bio-Rad FT 165 Spectrophotometer from 4000 to 400 cm⁻¹ with subtraction of peaks for the solvent. Mass spectra were obtained from a Finnigan MAT 95 mass spectrometer for both low resolution and high resolution, with accurate mass reported for the molecular ion (M⁺) or the next largest fragment thereof.

Reactions were performed in oven-dried glassware under argon using standard inert atmosphere techniques. Flash column chromatography was performed on E. Merck silica gel 60 (230–400 mesh ASTM).

Toluene was distilled from CaH₂ and degassed before use. [(Ph₃P)CuH]₆ (**1**) was synthesized,^{6b} then stored, and

weighed inside a dry box. Tributyltin hydride and methyl 2-butyrate (**2a**) are used as received. Vinylstannanes (*E*)-**3b**,^{2a} (*E*)-**3c**,^{9b} (*E*)-**3d**,^{9b} (*E*)-**3f**,^{9b} (*E*)-**3g**,^{9b} (*E*)-**3h**,^{9d} (*Z*)-**3h**,^{9c} (*Z*)-**3i**,^{9b,c} (*Z*)-**3j**,^{9b} (*Z*)-**3l**,^{9b} (*E*)-, and (*Z*)-**3m**,^{9b} have been previously reported.

4.2. General procedure for hydrostannation

CuCl (0.10 mmol), Ph₃P (0.15 mmol), and then KO*t*-Bu (0.1 mmol) are weighed out into a dry flask, which was then alternately evacuated and refilled with argon three times. The flask is charged with dry, degassed toluene (2 mL) under argon. The reaction mixture darkens in color upon stirring for 5 min at room temperature. To this is added Bu₃SnH (1.5 mmol) with stirring while the reaction mixture takes on a reddish brown color. (This is the characteristic color of active copper hydride reagent; and with inferior quality of Bu₃SnH, this color is not observed, and the consequent hydrostannation is also low yielding.) The alkyne (1.0 mmol) is then added as a solution in dry, degassed toluene (0.5 mL). The reaction mixture changes to dark brownish black and stirring is continued at room temperature while the reaction is being monitored by TLC. When the substrate has been fully consumed (~0.5 h), the solvent is removed in vacuo, and the residue is analyzed by ¹H NMR spectroscopy to record the ratio of components by integration. Then the crude material is purified quickly by flash chromatography on a short column of Et₃N-pretreated silica gel to afford the product.

4.2.1. (E)-Ethyl 2-tributylstannylpent-2-enoate (3a). Colorless oil; *R*_f (5% EtOAc/Hex)=0.71; ¹H NMR (CDCl₃, 400 MHz): δ 6.02 (t, ³*J*_{HH}=7.0 Hz, ³*J*_{SnH}=62.1/59.7 Hz, 1H), 4.13 (q, *J*=7.2 Hz, 2H), 2.42 (dq, *J*=7.3, 7.2 Hz, 2H), 1.50–1.45 (m, 6H), 1.32–1.24 (m, 9H), 1.02 (t, *J*=7.5 Hz, 3H), 0.95–0.91 (m, 6H), 0.87 (t, *J*=7.2 Hz, 9H) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ 171.4, 154.6 (²*J*_{SnC}=11.2 Hz), 134.7, 59.7, 28.7 (²*J*_{SnC}=19.8 Hz), 27.1 (³*J*_{SnC}=58.3 Hz), 25.1 (³*J*_{SnC}=40.2 Hz), 14.2, 13.6, 13.4, 10.0 (¹*J*_{SnC}=345.6/330.2 Hz) ppm; IR (CH₂Cl₂): 2967, 2928, 2872, 2851, 1698 (C=O), 1602, 1463, 1379, 1367 cm⁻¹; LRMS (EI, 20 eV) *m/z* (relative intensity): 361 ([M⁺-C₄H₉], 100), 317 (65), 315 (53), 261 (21). HRMS (EI) *m/z* calcd for C₁₅H₂₉O₂Sn [M⁺-C₄H₉]: 361.1190, found: 361.1183.

4.2.2. (E)-Ethyl 2-tributylstannylnon-2-enoate (3e). Colorless oil; *R*_f (10% EtOAc/Hex)=0.69; ¹H NMR (CDCl₃, 300 MHz): δ 6.04 (t, ³*J*_{HH}=7.1 Hz, ³*J*_{SnH}=62.3/59.9 Hz, 1H), 4.14 (q, *J*=7.1 Hz, 2H), 2.46–2.38 (dt, *J*=7.2, 7.0 Hz, 2H), 1.54–1.43 (m, 8H), 1.34–1.25 (m, 15H), 0.98–0.86 (m, 18H) ppm; ¹³C NMR (CDCl₃, 75 MHz): δ 171.6, 154.0 (²*J*_{SnC}=11.2 Hz), 135.9, 60.3, 32.2 (³*J*_{SnC}=39.6 Hz), 32.0, 29.6, 29.3 (²*J*_{SnC}=20.0 Hz), 27.6 (³*J*_{SnC}=57.7 Hz), 22.9, 14.8, 14.4, 14.0, 10.6 (¹*J*_{SnC}=345.1/329.8 Hz) ppm; IR (CH₂Cl₂): 2961, 2929, 2872, 2855, 1694 (C=O), 1602, 1465, 1377, 1367, 1348 cm⁻¹; LRMS (EI, 20 eV) *m/z* (relative intensity): 417 ([M⁺-C₄H₉], 100), 373 (69), 371 (35), 369 (27). HRMS (EI) *m/z* calcd for C₁₉H₃₇O₂Sn [M⁺-C₄H₉]: 417.1818, found: 417.1819.

4.2.3. 3-Phenyl-2-tributylstannylacrylic acid methyl ester (3g). (*E*)-**3g** and (*Z*)-**3g** were obtained as an inseparable 4.7:1 mixture. (*E*)-**3g**: distinguishable peaks: ¹H NMR

(CDCl₃, 300 MHz): δ 6.73 (s, $^3J_{\text{SnH}}=59.3/58.2$ Hz, 1H), 4.19 (q, $J=7.1$ Hz, 2H), 1.21 (t, $J=7.1$ Hz, 6H), 0.93 (t, $J=7.3$ Hz, 9H) ppm. The characterization corresponded to that reported in the literature.^{9d} (Z)-**3g**: distinguishable peaks: ¹H NMR (CDCl₃, 300 MHz): δ 8.40 (s, $^3J_{\text{SnH}}=103.3/98.9$ Hz, 1H), 7.39–7.22 (m, 5H), 4.27 (q, $J=7.1$ Hz, 2H) ppm.

4.2.4. (Z)-3-Tributylstannyloct-3-en-2-one (3k). Colorless oil; $R_f=0.6$ (CH₂Cl₂/Hex=1:1); ¹H NMR (CDCl₃, 300 MHz): δ 7.17 (t, $^3J_{\text{HH}}=7.3$ Hz, $^3J_{\text{SnH}}=116.9/111.9$ Hz, 1H), 2.27 (s, 3H), 2.22 (dt, $J=7.4, 7.2$ Hz, 2H), 1.50–1.26 (m, 16H), 0.99–0.85 (m, 18 H) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ 204.6, 156.5, 148.9, 33.9, 31.3, 28.9 ($^2J_{\text{SnC}}=19.5$ Hz), 27.1 ($^3J_{\text{SnC}}=60.8$ Hz), 25.6, 22.4, 13.8, 13.5, 11.3 ($^1J_{\text{SnC}}=345.0/329.6$ Hz) ppm; IR (CH₂Cl₂): 2961, 2922, 2872, 2861, 1669 (C=O), 1618, 1519, 1464, 1368, 1274 cm⁻¹; LRMS (EI, 20 eV) m/z (relative intensity): 359 ([M⁺-C₄H₉], 18), 293 (31), 291 (29). HRMS (EI) m/z calcd for C₁₆H₃₁OSn [M⁺-C₄H₉]: 359.1397, found: 359.1388.

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