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Copper-Catalyzed Hydrostannation of Activated Alkynes

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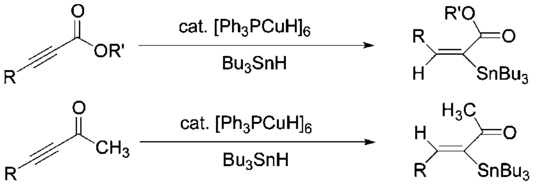
ABSTRACT



exclusive α-stannation

$[(Ph_3P)CuH]_6$ effectively catalyzes the hydrostannation of activated alkynes with exclusive regioselectivity for α-stannation. Syn hydrostannation is observed exclusively for alkynoates. Anti or syn hydrostannation adducts are obtained as products for alkynone substrates.

While a variety of palladium-catalyzed carbon−carbon bond forming reactions have been developed, the Stille reaction remains as one of the most extensively utilized processes, and examples of these reactions of functionalized vinylstannanes in the syntheses of natural products abound.[1]

The success of the Stille vinylation reaction is intimately dependent on the ability to acquire vinylstannanes of high purity.[2] The challenge in the synthesis of vinylstannanes is to directly produce these compounds with high regio- and stereoselectivity, because diastereomeric mixtures of vinylstannanes are typically very nonpolar and tedious to separate. Moreover, silica gel column chromatography is not well-tolerated by vinylstannanes and prolonged adsorption on silica leads to eventual decomposition and diminished returns.

Currently, the most commonly used strategy to synthesize vinylstannanes is the hydrostannation of alkynes.[3] Hydrostannations of alkynes have been mediated by various transition metals, including Mo,[4] Rh,[5] Ni,[5,6] Co,[5] Pt,[5] Ru,[5] and Pd, with Pd being the most popular metal catalyst.[4a,7] Although palladium- or molybdenum-catalyzed hydrostannations of alkynes occur efficiently in very good yields, the direction provided by the steric and electronic factors of alkyne substrates is often insufficiently high, resulting in diastereomeric mixtures of vinylstannanes as products. For activated alkynes, although the regioselectivity favors α-stannation, this is frequently accompanied by the formation of a minor, β-stannated vinylstannane.[8] Therefore, finding new

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[1] Some recent examples: (a) Overman, L. E.; Peterson, E. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 2525. (b) Nicolaou, K. C.; Li, Y.; Sugita, K.; Monenschein, H.; Guntupalli, P.; Mitchell, H. J.; Fylaktakidou, K. C.; Vourloumis, D.; Giannakakou, P.; O'Brate, A. *J. Am. Chem. Soc.* **2003**, *125*, 15443. (c) Lebsack, A. D.; Link, J. T.; Overman, L. E.; Stearns, B. A. *J. Am. Chem. Soc*. **2002**, *124*, 9008. (d) Trost, B. M.; Gunzner, J. L.; Dirat, O.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 10396. (e) Fuwa, H.; Kainuma, N.; Tachibana, K.; Sasaki, M. *J Am Chem Soc.* **2002**, *124*, 14983. (f) Govek, S. P.; Overman, L. E. *J. Am. Chem. Soc*. **2001**, *123*, 9468. (g) White, J. D.; Carter, R. G.; Sundermann, K. F.; Wartmann, M. *J. Am. Chem. Soc.* **2001**, *123*, 5407.

[2] (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Davies, A. G. *Organotin Chemistry*; Wiley-VCH: Weinheim, Germany, 2004. (c) Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworth: London, UK, 1987. (d) Orita, A.; Otera, J. In *Main Group Metals in Organic Synthesis*; Yamamoto, H., Oshima, K., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Chapter 12, p 621.

[3] Smith, N. D.; Mancuso, J.; Lautens, M. *Chem. Rev.* **2000**, *100*, 3257.

[4] (a) Zhang, H. X.; Guibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857. (b) Kazmaier, U.; Schauss, D.; Pohlman, M. *Org. Lett.* **1999**, *1*, 1017. (c) Kazmaier, U.; Pohlman, M.; Schauss, D. *Eur. J. Org. Chem.* **2000**, 2761.

[5] Kikukawa, K.; Umekawa, H.; Wada, F.; Matsuda, T. *Chem. Lett.* **1988**, 881.

[6] Bamba, M.; Nishikawa, T.; Isobe, M. *Tetrahedron Lett.* **1996**, *37*, 8199.

[7] (a) Ichinose, Y.; Oda, H.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3468. (b) Miyake, H.; Yamamura, K. *Chem. Lett.* **1989**, 981. (c) Rossi, R.; Carpita, A.; Cossi, P. *Tetrahedron Lett.* **1992**, *33*, 4495. (d) Cochran, J. C.; Bronk, B. S.; Terrence, K. M.; Phillips, H. K. *Tetrahedron Lett.* **1990**, *31*, 6621.

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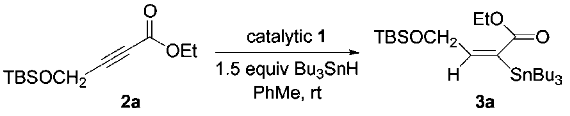
catalysts and conditions to achieve more selective hydrostannations of alkynes remains a challenge with implications for the applications of the Stille coupling reaction in total synthesis.

We disclose herein a novel, regioselective hydrostannation reaction of activated alkynes catalyzed by Stryker's reagent $[(Ph_3P)CuH]_6$ (**1**).[9,10] At 1 mol % catalysis, **1** mediates hydrostannation with exclusive α-stannation. With respect to conventional catalysis by palladium, copper-catalyzed hydrostannation typically generates vinylstannanes with comparable yields but higher regioselectivities, and is a useful, alternative method for the selective synthesis of vinylstannanes.

In the course of our investigations on the copper-catalyzed reductive aldol cyclization reaction,[11] we found that **1** efficiently catalyzed the syn addition of Bu_3SnH to alkynyl esters such as **2a** (Table 1).[12,13] Stryker's reagent (**1**), a copper(I) hydride complex,[14] was found to be an effective catalyst, whereas other copper complexes, including CuCl, CuBr, CuCN, $Cu(OAc)_2$, $Cu(acac)_2$, and $Cu(PF_4)MeCN$,[15] did not facilitate hydrostannation to any great extent. To the best of our knowledge, this is the first report in the literature of copper as a transition metal for the catalysis of hydrostannation.[16] (*E*)-α-Tributylstannanylbut-2-enoate **3a** was obtained as the sole stannylated product, with no (*Z*)-diastereomer or *β*-stannylation product **4a** observed (Figure 1). The only side product detected (<10%) was the saturated ester **5a**.

Table 1. Hydrostannation of **2a** with Various Amounts of **1**



entry	mol % of **1**[a]	yield of **3a** (%)
1	1	81
2	5	81
3	10	83
4	50	50
5	100	44

[a] mol % calculated on the basis of Cu.

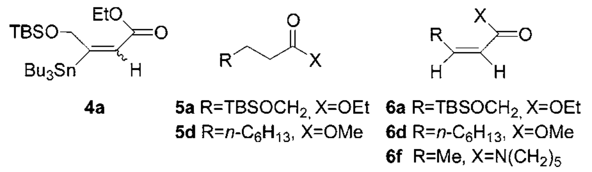
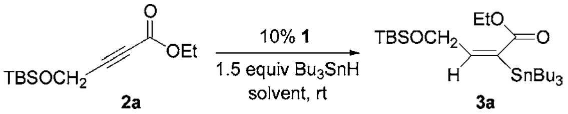


Figure 1. Side products of hydrostannation.

Catalyst levels of 1−10 mol % of **1** were found to be effective in mediating hydrostannation of **2a** (Table 1, entries 1−3). However, high levels of catalyst resulted in decreased yields of the hydrostannation product **3a**, with a concomitant accumulation of saturated ester **5a** (Table 1, entries 4−5). Ester **5a** is presumably derived from the conjugate reduction of destannylated alkenoate **6a** by **1**. This is consistent with previous observations which suggested that **1** quenches and reduces vinylcopper intermediates.[10d] The reduction of the intermediate by **1** can also account for some destannylation that always accompanies hydrostannation.[17]

A study of the hydrostannation reaction of alkynoate **2a** with respect to solvent effects was conducted (Table 2). Toluene was a good solvent for this reaction, as had been found in many other reactions involving **1**. Other solvents tried led to satisfactory but inferior yields.

Table 2. Hydrostannation of **2a** in Various Solvents



entry	solvent	yield of **3a** (%)
1	PhMe	83
2	PhH	76
3	cyclohexane[a]	64
4	THF	76
5	CH_2Cl_2	76
6	MeCN:PhMe (1:1)[b]	78

[a] **1** was moderately soluble in C_6H_{12}. [b] **1** was insoluble in neat MeCN.

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(8) On occasion, the diastereomeric mixture of vinylstannanes had to be used in the synthesis because the isomers were inseparable, see: Rossi, R.; Carpita, A.; Cossi, P. *Synth. Commun.* **1993**, *23*, 143.

(9) Stryker's reagent (**1**) is commercially available, and is also conveniently prepared in the laboratory: (a) Brestensky, D. M.; Stryker, J. M. *Tetrahedron Lett.* **1988**, 29, 3749. (b) Chiu, P.; Li, Z.; Fung, C. M. *Tetrahedron Lett.* **2003**, 44, 455. (c) Lee, D.; Yun, J. *Tetrahedron Lett.* **2005**, 46, 2037.

(10) (a) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291. (b) Mahoney, W. S.; Stryker, J. M. *J. Am. Chem. Soc.* **1989**, *111*, 8818. (c) Brestensky, D. M.; Stryker, J. M. *Tetrahedron Lett.* **1989**, *30*, 5677. (d) Daeuble, J. F.; McGettigan, C.; Stryker, J. M. *Tetrahedron Lett.* **1990**, *31*, 2397. (e) Koenig, T. M.; Daeuble, J. F.; Brestensky, D. M.; Stryker, J. M. *Tetrahedron Lett.* **1990**, *31*, 3237.

(11) (a) Chiu, P.; Leung, S. K. *Chem. Commun.* **2004**, 2308. (b) Chiu, P.; Chung, W. K. *Synlett* **2005**, 55. (c) Chiu, P.; Szeto, C. P.; Geng. Z.; Cheng, K. F. *Org. Lett.* **2001**, *3*, 1901. (d) Chiu, P.; Chen, B.; Cheng, K. F. *Tetrahedron Lett.* **1998**, *39*, 9229.

(12) The cis-reduction of unactivated alkynes with stoichiometric and catalytic **1** has been reported: ref 10d. High reaction temperatures (ambient to 80 °C) and catalyst loadings (~50 mol %) were required for these reductions.

(13) Bu_3SnH has stoichiometrically induced the conjugate reduction of activated olefins under catalysis by **1**: Lipshutz, B. H.; Keith, J.; Papa, P.; Vivian, R. *Tetrahedron* **1998**, *39*, 4627.

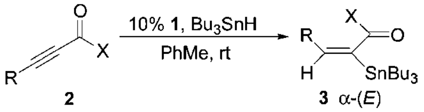
(14) Hexameric **1** exists as lower aggregates in solution; the monomers or dimers are likely to be the actual catalytic species.

(15) The copper complexes were not very soluble in PhMe or THF; $Cu(PF_4)MeCN$, though soluble in MeCN, also did not catalyze hydrostannation.

(16) However, Cu(I) is a common transition metal catalyst for the related stannylmetalation reaction: (a) Hibino, J.; Matsubara, S.; Morizawa, Y.; Oshima, K. *Tetrahedron Lett.* **1984**, *25*, 2151. (b) Aksela, R.; Oehlschlager, A. C. *Tetrahedron* **1991**, *47*, 1163.

Having surveyed the reaction conditions, the hydrostannation of other alkynyl esters was investigated (Table 3).

Table 3. Hydrostannation of Alkynyl Esters and Amides Catalyzed by **1**



entry	substrate	yield of **3** (%)	comparison with cat. Pd, % yield (**3**:**4**)
1	**2a** (R = TBSOCH$_2$, X = OEt)	83	86−92 (>10:1)[a]
2	**2b** (R = Me, X = OMe)	62	67 (5:1)[b] 79 (2.8:1)[c]
3	**2c** (R = *n*-Bu, X = OEt)	75	83 (3:1)[d]
4	**2d** (R = *n*-C$_6$H$_{13}$, X = OMe)	70	75 (4:1)[c]
5	**2e** (R = *n*-C$_6$H$_{13}$, X = O*i*-Bu)	77	83 (2:1)[c]
6	**2f** (R = Me, X = N(CH$_2$)$_5$)	41[e]	87 (>10:1)[c]

[a] Reference 7c. [b] Reference 7d. Me$_3$SnH used instead of Bu$_3$SnH. [c] Ratio determined by integration of the ^{1}H NMR of the mixture. [d] Reference 4a. [e] 17% of **6f** and 28% of unreacted **2f** recovered.

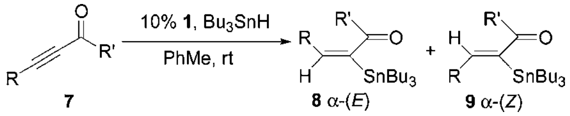
The hydrostannations catalyzed by **1** are generally complete within 1 h at room temperature. As in palladium-catalyzed hydrostannations, only syn adducts are formed in comparably good yields.[18] However, compared to Pd- or Mo-catalyzed hydrostannations, the selectivity for α-stannation was superior, and in fact exclusive under catalysis by **1**. Even for the challenging case of an alkynyl ester bearing a bulky OR′ group (Table 3, entry 5), in which directions by steric and electronic factors are working in opposition, the hydrostannation catalyzed by **1** showed exclusive selectivity for stannation at the α-position, compared to a dramatic decrease in the regioselectivity in the palladium-catalyzed hydrostannation.

An alkynyl amide **2f** was hydrostannated also with excellent regioselectivity, but at a very slow reaction rate (Table 3, entry 6). After 18 h, only a 41% yield of **3f** was obtained, with 28% of the starting material being recovered. With this particular substrate, the Pd-catalyzed hydrostannation was much more efficient.

To explore the scope of the reaction further, we then examined the hydrostannation of alkynyl ketones **7** (Table 4). These studies are technically more challenging due to the known vulnerability of stannylated enone products to decomposition by protodestannylation.[4a] Under palladium catalysis, syn and anti hydrostannation of alkynyl ketone substrates have been reported, the selectivity for α-stannation being good to exclusive (Table 4, entries 1 and 2).[19]

Under catalysis by **1**, high regioselectivity for α-stannation is maintained in the hydrostannation of alkynones (Table 4).

Table 4. Hydrostannation of Alkynyl Ketones Catalyzed by **1**



entry	substrate	yield of **8** + **9** (**8**:**9**)	comparison with cat. Pd, % yield (**8**:**9**)
1	**7a** (R = Et, R′ = Me)	55 (0:100)	58 (0:100)[a]
2	**7b** (R = *n*-C$_6$H$_{13}$, R′ = Me)	48 (0:100)	0 (100:0)[b]
3	**7c** (R = *n*-Bu, R′ = Et)	69 (12:88)[c,e]	
4	**7d** (R = *n*-Bu, R′ = *t*-Bu)	61 (21:79)[d,e]	

[a] Reference 7d. Me$_3$SnH used instead of Bu$_3$SnH. [b] Reference 4a, total destannylation occurred upon isolation, but in situ DIBAL-H reduction gave the alcohol derived from **8a** in 61% yield. [c] **8c** could not be obtained pure. [d] **8d/9d** could not be separated. [e] Ratios were determined by integration of the ^{1}H NMR spectra of the product mixtures, see the Supporting Information.

No β-stannation was observed for any of the alkynones examined. The major stannylated enone diastereomers resulted from the anti addition of Bu$_3$SnH, in contrast to the syn-selective hydrostannation of alkynyl esters and amides. While syn and anti addition of tin hydride were reported for the palladium-catalyzed hydrostannation of **7a** and **7b**, respectively,[4a,7d] anti hydrostannation was found for both substrates under catalysis by **1**. Syn and anti addition appears to be governed in part by the steric demands of the R′ group (Table 4, entries 3 and 4). Increasing the steric bulk of R′ corresponded to increased addition via the syn mode. Protodestannylation on silica gel was mainly responsible for the lower yields of products.

The alkynes that undergo hydrostannation in the presence of **1** are electron-deficient, activated alkynes.The hydrostannation of unpolarized alkynes, e.g., diphenylacetylene, fails altogether under catalysis by **1** returning only unreacted starting materials.[20]

The excellent regioselectivity of the hydrostannation catalyzed by **1** for α-stannation correlates to the concomitant regioselective delivery of hydride to the electron-deficient β-position. The active species reacting with the alkyne is presumably more polarized and hydridic in nature than the corresponding palladium hydrides. The failure to induce hydrostannation of unactivated alkynes, and the attenuated reactivity toward the less electrophilic alkynyl amides further support the regiochemical pathway being dominated by hydride addition.

The observation that the treatment of a red solution of **1** with Bu$_3$SnH induces a color change from red to dark brown infers the disappearance of **1** and the formation of a new species. Since the chemistry of the new catalytic species parallels the reactivity of **1** as a hydride source for the reduction of activated alkenes and alkynes, it is possible that the active species resembles copper hydrides.[21]

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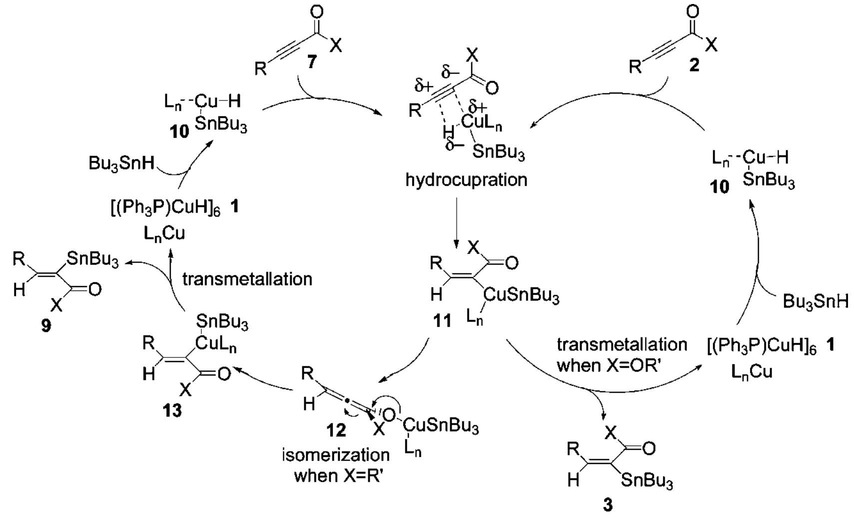
(17) Reduced esters **5d** and **6d** were detected in the course of the hydrostannation of **2d** catalyzed by **1** in anhydrous C$_6$D$_6$ as monitored by ^{1}H NMR.

(18) The configurations of vinylstannanes were elucidated by ^{1}H NMR spectroscopy. The $^3J_{\mathrm{SnH}}$ values for cis and trans H−C=C−Sn bonds are 58−62 and 112−118 Hz, respectively.

(19) For the same propargyl ketone HC≡CCOMe, a 51% yield of 1:1 *E*:*Z* α-stannated products by cat. Pd/Me$_3$SnH (ref 7d) and a 65% yield of 82:18 α:β stannation by cat. Pd/Bu$_3$SnH (ref 4a) have been reported.

Scheme 1. Proposed Mechanism for the Hydrostannation of Alkynones and Alkynoates Induced by **1**



We propose that the Cu-catalyzed hydrostannation follows a hydrometalation mechanism (Scheme 1). Thus **1** enters the catalytic cycle and reacts with Bu_3SnH to generate the catalytic species **10**, a stannylated copper hydride. Hydrocupration by **10** occurs as directed by the polarization of the triple bond. When the substrate is an alkynyl ester (X = OR′), transmetalation then takes place in the (*E*)-vinylcopper intermediate **11**, thereby producing the vinylstannane, and regenerating the copper catalyst to complete the cycle.

For alkynones, the (*E*)-vinylcopper intermediate **11** (X = R′) isomerizes to the (*Z*)-vinylcopper intermediate **13** before transmetalation to tin to give **9**.[22] This pathway is made kinetically viable by the electron-withdrawing ability of the ketone via the formation of allenolate **12**, and thermodynamically favorable by the alleviation of 1,3-allylic strain between the alkanoyl group and the R group in the (*E*)-intermediate **11**. The appearance of (*E*)-**8c** and (*E*)-**8d** infers the relative stabilities of their precursors **11**, and may reflect decreased facility of isomerization to the allenolate **12** with increasing steric demands of R′.

We have described a novel copper-catalyzed hydrostannation of alkynoates which produces high yields of single diastereomers of (*E*)-α-stannylated alkenoates. Hydrostannation of alkynones catalyzed by **1** occurs with superior diastereoselectivities compared with the Pd-catalyzed process. This method complements the selectivity of stannylcupration reactions for both (*E*)- and (*Z*)-*β*-stannylated alkenoates,[22] and should find use in the preparation of this class of vinylstannanes. Further investigations on the scope and mechanism of this reaction are being pursued.

Acknowledgment. This work is supported by the University of Hong Kong (CRCG), and by a grant from the Research Grants Council of Hong Kong SAR, P. R. China (Project No. HKU 7102/02P). S.K.L. thanks the University of Hong Kong for a conference travel grant.

Supporting Information Available: Experimental procedures, full characterization, and ^{1}H, ^{13}C NMR spectra for **2e**, **3a**−**f**, **7b**,**c**, and **9a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Complex mixtures of vinylstannane isomers and reduction products were obtained for propargylic alcohol derivatives, unactivated alkyl and aryl alkynes.

(21) However, the possibility of the active species being dimeric “$Ph_3PCuH_2SnBu_3$”, as suggested by one reviewer, cannot be precluded.

(22) Piers, E.; Morton, H. E. *J. Org. Chem.* **1980**, *45*, 4263.