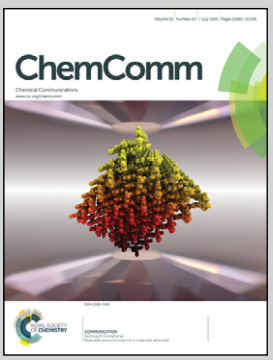
Title	Copper-catalyzed α-selective hydrostannylation of alkynes for the synthesis of branched alkenylstannanes
Auther(s)	Yoshida, H.; Shinke, A.; Kawano, Y.; Takaki, K.
Citation	Chemical Communications , 51 : 10616 - 10619
Issue Date	2015-04-27
DOI	10.1039/c5cc02720a
Self DOI	
URL	http://ir.lib.hiroshima-u.ac.jp/00048771
Right	This journal is © The Royal Society of Chemistry 2015. This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.
Relation	

Showcasing research from Dr Hiroto Yoshida's Laboratory/ Department of Applied Chemistry, Hiroshima University, Japan

Copper-catalyzed α-selective hydrostannylation of alkynes for synthesis of branched alkenylstannanes

A variety of branched alkenylstannanes can directly be synthesized depending upon the α-selective hydrostannylation of terminal alkynes by use of a distannane or a silylstannane under copper catalysis.

As featured in:



See H. Yoshida *et al.*, *Chem. Commun.*, 2015, **51**, 10616.

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Registered charity number: 207890

ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2015, **51**, 10616

Received 1st April 2015,
Accepted 24th April 2015

DOI: 10.1039/c5cc02720a

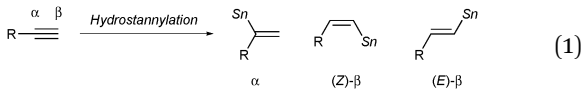
www.rsc.org/chemcomm

Copper-catalyzed α-selective hydrostannylation of alkynes for the synthesis of branched alkenylstannanes†

H. Yoshida,*[ab] A. Shinke,[a] Y. Kawano[a] and K. Takaki[a]

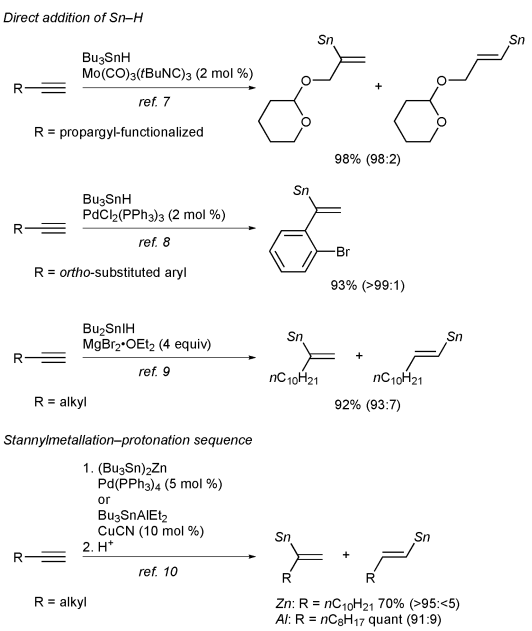
A variety of branched alkenylstannanes can directly be synthesized with excellent α-selectivity by the copper-catalyzed hydrostannylation using a distannane or a silylstannane, irrespective of the electronic and steric characteristics of terminal alkynes employed. Synthetic utility of the resulting branched alkenylstannane has been demonstrated by the total synthesis of bexarotene.

In view of the high synthetic versatility of alkenylstannanes, especially in carbon–carbon bond-forming processes *via* Migita–Kosugi–Stille coupling, tin–lithium exchange reaction, *etc.*, the development of potent methods for making alkenylstannanes with defined structures in a regio- and stereoselective manner has continued to be a key subject in modern synthetic organic chemistry.[1] One of the most popular and straightforward routes to alkenylstannanes would be hydrostannylation of alkynes,[2] and three isomers, namely the α-adduct and the (*E*/*Z*)-β-adduct, can be generated in the case of terminal alkynes (eqn (1)).[3] Hence the regio- and stereocontrol of hydrostannylation is a pivotal issue, and (*Z*)- or (*E*)-linear alkenylstannanes have successfully been synthesized with high β-selectivity under radical conditions,[4] Lewis acid[5] or transition metal catalysis.[6] Although selective access to branched alkenylstannanes has also been achieved in some cases depending upon direct addition of a tin hydride[7–9] or a stannylmetallation–protonation sequence,[10] the existing methods are still not versatile, owing to limited substrate scope of alkynes in every reaction and the use of an excess amount of a stannylmetal reagent in the latter case (Scheme 1). Therefore the development of a universal system for α-selective hydrostannylation of terminal alkynes, which gives direct and efficacious access to pharmacologically important 1,1-disubstituted alkenes such as bexarotene[11] and isocombretastatin A-4,[12] has been a long-awaited goal.



(1)

We have recently riveted our attention on potential copper catalysis for metallation reactions of unsaturated carbon–carbon bonds, and have already disclosed that distannylation[13] as well as various borylations[14] of alkynes and alkenes facilely occur to afford organostannanes and -boranes with structural diversity by employing a distannane and a diboron as a metallating reagent. The distannylation of alkynes was found to proceed through intermediary formation of a β-stannylalkenylcopper species with enough nucleophilicity, which was finally converted into *vic*-distannylalkenes by capturing a tin electrophile. Therefore, we envisioned that a copper catalyst would also promote

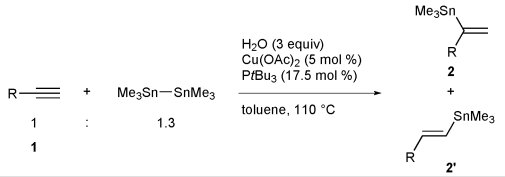


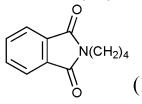
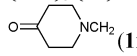
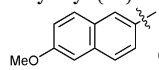
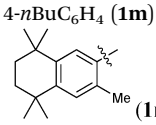
Scheme 1 Reported α-selective hydrostannylation of terminal alkynes.

[a] *Department of Applied Chemistry, Graduate School of Engineering, Hiroshima University, Higashi-Hiroshima 739-8527, Japan. E-mail: yhiroto@hiroshima-u.ac.jp; Fax: +81-82-424-5494; Tel: +81-82-424-7724*
[b] *ACT-C, Japan Science and Technology Agency, Higashi-Hiroshima 739-8527, Japan*

† Electronic supplementary information (ESI) available: Experimental procedures and characterization data. See DOI: 10.1039/c5cc02720a

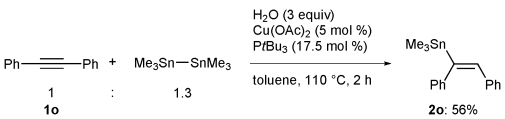
Table 1 Cu-catalyzed hydrostannylation with a distannane[a]



Entry	R	Time (h)	Yield[b] (%)	2 : 2′	Products
1	$nC_{12}H_{25}$ (**1a**)	1.5	75	98 : 2	**2a**,**2′a**
2	$nC_{10}H_{21}$ (**1b**)	2	89	97 : 3	**2b**,**2′b**
3	 (**1c**)	1.5	89	97 : 3	**2c**,**2′c**
4	$THPO(CH_2)_4$ (**1d**)	1	84	94 : 6	**2d**,**2′d**
5	$TBSO(CH_2)_2$ (**1e**)	1.5	85	96 : 4	**2e**,**2′e**
6	$BnO(CH_2)_2$ (**1f**)	1	76	97 : 3	**2f**,**2′f**
7	$HO(CH_2)_8$ (**1g**)	3	76	>99 : 1	**2g**
8	$Br(CH_2)_8$ (**1h**)	24	43	89 : 11	**2h**,**2′h**
9	 (**1i**)	8	63	>99 : 1	**2i**
10	$BnOCH_2$ (**1j**)	6	37	92 : 8	**2j**,**2′j**
11	2-Pyridyl (**1k**)	5.5	68	>99 : 1	**2k**
12	 (**1l**)	6	68	86 : 14	**2l**,**2′l**
13	4-$nBuC_6H_4$ (**1m**)	24	61	>99 : 1	**2m**
14	 (**1n**)	2	80	>99 : 1	**2n**

[a] General procedure: **1** (0.30 mmol, 1 equiv.), Me_3Sn–$SnMe_3$ (0.39 mmol, 1.3 equiv.), H_2O (0.90 mmol, 3 equiv.), $Cu(OAc)_2$ (0.015 μmol, 5 mol%), $PtBu_3$ (0.053 mmol, 17.5 mol%), toluene (0.2 mL). [b] Isolated yield.

hydrostannylation of alkynes in the presence of a suitable protic reagent for trapping the β-stannylalkenylcopper intermediate.[15] Herein we report that the hydrostannylation of terminal alkynes smoothly takes place under the copper catalysis by use of water as a protic reagent, and that the universal system allows a variety of branched alkenylstannanes to be synthesized with excellent α-selectivity, irrespective of the electronic and steric characteristics of terminal alkynes.



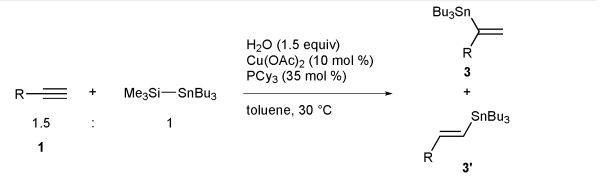
(2)

The α-selective hydrostannylation has proven to be feasible to provide a branched (**2a**) and a linear (**2′a**) alkenylstannane in 75% yield (**2a** : **2′a** = 98 : 2), when we treated 1-tetradecyne (**1a**) with hexamethyldistannane and water in toluene at 110 °C in the presence of the $Cu(OAc)_2$–$PtBu_3$ catalyst (Table 1, entry 1).[16,17] The reaction was also applicable to 1-dodecyne (**1b**) and an imide-substituted alkyne (**1c**), giving **2b** and **2c** with high degrees of α-selectivity in excellent yield (entries 2 and 3), and furthermore functionalized aliphatic alkynes bearing an acetal (**1d**), a silyl ether (**1e**) or a benzyl ether (**1f**) smoothly underwent the α-selective hydrostannylation, leaving these reactive moieties intact (entries 4–6). The high functional group compatibility was also demonstrated by the reaction of a hydroxyl- (**1g**) or a bromo-substituted alkyne (**1h**), and propargyl-functionalized alkynes (**1i** and **1j**), although the yields became moderate in some cases (entries 7–10). The regioselective installation of a stannyl group into an internal carbon of aromatic terminal alkynes was achieved under the present conditions as well, and thus pyridyl (**1k**), naphthyl (**1l**) and phenyl (**1m** and **1n**) acetylenes were efficiently transformed into the respective branched alkenylstannanes (**2k**–**2n**) (entries 11–14). An internal alkyne, diphenylacetylene (**1o**), could participate in the reaction to furnish (*E*)-trimethylstannylstilbene (**2o**) as the sole product (eqn (2)), showing that hydrostannylation completely proceeds in a *cis* fashion.[18]

With the successful synthesis of diverse branched alkenylstannanes having a trimethylstannyl moiety, we next investigated α-selective installation of a tributylstannyl moiety. Although the reaction of 1-octyne (**1p**) with hexabutyldistannane in the presence of the $Cu(OAc)_2$–PCy_3 catalyst[19] led to regioselective formation of a branched alkenylstannane (**3p**) in moderate yield (Table 2, entry 1), a silylstannane, tributyl(trimethylsilyl)stannane, turned out to serve as a more effective and reactive stannylating reagent to afford a 74% yield of **3p** and **3′p** (**3p** : **3′p** = 86 : 14) (entry 2).[17] It should be noted that a silyl moiety was not incorporated into an alkyne at all in the reaction with a silylstannane, which is in marked contrast to the copper-catalyzed selective silyl incorporation reactions into unsaturated hydrocarbons with a silylborane.[20] Hydrostannylation using a silylstannane also took place smoothly with 1-decyne (**1q**), 1-hexyne (**1r**) and branched aliphatic terminal alkynes (**1s** and **1t**) to provide **3q**–**3t** with high α-selectivity (entries 3–6), and furthermore functionalized terminal alkynes bearing a cyano (**1u**), a chloro (**1v**) or a benzyloxy moiety (**1f**), and 3-phenyl-1-propyne (**1w**) were transformed into the respective branched alkenylstannanes (entries 7–10).[21]

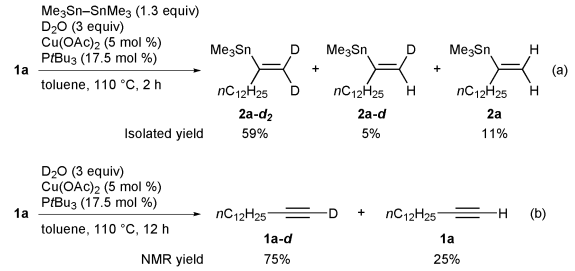
Since water can serve as a proton source in hydrostannylation, we expected that the present system may be extended to deuteriostannylation by use of deuterium oxide. Surprisingly, the

Table 2 Cu-catalyzed hydrostannylation with a silylstannane[a]

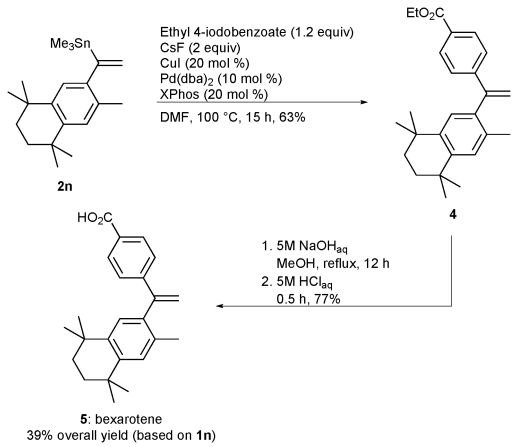


Entry	R	Time (h)	Yield[b] (%)	3 : 3′	Products
1[c]	nC_6H_{13} (**1p**)	43	43[d]	>99 : 1	**3p**
2	nC_6H_{13} (**1p**)	4	73	86 : 14	**3p**,**3′p**
3	nC_8H_{17} (**1q**)	2	74	88 : 12	**3q**,**3′q**
4	*n*Bu (**1r**)	2	74	85 : 15	**3r**,**3′r**
5	iAmyl (**1s**)	2	60	84 : 16	**3s**,**3′s**
6	iBu (**1t**)	2	48	92 : 8	**3t**,**3′t**
7	$NC(CH_2)_3$ (**1u**)	3	55	93 : 7	**3u**,**3′u**
8	$Cl(CH_2)_3$ (**1v**)	2	44	92 : 8	**3v**,**3′v**
9	$BnO(CH_2)_2$ (**1f**)	2	55	88 : 12	**3f**,**3′f**
10	Bn (**1w**)	2	46	93 : 7	**3w**,**3′w**

[a] General procedure: **1** (0.45 mmol, 1.5 equiv.), Me_3Si–$SnBu_3$ (0.30 mmol, 1 equiv.), H_2O (0.45 mmol, 1.5 equiv.), $Cu(OAc)_2$ (0.03 μmol, 10 mol%), PCy_3 (0.11 mmol, 35 mol%), toluene (0.2 mL). [b] Isolated yield. [c] Bu_3Sn–$SnBu_3$ was used instead of Me_3Si–$SnBu_3$. H_2O = 0.4 mL (74 equiv.). [d] NMR yield.



Scheme 2 Cu-catalyzed deuteriostannylation with deuterium oxide.

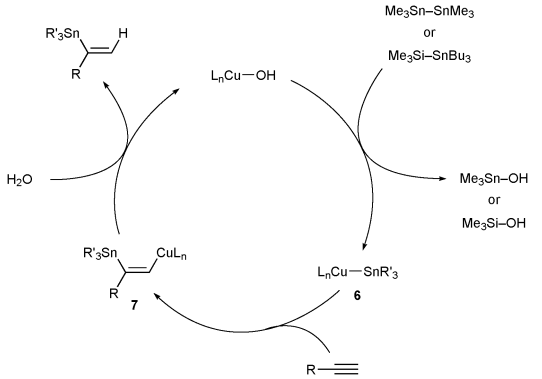


Scheme 3 Total synthesis of bexarotene.

copper-catalyzed reaction of 1-tetradecyne (**1a**) with hexamethyldistannane in the presence of deuterium oxide produced a dideuteriostannylation product (**2a-d_2**) predominantly (**2a-d_2 : 2a-*d* : 2a** = 79 : 7 : 14, eqn (a), Scheme 2). The formation of **2a-d_2** can be rationalized by considering the deuteriostannylation of 1-tetradecyne-*d* (**1a-*d***), which should be generated *in situ* prior to deuteriostannylation. Actually, hydrogen–deuterium exchange between **1a** and deuterium oxide was demonstrated to occur smoothly under the copper catalysis (eqn (b), Scheme 2).

As depicted in Scheme 3, the branched alkenylstannane (**2n**) was found to be facilely converted into 1,1-diarylalkene **4** by the Migita–Kosugi–Stille coupling with ethyl 4-iodobenzoate. Hydrolysis of the ester moiety of **4** provided bexarotene **5** in 39% overall yield (3 steps, based on alkyne **1n**), which is widely used in the treatment of cutaneous T-cell lymphoma,[11] demonstrating the synthetic significance of the present α-selective hydrostannylation.

Formation of a stannylcopper species (**6**) *via* σ-bond metathesis between a distannane (or silylstannane) and Cu–OH would initiate hydrostannylation (Scheme 4).[22] The resulting stannylcopper species (**6**) then adds across a carbon–carbon triple bond of a terminal alkyne (stannylcupration) to produce a β-stannylalkenylcopper species (**7**), which is finally transformed into a hydrostannylation product through protonation with water.[23] The formation of branched alkenylstannanes (**2** and **3**) with high α-selectivity should be attributed to the regioselective generation of **7**, possessing the stannyl moiety at the internal carbon, in the stannylcupration step, which has already been well documented to be kinetically



Scheme 4 A plausible catalytic cycle for hydrostannylation.

favored in a stoichiometric reaction of a stannylcopper species with a terminal alkyne.[24]

In conclusion, we have developed a universal system for the α-selective hydrostannylation of terminal alkynes by using a distannane or a silylstannane as a stannylating reagent in the presence of a copper–trialkylphosphine catalyst, which leads to a convenient and straightforward method for synthesizing diverse branched alkenylstannanes, irrespective of the electronic and steric nature of terminal alkynes employed. The resulting branched alkenylstannane has been demonstrated to be facilely transformed into bexarotene of pharmacologically importance *via* the cross-coupling reaction. Further studies on copper-catalyzed stannylation reactions using a distannane or a silylstannane are in progress.

Notes and references

1 (*a*) M. Pereyre, J. P. Quintard and A. Rahm, *Tin in Organic Synthesis*, Butterworth, London, 1987; (*b*) V. Farina, V. Krishnamurthy and W. J. Scott, *Org. React.*, 1997, **50**, 1; (*c*) A. Orita and J. Otera, in *Tin in Organic Synthesis, Main Group Metals in Organic Synthesis*, ed. H. Yamamoto and K. Oshima, Wiley-VCH, Weinheim, 2004, pp. 621–720; (*d*) T. N. Mitchell, Organotin Reagents in Cross-Coupling Reactions, in *Metal-Catalyzed Cross-Coupling Reactions*, ed. A. de Meijere and F. Diederich, Wiley-VCH, Weinheim, 2004, pp. 125–161; (*e*) A. G. Davies, *Organotin Chemistry*, Wiley-VCH, Weinheim, 2004.

2 (*a*) N. D. Smith, J. Mancuso and M. Lautens, *Chem. Rev.*, 2000, **100**, 3257; (*b*) B. M. Trost and Z. T. Ball, *Synthesis*, 2005, 853.

3 For leading references, see: (*a*) Y. Ichinose, H. Oda, K. Oshima and K. Utimoto, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 3468; (*b*) K. Kikukawa, H. Umekawa, F. Wada and T. Matsuda, *Chem. Lett.*, 1988, 881; (*c*) H. X. Zhang, F. Guibé and G. Balavoine, *J. Org. Chem.*, 1990, **55**, 1857.

4 (*a*) E. Nakamura, D. Machii and T. Inubushi, *J. Am. Chem. Soc.*, 1989, **111**, 6849; (*b*) E. Nakamura, Y. Imanishi and D. Machii, *J. Org. Chem.*, 1994, **59**, 8178; (*c*) K. Miura, D. Wang, Y. Matsumoto, N. Fujisawa and A. Hosomi, *J. Org. Chem.*, 2003, **68**, 8730; (*d*) K. Miura, D. Wang, Y. Matsumoto and A. Hosomi, *Org. Lett.*, 2005, **7**, 503.

5 (*a*) N. Asao, J.-X. Liu, T. Sudoh and Y. Yamamoto, *J. Chem. Soc., Chem. Commun.*, 1995, 2405; (*b*) N. Asao, J.-X. Liu, T. Sudoh and Y. Yamamoto, *J. Org. Chem.*, 1996, **61**, 4568; (*c*) V. Gevorgyan, J.-X. Liu and Y. Yamamoto, *Chem. Commun.*, 1998, 37.

6 (*a*) R. E. Maleczka Jr., L. R. Terrell, D. H. Clark, S. L. Whitehead, W. P. Gallagher and I. Terstiege, *J. Org. Chem.*, 1999, **64**, 5958; (*b*) A. Darwish, A. Lang, T. Kim and J. M. Chong, *Org. Lett.*, 2008, **10**, 861. See also ref. 3*c*.

7 (*a*) U. Kazmaier, D. Schauss and M. Pohlman, *Org. Lett.*, 1999, **1**, 1017; (*b*) U. Kazmaier, M. Pohlman and D. Schauß, *Eur. J. Org. Chem.*, 2000, 2761; (*c*) S. Braune and U. Kazmaier, *J. Organomet. Chem.*, 2002, **641**, 26; (*d*) S. Braune, M. Pohlman and U. Kazmaier,

J. Org. Chem., 2004, **69**, 468; (*e*) H. Lin and U. Kazmaier, *Eur. J. Org. Chem.*, 2007, 2839; (*f*) N. Jena and U. Kazmaier, *Eur. J. Org. Chem.*, 2008, 3852; (*g*) H. Lin and U. Kazmaier, *Eur. J. Org. Chem.*, 2009, 1221.

8 A. Hamze, D. Veau, O. Provot, J.-D. Brion and M. Alami, *J. Org. Chem.*, 2009, **74**, 1337.

9 I. Shibata, T. Suwa, K. Ryu and A. Baba, *J. Am. Chem. Soc.*, 2001, **123**, 4101.

10 (*a*) J. Hibino, S. Matsubara, Y. Morizawa, K. Oshima and H. Nozaki, *Tetrahedron Lett.*, 1984, **25**, 2151; (*b*) S. Matsubara, J. Hibino, Y. Morizawa, K. Oshima and H. Nozaki, *J. Organomet. Chem.*, 1985, **285**, 163; (*c*) S. Sharma and A. C. Oehlschlager, *Tetrahedron Lett.*, 1986, **27**, 6161; (*d*) S. Sharma and A. C. Oehlschlager, *Tetrahedron Lett.*, 1988, **29**, 261; (*e*) S. Sharma and A. C. Oehlschlager, *J. Org. Chem.*, 1989, **54**, 5064.

11 T. Illidge, C. Chan, N. Counsell, S. Morris, J. Scarisbrick, D. Gilson, B. Popova, P. Patrick, P. Smith, S. Whittaker and R. Cowan, *Br. J. Cancer*, 2013, **109**, 2566.

12 J. Aziz, E. Brachet, A. Hamze, J.-F. Peyrat, G. Bernadat, E. Morvan, J. Bignon, J. Wdzieczak-Bakala, D. Desravines, J. Dubois, M. Tueni, A. Yassine, J.-D. Brion and M. Alami, *Org. Biomol. Chem.*, 2013, **11**, 430.

13 H. Yoshida, A. Shinke and K. Takaki, *Chem. Commun.*, 2013, **49**, 11671.

14 (*a*) H. Yoshida, S. Kawashima, Y. Takemoto, K. Okada, J. Ohshita and K. Takaki, *Angew. Chem., Int. Ed.*, 2012, **51**, 235; (*b*) Y. Takemoto, H. Yoshida and K. Takaki, *Chem. – Eur. J.*, 2012, **18**, 14841; (*c*) H. Yoshida, I. Kageyuki and K. Takaki, *Org. Lett.*, 2013, **15**, 952; (*d*) I. Kageyuki, H. Yoshida and K. Takaki, *Synthesis*, 2014, 1924; (*e*) H. Yoshida, Y. Takemoto and K. Takaki, *Chem. Commun.*, 2014, **50**, 8299; (*f*) Y. Takemoto, H. Yoshida and K. Takaki, *Synthesis*, 2014, 3024; (*g*) H. Yoshida, Y. Takemoto and K. Takaki, *Asian J. Org. Chem.*, 2014, **3**, 1204; (*h*) H. Yoshida, Y. Takemoto and K. Takaki, *Chem. Commun.*, 2015, **51**, 6297.

15 For stoichiometric formation of a β-stannylalkenylcopper species, followed by its capture with an electrophile including protons, see: (*a*) A. Barbero, P. Cuadrado, I. Fleming, A. M. González and F. J. Pulido, *J. Chem. Soc., Chem. Commun.*, 1992, 351; (*b*) A. Barbero, P. Cuadrado, I. Fleming, A. M. González, F. J. Pulido and R. Rubio, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1657.

16 B. Hammond, F. H. Jardine and A. G. Vohra, *J. Inorg. Nucl. Chem.*, 1971, **33**, 1017.

17 For optimization of reaction conditions (ligand, protic reagent, solvent, *etc.*), see ESI†.

18 The reaction of 1-phenyl-1-butyne did not give a hydorostannylation product.

19 The use of Cu(I) sources such as CuCl (with NaO*t*Bu) and Cu(I)-thiophene-2-carboxylate resulted in lower yield.

20 For representative examples, see: (*a*) A. H. Hoveyda and K.-S. Lee, *J. Am. Chem. Soc.*, 2010, **132**, 2898; (*b*) D. J. Vyas and M. Oestreich, *Angew. Chem., Int. Ed.*, 2010, **49**, 8513; (*c*) P. Wang, X.-L. Yeo and T.-P. Loh, *J. Am. Chem. Soc.*, 2011, **133**, 1254; (*d*) T. Fujihara, Y. Tani, K. Semba, J. Terao and Y. Tsuji, *Angew. Chem., Int. Ed.*, 2012, **51**, 11487.

21 The relatively low yields with $TMSSnBu_3$ compared with those with $Me_3Sn–SnMe_3$ are ascribed to the formation of $Bu_3Sn–SnBu_3$ as a by-product, which has been demonstrated to occur only in the presence of a Cu catalyst and a proton source. See ESI† for details.

22 For generation of a stannylcopper species by use of a distannane or a silylstannane, see: (*a*) A. C. Oehlschlager, M. W. Hutzinger, R. Aksela, S. Sharma and S. M. Singh, *Tetrahedron Lett.*, 1990, **31**, 165; (*b*) B. H. Lipshutz, D. C. Reuter and E. L. Ellsworth, *J. Org. Chem.*, 1989, **54**, 4975.

23 Addition of a stannylcopper species to an alkyne and subsequent protonation of the resulting β-stannylalkenylcopper species have been established steps in the stoichiometric stannylcupration of alkynes. See: (*a*) A. Barbero and F. J. Pulido, *Chem. Soc. Rev.*, 2005, **34**, 913; (*b*) F. J. Pulido and A. Barbero, Silyl and Stannyl Derivatives of Organocopper Compounds, in *The Chemistry of Organocopper Compounds*, ed. Z. Rappoport and I. Marek, John Wiley & Sons, Chichester, 2009, pp. 775–856.

24 R. D. Singer, M. W. Hutzzinger and A. C. Oehlschlager, *J. Org. Chem.*, 1991, **56**, 4933.