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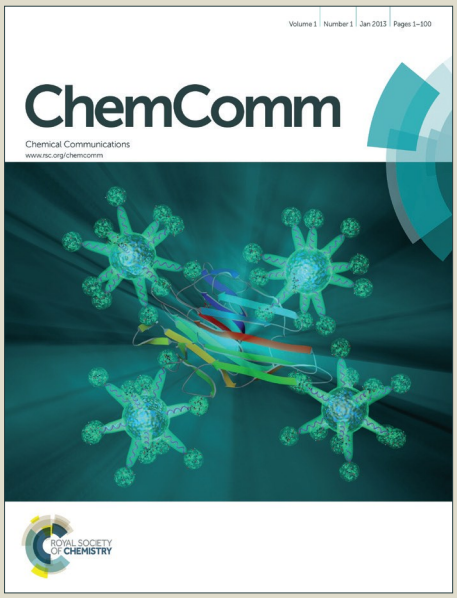

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Copper-catalyzed α-selective hydrostannylation of alkynes for synthesis of branched alkenylstannanes

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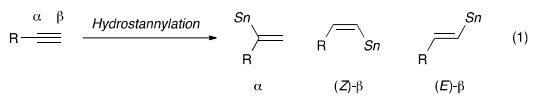
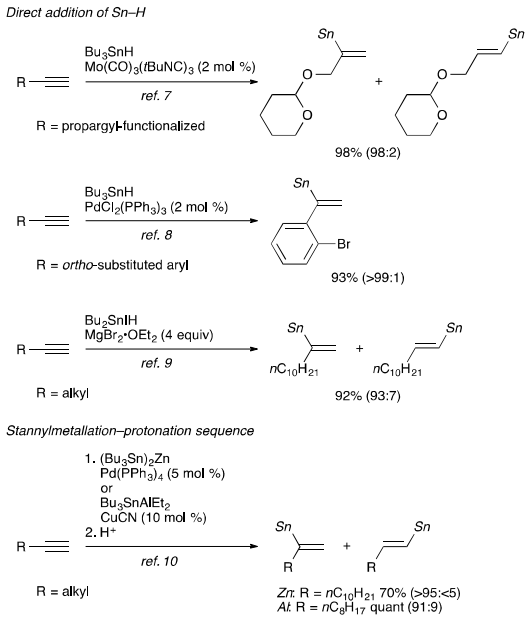
A variety of branched alkenylstannanes can directly be synthesized with excellent α-selectivity by the copper-catalyzed hydrostannylation using a distannane or a silylstannane, irrespective of electronic and steric characters of terminal alkynes employed. Synthetic utility of the resulting branched alkenylstannane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

In view of 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 of defined structure in regio- and stereoselective manners 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 α-adduct and (*E*/*Z*)-β-adduct, can be generated in the case of terminal alkynes (eqn (1)).[3] Hence the regio- and stereocontrol of the 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 stannylmetallation–protonation sequence,[10] the existing methods are still not versatile, owing to limited substrate scope on alkynes in every reaction and the use of an excess amount of





Scheme 1 Reported α-selective hydrostannylation of terminal alkynes.

the development of a universal system for α-selective hydrostannylation of terminal alkynes, which gives us a direct and efficacious way to such pharmacologically significant 1,1-disubstituted alkenes as bexarotene[11] and isocombretastatin A-4,[12] has been a long-awaited goal.

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 of structural diversity by

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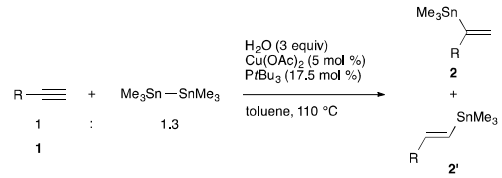
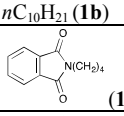
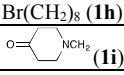
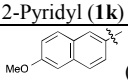
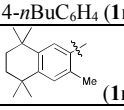
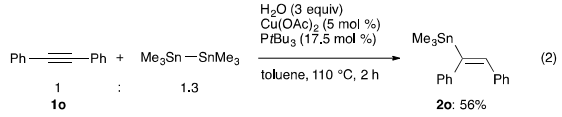
Table 1 Cu-catalyzed hydrostannylation with a distannane[a]



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$_6$H$_4$ (**1m**)	24	61	>99:1	**2m**
14	 (**1n**)	2	80	>99:1	**2n**

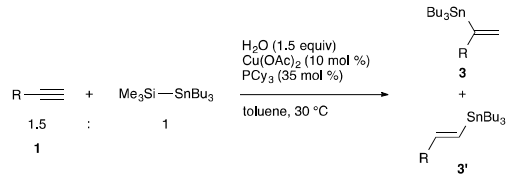
[a]General procedure: **1** (0.30 mmol, 1 equiv), Me_3Sn–$SnMe_3$ (0.39 mmol, 1.3 equiv), H_2O (0.90 mmol, 3 equiv), $Cu(OAc)_2$ (0.015 mmol, 5 mol %), PtBu$_3$ (0.053 mmol, 17.5 mol %), toluene (0.2 mL). [b]Isolated yield.



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 of enough nucleophilicity, which was finally convertible into *vic*-distannylalkenes by capturing with a tin electrophile. Therefore, we envisioned that a copper catalyst would also promote 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 electronic and steric characters of terminal alkynes.

The α-selective hydrostannylation has proven to be feasible to provide a branched (**2a**) and a linear (**2'a**) alkenylstannanes 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 $Cu(OAc)_2$–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

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	nBu (**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 mmol, 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.

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 transformable 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 the 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 $Cu(OAc)_2$–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

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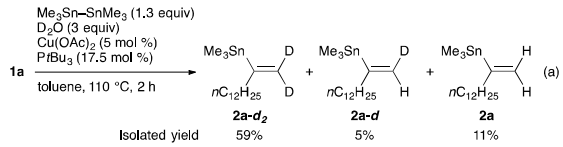
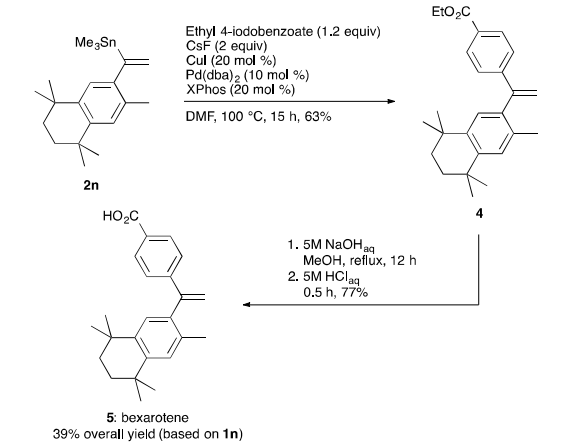


Scheme 2 Cu-catalyzed deuteriostannylation with deuterium oxide.

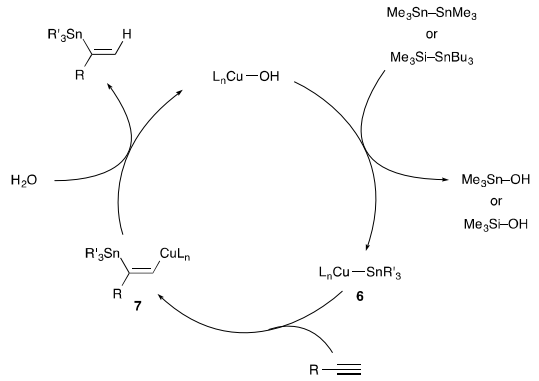


Scheme 3 Total synthesis of bexarotene.

silylborane.[20] The 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 transformable into the respective branched alkenylstannanes (entries 7–10).[21]

Since water can serve as a proton source in the hydrostannylation, we expected that the present system may be extend to deuteriostannylation by use of deuterium oxide. Surprisingly, the 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 the 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 convertible 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 as a treatment for cutaneous T-cell lymphoma,[11] demonstrating the synthetic significance of the



Scheme 4 A plausible catalytic cycle for the hydrostannylation.

present α-selective hydrostannylation.

Formation of a stannylcopper species (**6**) via σ-bond metathesis between a distannane (or silylstannane) and Cu–OH would initiate the 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 attributable 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 favored in a stoichiometric reaction of a stannylcopper species with a terminal alkyne.[24]

In conclusion, we have developed the 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, that leads to the convenient and straightforward method for synthesizing diverse branched alkenylstannanes, irrespective of electronic and steric nature of terminal alkynes employed. The resulting branched alkenylstannane has been demonstrated to be facilely transformable into bexarotene of pharmacologically significance via the cross-coupling reaction. Further studies on copper-catalyzed stannylation reactions using a distannane or a silylstannane are in progress.

Notes and references

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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 such Cu(I) source 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 lower yields with $TMSSnBu_3$ compared with those with $Me_3SnSnMe_3$ are ascribable to formation of $Bu_3SnSnBu_3$ 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.

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