Synthetic Methods

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Synthesis of Trisubstituted Alkenylstannanes through Copper-Catalyzed Three-Component Coupling of Alkylboranes, Alkynoates, and Tributyltin Methoxide**

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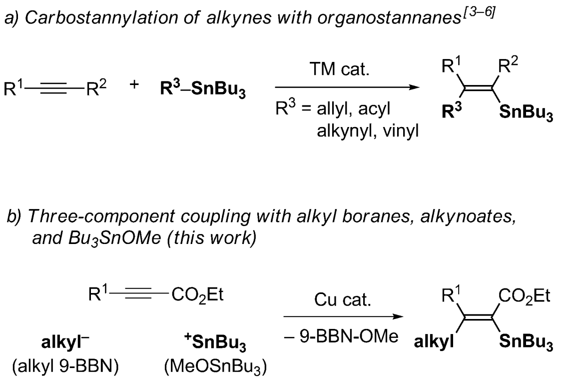
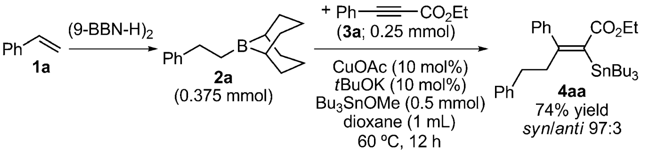
Alkenylstannanes are useful synthetic intermediates in organic synthesis because of their applicability in various transformations (e.g., Kosugi–Migita–Stille cross-coupling).[1] In particular, trisubstituted alkenylstannanes should be useful for the synthesis of various tetrasubstituted alkenes that are found in many important pharmaceuticals and bioactive natural products.[2] Among the routes to trisubstituted alkenylstannanes, transition-metal-catalyzed stereoselective carbostannylation of internal alkynes with organostannanes is the most straightforward and attractive (Scheme 1a).[3–7] This catalytic method allows the simultaneous formation of C–C and C–Sn bonds. Shirakawa, Hiyama, and co-workers developed the palladium- or nickel-catalyzed carbostannylation of internal alkynes with allyl-, acyl-, and alkynylstannanes.[3] These methods are useful for the preparation of trisubstituted alkenylstannanes, but require tedious preparation of the organostannane reagents. Additionally, sp^3-alkylstannanes have not been used for the introduction of alkyl groups.[5] Furthermore, the regioselectivity is not always reliable, especially as the regiocontrol is generally difficult even with alkynes that are desymmetrized by electronic effects.[3b]



Scheme 1. Synthesis of trisubstituted alkenylstannanes.

Herein, we report a copper-catalyzed three-component coupling of alkyl boranes (alkyl-9-BBN), alkynoates, and tributyltin methoxide (Bu_3SnOMe) as a versatile route to trisubstituted alkenylstannanes (Scheme 1b).[8–10] The alkyl and Sn moieties are introduced at the β and α carbon atoms of the alkynoates, respectively, in a formal *syn* addition mode with complete regioselectivity. A variety of functional groups are tolerated in the alkylboranes and alkynoates. Although the scope of the alkyne is limited to alkynoates, they are easily accessible and the alkoxycarbonyl group in the coupling products can be a point of diversification for synthesizing tetrasubstituted alkenes. These points can be synthetic merits of using alkynoates as substrates.

The reaction of alkylborane **2a** (0.375 mmol), which was prepared by hydroboration of styrene (**1a**) with 9-borabicyclo[3.3.1]nonane (9-BBN-H) dimer, with ethyl 3-phenylpropiolate (**3a**) and Bu_3SnOMe in the presence of CuOAc and *t*BuOK in 1,4-dioxane afforded trisubstituted alkenylstannane **4aa** in 74% yield with excellent *syn*/*anti* selectivity [Eq. (1)]. An exogenous ligand for the copper ion was not necessary. The three-component coupling was readily scalable: a gram-scale reaction with 1.0 g (5.7 mmol) of **3a** afforded **4aa** in 70% yield with also excellent stereoselectivity (*syn*/*anti* 97:3).



(1)

The use of CuCl or $Cu(OAc)_2$ instead of CuOAc resulted in significantly reduced yields (20 and 45%, respectively). When *t*BuOK was omitted, the trisubstituted alkenylstannane product was not obtained at all. The corresponding amides or ketones as well as nonpolar internal alkynes showed no reactivity as alkyne substrates under similar conditions. Our attempts to use phenyl-9-BBN, $PhB(OH)_2$, phenylboronic acid pinacolate ester, or vinylpinacolate ester instead of the alkyl 9-BBN reagents were unsuccessful.

This hydroboration/three-component coupling one-pot method afforded a variety of trisubstituted alkenylstannanes with high stereoselectivities (Table 1). The reaction tolerated functional groups such as methoxy, ester, acetal, benzyl ether,

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phthalimide, bromoaryl, silyl ether, and fluoroaryl moieties in the alkylborane and/or alkynoate (entries 1, 2, 5–7, 9–13).

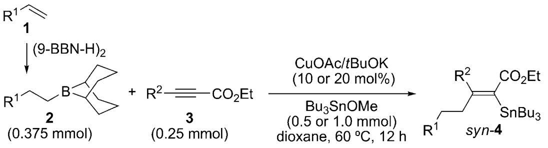
The alkynoate scope is shown in Table 1. Methoxy, ester, and fluoro groups were tolerated at the *para*-position of the β-aryl substituent (entries 1, 2, 13). The alkynoate **3h**, bearing a 2-thienyl group at the β-position, also underwent coupling in 65 % yield with 92:8 *syn* selectivity (entry 12). Alkyl groups were acceptable as β-substituent of the alkynoate (entries 4–7). The alkynoate with a methyl group at the β-position reacted with excellent *syn* selectivity (> 99:1, entry 4). The reactions of **3f** and **3g** having a $THPOCH_2$ and $BnOCH_2$ group, respectively, at the β-position also proceeded with > 99:1 *syn* selectivity (entries 5–7).

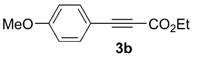
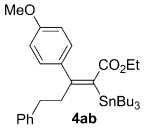
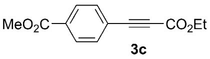
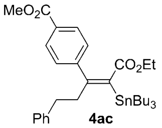
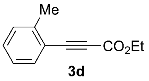
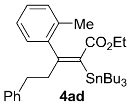
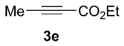
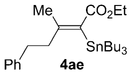
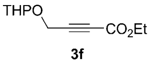
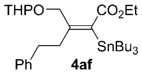
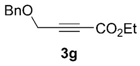
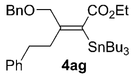
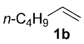
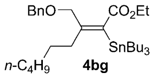
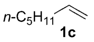
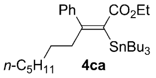
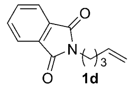
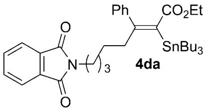
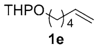
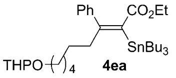
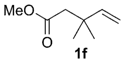
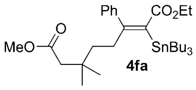
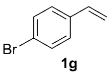
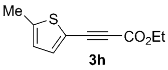
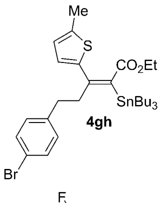
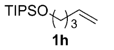
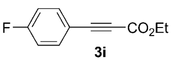
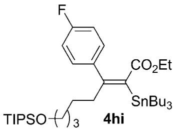
The tolerance toward steric demand in the alkylboranes **2** and alkynoates **3** is also shown in Table 1. A methyl group was acceptable as an *ortho*-substituent of the aromatic ring at the β-position (entry 3). Also the sterically more demanding alkylborane **2f**, which was derived from a terminal alkene (**1f**) bearing a tertiary alkyl substituent, afforded the corresponding product (**4fa**; 64 % yield, 91:9 *syn* selectivity; entry 11). However, the use of secondary alkylborane reagents prepared from internal alkenes resulted in no reaction (data not shown).

Alkene hydroboration of **1i** followed by copper-catalyzed cyclization gave the corresponding five-membered carbocycle **4i** in 80 % yield with > 99:1 *syn* selectivity [Eq. (2)].

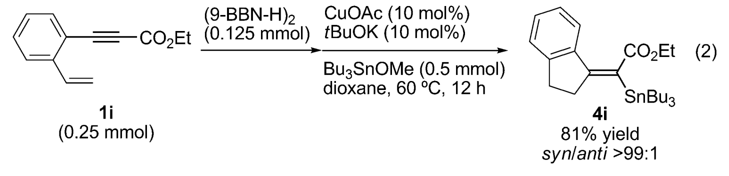
A possible catalytic cycle for this copper-catalyzed transformation is shown in Figure 1. The reaction of CuOAc and *t*BuOK forms alkoxocopper(I) complex **A**. B–Cu transmetalation between **A** and alkylborane **2** results in the alkylcopper(I) species **B** and an alkoxyborane (9-BBN-O*t*Bu or 9-BBN-OMe).[9,10] Species **B** then forms a π-complex (**C**) with alkynoate **3**. *Syn* carbocupration across the C≡C of **C** leads to alkenylcopper inter-

Table 1: Copper-catalyzed three-component coupling.[a]



Entry	Alkene	Alkynoate	Product	Yield [%][b]	*syn*/*anti*[c]
1	**1a**	 **3b**	 **4ab**	55	95:5
2	**1a**	 **3c**	 **4ac**	61	91:9
3[d]	**1a**	 **3d**	 **4ad**	71	> 99:1
4[e]	**1a**	 **3e**	 **4ae**	49	> 99:1
5[e]	**1a**	 **3f**	 **4af**	88	> 99:1
6[e]	**1a**	 **3g**	 **4ag**	74	> 99:1
7[e]	 **1b**	**3g**	 **4bg**	74	> 99:1
8	 **1c**	**3a**	 **4ca**	75	93:7
9	 **1d**	**3a**	 **4da**	68	94:6
10	 **1e**	**3a**	 **4ea**	77	96:4
11	 **1f**	**3a**	 **4fa**	64	91:9
12	 **1g**	 **3h**	 **4gh**	65	92:8
13	 **1h**	 **3i**	 **4hi**	63	93:7

[a] The reaction was carried out with **3** (0.25 mmol), **2** (0.375 mmol), CuOAc (10 mol %), *t*BuOK (10 mol %), and Bu_3SnOMe (0.5 mmol) in dioxane (1 mL) at 60 °C for 12 h. Alkylborane **2** was prepared in advance by hydroboration of **1** with the 9-BBN dimer at 60 °C for 1 h and used without purification. THP: tetrahydropyranyl; TIPS: triisopropylsilyl. [b] Yield of isolated product. The isolated products were contaminated with traces of unidentified materials (0.1–3 %). [c] Determined by ^1H NMR analysis of the purified product. [d] 20 mol % of CuOAc/*t*BuOK were used. [e] The reaction was carried out with CuOAc (20 mol %), *t*BuOK (20 mol %), and Bu_3SnOMe (1.0 mmol) in dioxane (0.5 mL).



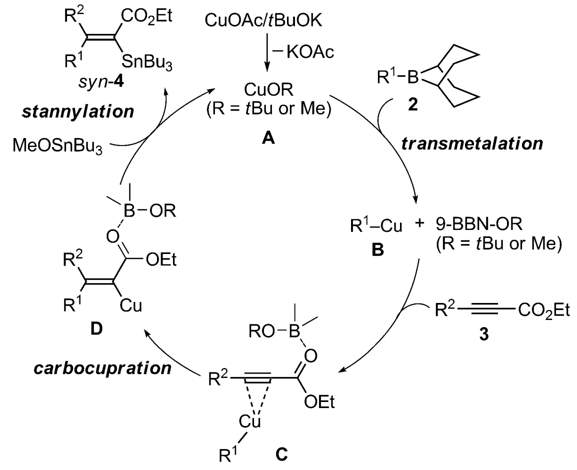
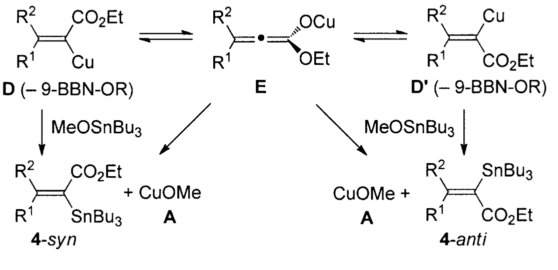


Figure 1. Putative mechanism of our copper-catalyzed synthesis of trisubstituted alkenylstannanes.

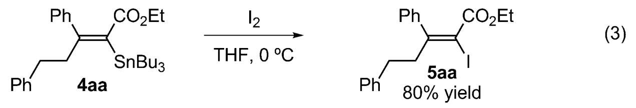
mediate **D**. Finally, stannylation by Bu$_3$SnOMe releases *syn*-**4**,[11] regenerating alkoxocopper(I) complex **A** for the next catalytic cycle. On this pathway, the alkoxyborane may play a role in activating the alkynoate through its Lewis-acidic character.[9a,10c,d]

The occurrence of *anti*-stannylation as a side reaction suggests the geometrical isomerization of the alkenylcopper species (**D**/**D′**) through a copper(I) allenoate complex (**E** in Scheme 2).[12,13] Stannylation of this allenoate can result in the formation of *syn*-**4** or *anti*-**4** depending on the substituent effects of R^1 and R^2, while the isomerized alkenyl copper(I) **D′** should preferentially yield the *anti*-stannylation product *anti*-**4**.

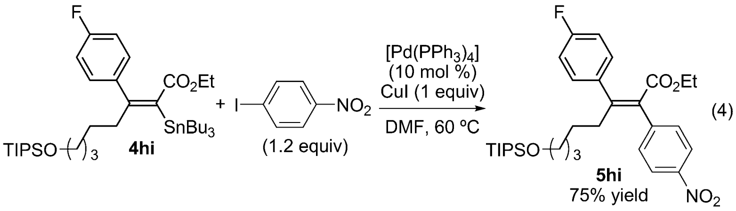


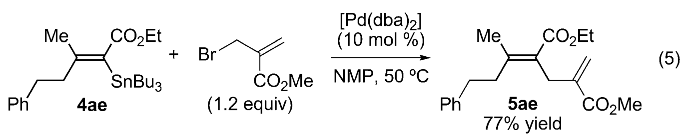
Scheme 2. Isomerization of the alkenyl copper intermediate.

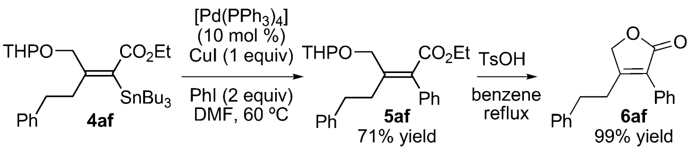
The trisubstituted alkenylstannanes obtained were used in several syntheses:[14] Stannane **4aa** was readily derivatized to the trisubstituted alkenyl iodide **5aa** [Eq. (3)], stannane **4hi** underwent Kosugi–Migita–Stille cross-coupling with 4-iodonitrobenzene to afford the corresponding tetrasubstituted alkene **5hi** [Eq. (4)], stannane **4ae** coupled with methyl 2-(bromoethyl)acrylate to afford allylation product **5ae** [Eq. (5)], and the Kosugi–Migita–Stille cross-coupling product **5af** underwent a THP deprotection followed by cyclization to afford α,β-butenolide **6af** [Eq. (6)].



In summary, we have developed a new approach to trisubstituted alkenylstannanes through copper-catalyzed three-component coupling of alkylboranes, alkynoates, and tributyltin methoxide, which proceeds with complete regioselectivity and high *syn* selectivity. A variety of functional groups are tolerated in the alkylborane and the alkynoate. Thus, this copper-catalyzed procedure gives straightforward access to functionalized, trisubstituted alkenylstannanes.







Experimental Section

Typical procedure [Eq. (1)]: Styrene (**1a**; 47.2 μL, 0.41 mmol) and (9-BBN-H)$_2$ (45.8 mg, 0.188 mmol) were placed in a vial containing a magnetic stirring bar. The vial was sealed with a Teflon-coated silicon rubber septum, evacuated, and filled with argon. 1,4-Dioxane (0.4 mL) was added to the vial, and the mixture was stirred at 60°C for 1 h to prepare the alkylborane **2a**. CuOAc (3.1 mg, 0.025 mmol) and *t*BuOK (2.8 mg, 0.025 mmol) were placed in another vial. The vial was also sealed with a Teflon-coated silicon rubber septum, evacuated, and filled with argon. After 1,4-dioxane (0.6 mL) was added, the mixture was stirred at 25°C for 1 h. Next, the alkyl borane solution was transferred to the vial containing the Cu^I complex, followed by addition of alkynoate **3a** (43.6 mg, 0.25 mmol) and Bu$_3$SnOMe (160.5 mg, 0.5 mmol). After stirring for 12 h at 60°C, diethyl ether was added to the mixture. The mixture was filtered through a short plug of Al_2O_3, which was then washed with diethyl ether. After removing the solvent under reduced pressure, gel permeation chromatography ($CHCl_3$) provided **4aa** (105.3 mg, 0.185 mmol) in 74% yield with 97:3 *syn*/*anti* selectivity.

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Keywords: alkylboranes · copper · stannylation · trisubstituted alkenylstannanes

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