Stannanes

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Direct Synthesis of Alkynylstannanes: $ZnBr_2$ Catalyst for the Reaction of Tributyltin Methoxide and Terminal Alkynes**

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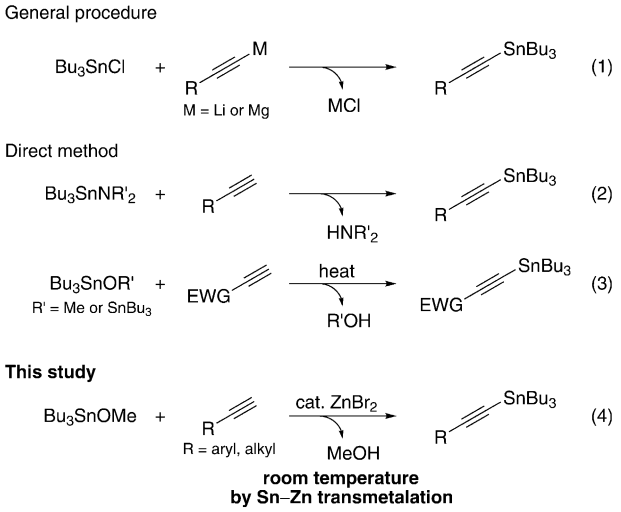
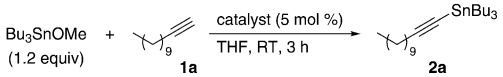
A carbon–carbon triple bond is a highly valuable and versatile functional group in many natural products, bioactive compounds,[1] and organic materials.[2] Alkynylstannanes, which have high stability, reactivity, and functional group tolerance, are important reagents for introducing an alkynyl moiety into organic molecules.[3] In particular, the Migita–Kosugi–Stille coupling using alkynylstannanes is widely used for the construction of C(sp)–C(sp^2) bonds in the synthesis of aryl alkynes or conjugated enynes.[4] Transmetalation between an organotin halide and an alkynyllithium or alkynylmagnesium compound is the most common route to alkynylstannanes [Eq. (1), Scheme 1].[5] However, the method using those alkynylmetals has some drawbacks such as poor functional group tolerance and the production of an equimolar amount of metal salts. The direct reaction of a tin amide with a terminal alkyne is also employed for the synthesis of alkynylstannanes, but its substrate scope is narrow because of the strong basicity of a tin amide and the production of basic amine by-products [Eq. (2), Scheme 1].[6] In contrast, the direct condensation reaction between a tin alkoxide and a terminal alkyne is regarded as a promising process that is mild because no strong base is required and an alcohol is the only by-product. Only alkynes bearing electron-withdrawing groups (EWGs), however, have been reported to react under reaction conditions requiring heat thus far [Eq. (3), Scheme 1].[7] Activation of alkynes by Lewis acids, instead of EWGs, was expected to achieve this direct coupling under milder reaction conditions as a way to develop a more versatile synthetic method of alkynylstannanes with various types of functional groups. We report herein our serendipitous discovery that a catalytic amount of $ZnBr_2$ effectively promoted a coupling reaction between Bu_3SnOMe and terminal alkynes at room temperature; the $ZnBr_2$ was transmetalated with Bu_3SnOMe rather than acting as a Lewis acid [Eq. (4), Scheme 1]. This reaction system is applicable to various types of aliphatic and aromatic terminal alkynes. In addition, the mild reaction conditions, in which methanol is the only waste, enables the one-pot synthesis of aryl alkynes by the Migita–Kosugi–Stille coupling.



Scheme 1. Synthetic methods for alkynylstannanes.

Initially, the addition of weak Lewis acids, which were expected to characteristically interact with alkynes,[8] was examined in the reaction of Bu_3SnOMe with 1-dodecyne (**1a**), as partially summarized in Table 1. Only a trace amount of the product **2a** was formed in the absence of a catalyst even when heated (Table 1, entry 1). In the presence of the transition-metal catalysts $PdCl_2$ and CuBr, **2a** was obtained in modest yields (Table 1, entries 2 and 3). While soft Lewis acids like $BiBr_3$ and $InBr_3$ did not improve the yields (Table 1, entries 4 and 5),[9] $Zn(OTf)_2$ produced a high product yield (Table 1, entry 6).[10] In the search for more efficient catalysts, we were delighted to find that inexpensive $ZnBr_2$ was the most practical catalyst employed (Table 1, entries 7 and 8). At

Table 1: Effect of catalysts.[a]



Entry	Catalyst	Yield [%][b]	Entry	Catalyst	Yield [%][b]
1[c]	none	< 5	5	$InBr_3$	25
2	$PdCl_2$	14	6	$Zn(OTf)_2$	68
3	CuBr	40	7	$ZnCl_2$	42
4	$BiBr_3$	< 5	8	$ZnBr_2$	68

[a] Reaction conditions: Bu_3SnOMe (1.2 mmol), **1a** (1 mmol), catalyst (0.05 mmol), THF (1 mL), RT, 3 h. [b] Determined by ^1H NMR spectroscopy using 1,1,2,2-tetrachloroethane as the internal standard. [c] Reaction was performed at 60 °C. THF = tetrahydrofuran.

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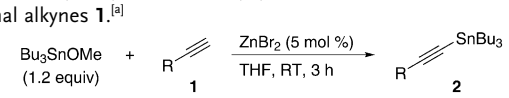
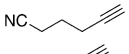
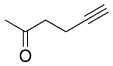
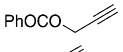
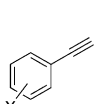
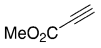
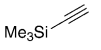
ambient temperature, 5 mol% of $ZnBr_2$ afforded the desired alkynylstannane **2a** in 68% yield.

Under the optimized reaction conditions, reactions with various terminal alkynes were carried out. As summarized in Table 2, a wide range of functional groups were compatible with the reaction conditions.[11] Aliphatic terminal alkynes, including base-labile ones bearing a cyano or carbonyl group, afforded the corresponding products **2a**–**2e** in high yields (Table 2, entries 1–5). The products **2f**, **2g**, and **2h** were also obtained effectively from propargyl chloride (**1f**), the propargyl ether **1g**, and propargyl ester **1h**, respectively (Table 2, entries 6–8). Unfortunately, the reaction of propargyl alcohol (**1i**) was suppressed, probably because of the hydroxy proton (Table 2, entry 9). This method was also applicable to aromatic alkynes bearing an electron-donating or electron-withdrawing group (Table 2, entries 10–15). Heteroaromatic compounds **1p** and **1q** gave high yields, as well (Table 2, entries 16 and 17). In addition, alkynes directly connected by ester and silyl moieties are suitable for coupling to produce the corresponding alkynylstannanes **2r** and **2s**, respectively (Table 2, entries 18 and 19).

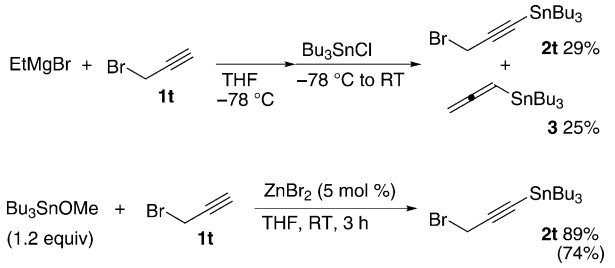
Table 2: Catalytic synthesis of alkynylstannanes **2** from Bu_3SnOMe and terminal alkynes **1**.[a]



Entry	Alkyne **1**		**2**	Yield [%][b]
1		**1a**	**2a**	68 (61)
2		**1b**	**2b**	78 (70, 97[c])
3[d]		**1c**	**2c**	72 (75)
4		**1d**	**2d**	73 (77)
5		**1e**	**2e**	68 (39, 79[c])
6		**1f**	**2f**	75 (62)
7		**1g**	**2g**	56 (46, 92[c])
8		**1h**	**2h**	76 (47)
9		**1i**	**2i**	n.d.
10		**1j** (X = H)	**2j**	75 (77)
11		**1k** (X = 4-MeO)	**2k**	79 (80)
12[d]		**1l** (X = 4-*t*Bu)	**2l**	78 (72)
13		**1m** (X = 3-Me)	**2m**	80 (69, 94[c])
14		**1n** (X = 3-Cl)	**2n**	84 (61, 84[c])
15		**1o** (X = 2-F)	**2o**	88 (74)
16		**1p**	**2p**	72 (74, 92[c])
17		**1q**	**2q**	80 (79)
18[d]		**1r**	**2r**	84 (58, 77[c])
19[d,e]		**1s**	**2s**	65 (49)

[a] Reaction conditions: Bu_3SnOMe (1.2 mmol), **1** (1 mmol), $ZnBr_2$ (0.05 mmol), THF (1 mL), RT, 3 h. [b] Yields of crude products determined by ^1H NMR spectroscopy using 1,1,2,2-tetrachloroethane as the internal standard. Values in parentheses are yields of isolated products. [c] Purity of the products as determined by ^1H NMR spectroscopy using 1,1,2,2-tetrachloroethane as the internal standard. [d] MeCN was used instead of THF. [e] Bu_3SnOMe (1 mmol) and **1s** (2 mmol) were used.

The synthesis of tributyl(3-bromopropynyl)stannane (**2t**) was examined, because the general reaction using ethylmagnesium bromide, propargyl bromide (**1t**), and Bu_3SnCl resulted in a mixture of **2t** (29%) and **3** (25%) even under controlled reaction conditions (Scheme 2).[12] The generation of 3-bromo-1-propynylmagnesium bromide and propargylmagnesium bromide in the first step led to the formation of the mixture.[13] However, our method provided the desired reaction and produced **2t** in 89% yield with no side reactions. One possible reason might have been that the catalytic amount of $ZnBr_2$ was sufficient and no base stronger than Bu_3SnOMe appeared in the system.



Scheme 2. Synthesis of tributyl(3-bromopropynyl)stannane (**2t**). Yields were determined by ^1H NMR spectroscopy using 1,1,2,2-tetrachloroethane as the internal standard. The value in parenthesis is the yield of the isolated product.

To gain insight into the reaction mechanism, a mixture of Bu_3SnOMe and $ZnBr_2$ was monitored by ^{13}C NMR spectroscopy (Figure 1). When $ZnBr_2$ and 2 equivalents of Bu_3SnOMe were mixed in $[D_8]$THF at room temperature, the generation of Bu_3SnBr (**5**; $\delta(^{13}C) = 30.0, 27.6, 18.3$, and 13.8 ppm) and the complete consumption of the starting Bu_3SnOMe were

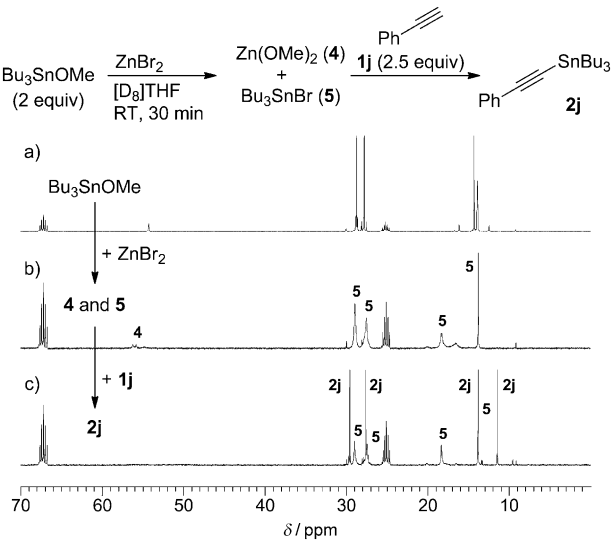
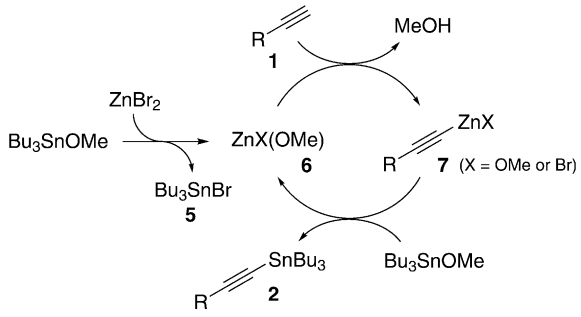


Figure 1. ^{13}C NMR spectra in $[D_8]$THF: a) Bu_3SnOMe. b) The mixture of $ZnBr_2$ and 2 equivalents of Bu_3SnOMe. c) Just after the addition of alkyne **1j** (2.5 equiv) to the mixture (b). See the Supporting Information for the experimental details.

observed (Figure 1b).[14] These results indicate that transmetalation between Bu_3SnOMe and $ZnBr_2$ occurred to give $Zn(OMe)_2$ (**4**; $\delta = 56.5$ ppm; Figure 1b).[15] The addition of phenylacetylene (**1j**) to the mixture furnished the corresponding alkynylstannane **2j** (Figure 1c). In contrast, when $Zn(OTf)_2$ instead of $ZnBr_2$ was treated with Bu_3SnOMe, no transmetalation was observed (see the Supporting Information). Apparently, an alternative mechanism should be considered.

On the basis of the NMR study, a plausible reaction mechanism is shown in Scheme 3. First, the transmetalation between Bu_3SnOMe and $ZnBr_2$ gives the zinc methoxide **6**,



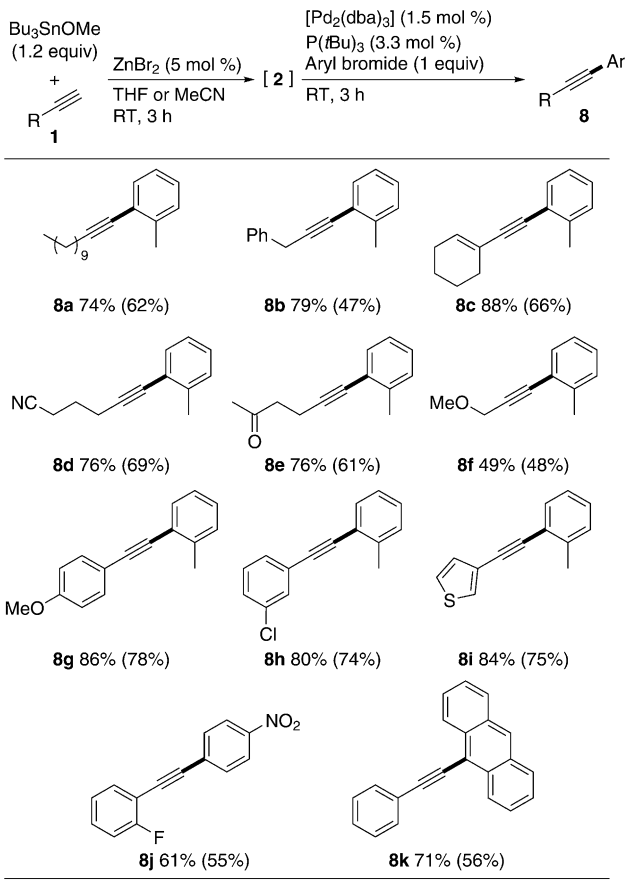
Scheme 3. Plausible reaction mechanism.

which should be $Zn(OMe)_2$ because Bu_3SnOMe is in large excess of $ZnBr_2$ in the reaction mixture.[16] Next, an abstraction of the terminal proton from alkyne **1** by **6** provides the alkynylzinc species **7**.[17] Finally, the reaction of **7** with Bu_3SnOMe affords the alkynylstannane **2** with the regeneration of **6**. The mechanism using a $Zn(OTf)_2$ catalyst may be the usual one (Table 1, entry 6), whereby the reaction would be started from the activation of the alkyne **1** by coordination to $Zn(OTf)_2$.[18]

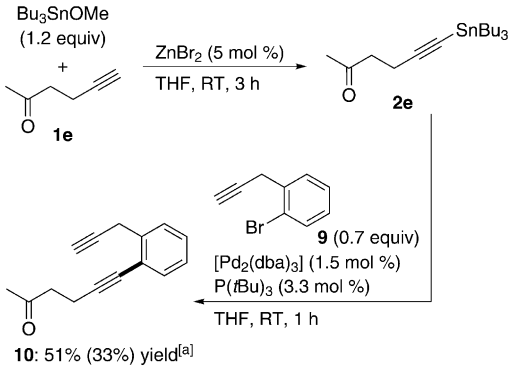
This catalytic method allowed the one-pot synthesis of various functionalized aryl alkynes by the Migita–Kosugi–Stille coupling (Scheme 4). The $ZnBr_2$-catalyzed formation of alkynylstannanes **2** was directly followed by palladium-catalyzed coupling with aryl bromides to furnish the corresponding aryl alkynes **8** in good to high yields.[19] In most cases, the yields of coupling products **8** paralleled those of alkynylstannanes **2**, as shown in Table 2. These results indicate that in situ generated alkynylstannanes were fully converted into coupling products without suppression by a zinc catalyst or the by-products MeOH and Bu_3SnBr.

To further expand the utility of this reaction, the synthesis of a diyne compound was investigated.[20] After the $ZnBr_2$-catalyzed reaction of Bu_3SnOMe with **1e**, the resulting **2e** (unpurified) was subjected to the coupling with the aryl bromide **9** bearing a terminal alkyne moiety to give the corresponding product **10** in 51% yield (Scheme 5). On the contrary, when **1e** was treated with **9** under the standard Sonogashira conditions, no product **10** was obtained (Scheme 6).[21,22] The zinc-catalyzed synthesis of alkynylstannanes/Migita–Kosugi–Stille coupling sequence is expected to be a helpful tool in the synthesis of more elaborate molecules.

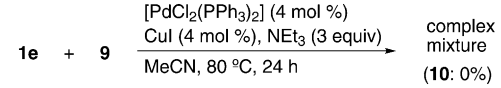
In summary, the $ZnBr_2$-catalyzed synthesis of alkynylstannanes with a wide range of functional group compatibility was achieved. As far as can be ascertained, this is the first



Scheme 4. One-pot synthesis of aryl alkynes by the Migita–Kosugi–Stille coupling. See the Supporting Information for experimental details. Yields were determined by ^1H NMR spectroscopy using 1,1,2,2-tetrachloroethane as the internal standard. Values in parentheses are yields of isolated products.



Scheme 5. Synthesis of diyne compound **10**. [a] Yield was determined by ^1H NMR spectroscopy using 1,1,2,2-tetrachloroethane as the internal standard. The value in parenthesis is the yield of the isolated product.



Scheme 6. Sonogashira reaction of **1e** with **9**.

example of the versatile synthesis of alkynylstannanes from Bu_3SnOMe and terminal alkynes under very mild reaction conditions. The transmetalation between Bu_3SnOMe and $ZnBr_2$ to generate $Zn(OMe)_2$ is proposed as a key process to complete the catalytic cycle. Moreover, aryl alkynes were synthesized using a one-pot protocol that included the Migita–Kosugi–Stille coupling. Additional investigations will focus on the reaction mechanism and synthetic applications of this catalytic method.

Experimental Section

Typical procedure (Table 2): Bu_3SnOMe (1.2 mmol) was added to a solution of $ZnBr_2$ in THF (0.05 M, 1 mL) and alkyne **1** (1 mmol). The mixture was stirred for 3 h at room temperature, and then quenched by H_2O (10 mL). The mixture was extracted with diethyl ether (3 × 10 mL). The collected organic layers were dried ($MgSO_4$), and evaporation of volatiles gave the crude product, which was analyzed by ^1H NMR spectroscopy. The crude product was diluted with AcOEt (30 mL) and washed with NH_4F (aq) (10%, 20 mL). The obtained white precipitate was filtered off, and the filtrate was dried ($MgSO_4$). Evaporation of volatiles gave the product.

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[10] $Zn(OTf)_2$ was used for the silylation of terminal alkynes as a catalyst, where an excess amount of base was required; see: a) H. Jiang, S. Zhu, *Tetrahedron Lett.* **2005**, *46*, 517; b) R. J. Rahaim, Jr., J. T. Shaw, *J. Org. Chem.* **2008**, *73*, 2912.

[11] The products, alkynylstannanes **2**, were decomposed during isolation by column chromatography using silica gel.

[12] Even though *n*BuLi or NaH was used instead of EtMgBr, the yields of **2t** were very low (*n*BuLi: 17% and NaH: 13%). The by-products have not been fully identified.

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[15] The transmetalation between a tin alkoxide and zinc halide has been proposed; see: a) M. Yasuda, S. Tsuji, I. Shibata, A. Baba, *J. Org. Chem.* **1997**, *62*, 8282; b) M. Yasuda, S. Tsuji, Y. Shigeyoshi, A. Baba, *J. Am. Chem. Soc.* **2002**, *124*, 7440.

[16] We used $Zn(OMe)_2$, which was prepared according to the literature (R. C. Mehrotra, M. Arora, *Z. Anorg. Allg. Chem.* **1969**, *370*, 300), as a catalyst instead of $ZnBr_2$ in the reaction of Bu_3SnOMe with phenylacetylene **1j**. The corresponding product **2j** was obtained in 11% yield. This result supports the catalytic cycle in Scheme 3 including $Zn(OMe)_2$. The solid zinc species employed was not soluble in the reaction mixture, and it might be a reason for the low yield. In situ generated $Zn(OMe)_2$ may have high reactivity owing to low aggregation. The detail of the zinc species will be investigated.

[17] The generation of **6** has not been directly observed yet. The detail investigation of the mechanism is now underway.

[18] $Zn(OTf)_2$ is an effective catalyst for the synthesis of alkynylzinc species, and the mechanism involving an activation of an alkyne by the coordination to $Zn(OTf)_2$ has been proposed; see: R. Fassler, C. S. Tomooka, D. E. Frantz, E. M. Carreira, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5843.

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[20] Diyne compounds are good precursors for cycloaddition reactions; see: a) D. Rodríguez, A. Navarro, L. Castedo, D. Domínguez, C. Saá, *Org. Lett.* **2000**, *2*, 1497; b) D. Rodríguez, M. F. Martínez-Esperón, A. Navarro-Vázquez, L. Castedo, D. Domínguez, C. Saá, *J. Org. Chem.* **2004**, *69*, 3842; c) J. Zhao, C. O. Hughes, F. D. Toste, *J. Am. Chem. Soc.* **2006**, *128*, 7436.

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[22] Although the reaction of **1e** with **9** was also carried out under copper and amine-free Sonogashira conditions (**1e** (0.5 mmol), **9** (0.5 mmol), $[Pd_2(dba)_3]$ (2 mol%), Bu_4NOAc (1.5 mmol), DMF (2 mL), RT, 24 h), product **10** was not obtained. 2-Allenyl bromobenzene (9%) was obtained as a by-product: S. Urgaonkar, J. G. Verkade, *J. Org. Chem.* **2004**, *69*, 5752.

