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**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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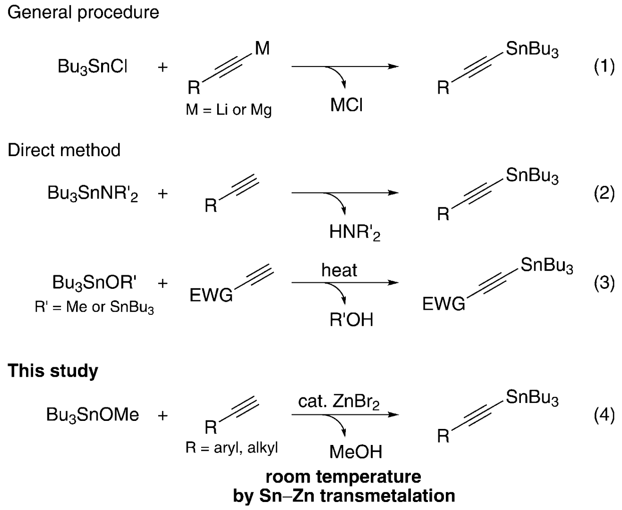
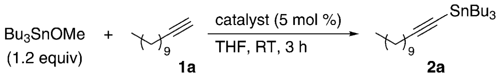
A carbon–carbon triple bond is a highly valuable and versatile functional group in many natural products, bioactive compounds,[1] and organic materials.[2] Alkynylstannanes, which have high stability, reactivity, and functional group tolerance, are important reagents for introducing an alkynyl moiety 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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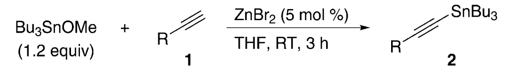
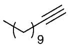
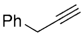
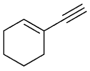
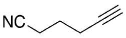
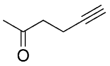
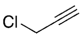
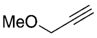
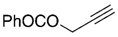
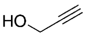
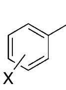
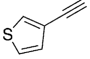
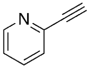
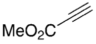
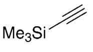
ambient temperature, 5 mol% of ZnBr$_2$ afforded the desired alkynylstannane **2a** in 68% yield.

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).

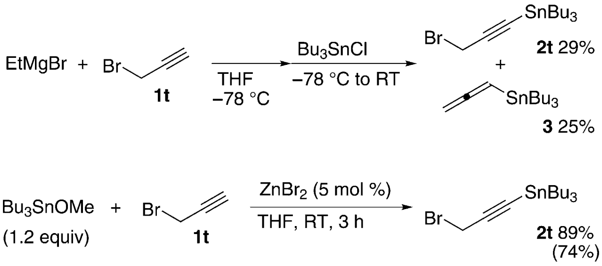
*Table 2:* Catalytic synthesis of alkynylstannanes **2** from Bu$_3$SnOMe and terminal alkynes **1**.[a]



| 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$_3$SnOMe (1.2 mmol), **1** (1 mmol), ZnBr$_2$ (0.05 mmol), THF (1 mL), RT, 3 h. [b] Yields of crude products determined by $^1$H 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 $^1$H NMR spectroscopy using 1,1,2,2-tetrachloroethane as the internal standard. [d] MeCN was used instead of THF. [e] Bu$_3$SnOMe (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$_3$SnCl 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$_3$SnOMe appeared in the system.



*Scheme 2.* Synthesis of tributyl(3-bromopropynyl)stannane (**2t**). Yields were determined by $^1$H 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$_3$SnOMe and ZnBr$_2$ was monitored by $^{13}$C NMR spectroscopy (Figure 1). When ZnBr$_2$ and 2 equivalents of Bu$_3$SnOMe were mixed in [D$_8$]THF at room temperature, the generation of Bu$_3$SnBr (**5**; $\delta(^{13}C) = 30.0, 27.6, 18.3$, and 13.8 ppm) and the complete consumption of the starting Bu$_3$SnOMe were

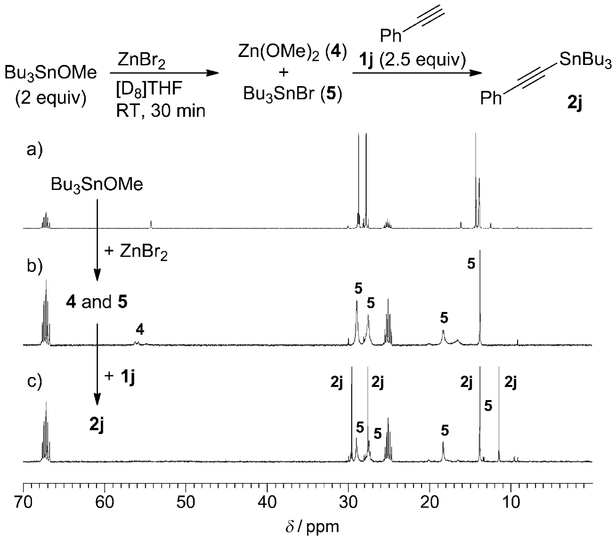
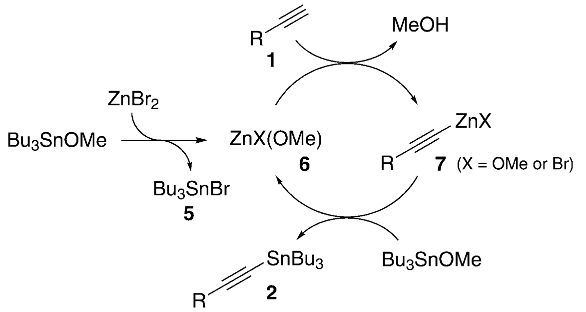


*Figure 1.* $^{13}$C NMR spectra in [D$_8$]THF: a) Bu$_3$SnOMe. b) The mixture of ZnBr$_2$ and 2 equivalents of Bu$_3$SnOMe. c) Just after the addition of alkyne **1j** (2.5 equiv) to the mixture (b). See the Supporting Information for the experimental details.

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**, 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]

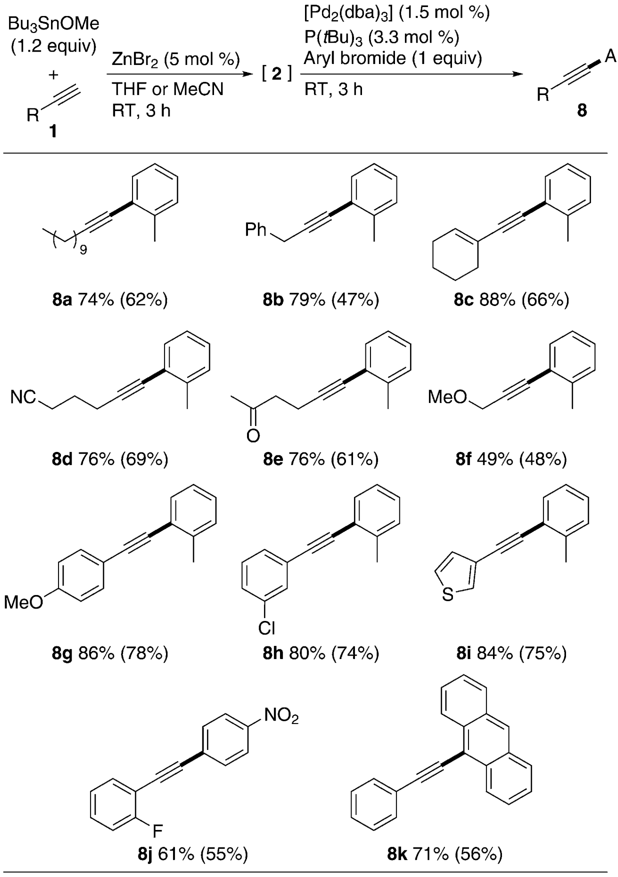


***Scheme 3.*** Plausible reaction mechanism.

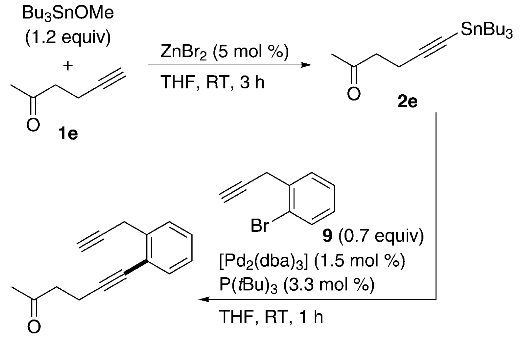
This catalytic method allowed the one-pot synthesis of various functionalized aryl alkynes by the Migita–Kosugi–Stille coupling (Scheme 4). The $ZnBr_2$-catalyzed formation of alkynylstannanes **2** was directly followed by palladium-catalyzed coupling with aryl bromides to furnish the corresponding 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.



**10**: 51% (33%) yield[a]

***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.

$$\mathbf{1e} + \mathbf{9} \xrightarrow[\text{MeCN, 80 °C, 24 h}]{[PdCl_2(PPh_3)_2]\ (4\ \text{mol \%}),\ \text{CuI}\ (4\ \text{mol \%}),\ NEt_3\ (3\ \text{equiv})} \begin{array}{c}\text{complex}\\ \text{mixture}\\ (\mathbf{10}\text{: 0\%})\end{array}$$

***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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[1] a) K. C. Nicolaou, W.-M. Dai, *Angew. Chem.* **1991**, *103*, 1453; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1387; b) M. E. Maier, *Synlett* **1995**, 13; c) A. L. K. Shi Shun, R. R. Tykwinski, *Angew. Chem.* **2006**, *118*, 1050; *Angew. Chem. Int. Ed.* **2006**, *45*, 1034.

[2] a) R. E. Martin, F. Diederich, *Angew. Chem.* **1999**, *111*, 1440; *Angew. Chem. Int. Ed.* **1999**, *38*, 1350; b) U. H. F. Bunz, *Chem. Rev.* **2000**, *100*, 1605; c) J. M. Tour, *Acc. Chem. Res.* **2000**, *33*, 791; d) J. Liu, J. W. Y. Lam, B. Z. Tang, *Chem. Rev.* **2009**, *109*, 5799.

[3] For selected examples of the reactions using alkynylstannanes, see: a) E. Shirakawa, Y. Yamamoto, Y. Nakao, S. Oda, T. Tsuchimoto, T. Hiyama, *Angew. Chem.* **2004**, *116*, 3530; *Angew. Chem. Int. Ed.* **2004**, *43*, 3448; b) E. Shirakawa, R. Morita, T. Tsuchimoto, Y. Kawakami, *J. Am. Chem. Soc.* **2004**, *126*, 13614; c) M. Ochiai, Y. Nishi, S. Goto, H. J. Frohn, *Angew. Chem.* **2005**, *117*, 410; *Angew. Chem. Int. Ed.* **2005**, *44*, 406; d) A. Yamamoto, M. Suginome, *J. Am. Chem. Soc.* **2005**, *127*, 15706; e) Y. Zhao, H. Wang, X. Hou, Y. Hu, A. Lei, H. Zhang, L. Zhu, *J. Am. Chem. Soc.* **2006**, *128*, 15048; f) A. M. González-Nogal, M. Calle, P. Cuadrado, R. Valero, *Tetrahedron* **2007**, *63*, 224; g) J. R. Perkins, R. G. Carter, *J. Am. Chem. Soc.* **2008**, *130*, 3290; h) L. Jin, Y. Zhao, H. Wang, A. Lei, *Synthesis* **2008**, 649.

[4] a) W. E. Davidsohn, M. C. Henry, *Chem. Rev.* **1967**, *67*, 73; b) E. Negishi, L. Anastasia, *Chem. Rev.* **2003**, *103*, 1979.

[5] For selected examples using alkynyllithium, alkynylmagnesium, and alkynylsodium reagents, see: a) H. Hertmann, *Z. Anorg. Allg. Chem.* **1954**, *276*, 20; b) H. Hartmann, H. Honig, *Angew. Chem.* **1957**, *69*, 614; c) H. Hartmann, H. Niemoeller, W. Reiss, B. Karbstein, *Naturwissenschaften* **1959**, *46*, 321; d) H. G. Viehe, *Chem. Ber.* **1959**, *92*, 1270.

[6] a) K. Jones, M. F. Lappert, *J. Chem. Soc.* **1965**, 1944; b) K. Jones, M. F. Lappert, *J. Organomet. Chem.* **1965**, *3*, 295; c) J. C. Pommier, *J. Organomet. Chem.* **1973**, *57*, 139.

[7] a) W. P. Neumann, F. G. Kleiner, *Tetrahedron Lett.* **1964**, *5*, 3779; b) A. G. Davies, D. C. Kleinschmidt, P. R. Palan, S. C. Vasishtha, *J. Chem. Soc. C* **1971**, 3972; c) F. G. Kleiner, W. P. Neumann, *Justus Liebigs Ann. Chem.* **1968**, *716*, 19.

[8] Y. Yamamoto, *J. Org. Chem.* **2007**, *72*, 7817.

[9] a) R. Takita, Y. Fukuta, R. Tsuji, T. Ohshima, M. Shibasaki, *Org. Lett.* **2005**, *7*, 1363; b) R. Takita, K. Yakura, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 13760; c) K. Miura, N. Fujisawa, S. Toyohara, A. Hosomi, *Synlett* **2006**, 1883; d) Y. Nishimoto, R. Moritoh, M. Yasuda, A. Baba, *Angew. Chem.* **2009**, *121*, 4647; *Angew. Chem. Int. Ed.* **2009**, *48*, 4577; e) Y. Nishimoto, H. Ueda, Y. Inamoto, M. Yasuda, A. Baba, *Org. Lett.* **2010**, *12*, 3390; f) B. Montaignac, M. R. Vitale, V. Ratovelomanana-Vidal, V. Michelet, *J. Org. Chem.* **2010**, *75*, 8322.

[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.

[13] A. Boaretto, D. Marton, G. Tagliavini, *J. Organomet. Chem.* **1985**, *297*, 149.

[14] The generation of $Bu_3SnBr$ was also confirmed by $^{119}Sn$ NMR spectroscopy (see the Supporting Information).

[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.

[19] A. F. Littke, L. Schwarz, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 6343.

[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.

[21] a) K. Sonogashira, *J. Organomet. Chem.* **2002**, *653*, 46; b) R. Chinchilla, C. Nájera, *Chem. Rev.* **2007**, *107*, 874; c) H. Plenio, *Angew. Chem.* **2008**, *120*, 7060; *Angew. Chem. Int. Ed.* **2008**, *47*, 6954.

[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.