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COMMUNICATION

Copper-Catalyzed Arylstannylation of Arynes in Sequence

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Copper-catalyzed arylstannylation of arynes has been developed. This transformation enables variously substituted *ortho*-stannylbiaryls and teraryls to be constructed straightforwardly. Electron-deficiency of a tin center is a key, and thus the single or dual insertion of arynes into arylstannanes is precisely controllable by simply changing the equivalence of the aryne precursors.

ortho-Substituted biaryls, *ortho*-linked teraryls and tetraaryls constitute an invaluable class of molecules such as ligands,¹ biologically active compounds² and functional materials.³ While cross-coupling has been most commonly employed for constructing their C(aryl)–C(aryl) bonds,⁴ arylmetalation of arynes is an attractive option because it enables synchronous construction of C(aryl)–C(aryl) and C(aryl)–metal bonds, thus being utilizable for further π -extension and functionalization. The arylmetalation of arynes has thus far been achieved with organometallic reagents of high nucleophilicity (M = Li, Mg, Cu) (Fig. 1A, *path a*), and attention has been mostly paid to the synthesis of biaryls via single insertion of arynes.⁵ Although there have been some reports on the dual insertion of same arynes, which provides *ortho*-teraryls straightforwardly,⁵ the synthetic potential of the arylmetalation remains yet to be explored; because, for example, sequential insertion of different arynes, which remarkably expands structural complexity and diversity of the *ortho*-teraryls to be accessed, has not been reported, to the best of our knowledge (Fig. 1A, *path b*). In addition, the use of the highly nucleophilic, moisture-sensitive organometallic reagents for the arylmetalation sacrifices functional group-compatibility, and the products' isolability and storability. In this context, our attention has been focused on the use of arylstannanes of less nucleophilicity, taking also into account that C(aryl)–Sn bonds are utilizable for the well-established C(aryl)–C and C(aryl)–heteroatom bond-forming reactions such as the Migita–

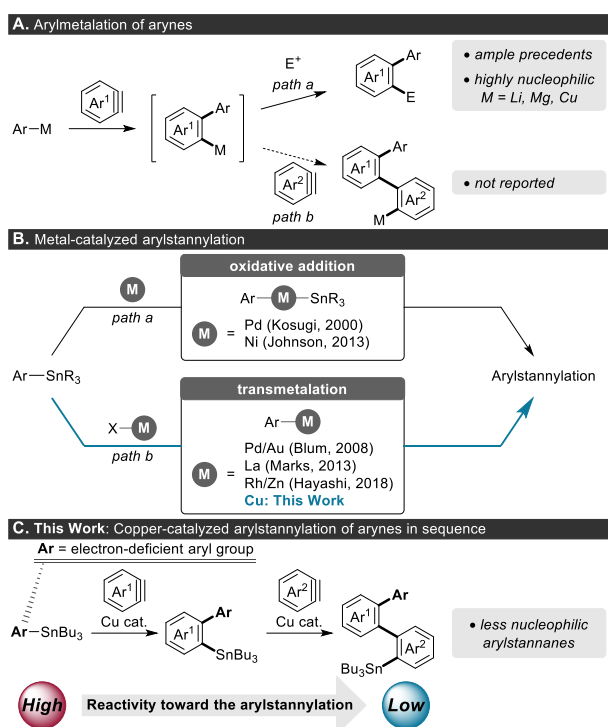


Fig. 1 (A) Arylmetalation of arynes. (B) Metal-catalyzed arylstannylation. (C) Copper-catalyzed arylstannylation of arynes in sequence.

Kosugi–Stille (MKS) coupling.⁶ Shirakawa and Hiyama have extensively studied the carbostannylation of unsaturated carbon linkages, where a C–Sn bond of alkynyl, allyl or acylstannanes is activated by oxidative addition to a Pd(0) or Ni(0) catalyst.⁷ In contrast, the paucity of arylstannylation should be because of the relatively oxidative addition-resistant property of arylstannanes, resulting in limited scope on the applicable arylstannanes (Fig. 1B, *path a*),⁸ and therefore development of different activation modes of C(aryl)–Sn bonds toward the arylstannylation is of high synthetic significance (Fig. 1B, *path b*).⁹ Recently, Hayashi has disclosed the Rh(I)–Zn(II)-cocatalyzed migratory arylstannylation of alkynes with various arylstannanes, in which C(aryl)–Sn bonds are activated

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by transmetalation.¹⁰ However, the use of precious metal or rare-earth catalysts is still inevitable for the transmetalation-based arylstannylation. We report herein on a unique catalysis of a Cu(I) salt, an abundant base metal, for the arylstannylation of arynes involving the transmetalation as a key step (Fig. 1C). Because the aryne insertion leads to a decrease in the reactivity of arylstannanes toward the arylstannylation, the single or dual insertion of arynes into arylstannanes is precisely controllable by simply changing the equivalence of the aryne precursors employed. Therefore, the sequential insertion of different arynes into the C(aryl)–metal bonds has first become feasible under the copper catalysis.

An initial investigation for the arylstannylation was undertaken by treating 1.0 equiv of benzyne (from 2-(trimethylsilyl)phenyl triflate (**2a**)¹¹ and KF/18-crown-6) with 1.0 equiv of tributyl(pentafluorophenyl)stannane (**1a**) in the presence of copper(I) 2-thiophenecarboxylate (CuTC, 5 mol %) in 1,2-diethoxyethane (DEE) at 130 °C (Fig. 2), and the arylstannylation was found to occur smoothly to provide *ortho*-stannylbiaryl (**3aa**) with 73% yield via single insertion of benzyne (see ESI for full optimization details[†]). Tetra- (**1b**), tri- (**1c**) and difluorophenylstannane (**1d**) were also efficiently convertible into the respective arylstannylation products (**3ba–3da**), whereas the reaction of monofluorophenylstannane (**1e**) resulted in a moderate yield of **3ea**. In addition, no desired product was available with phenylstannane (**1k**),¹² which reveals that the reaction efficiency is definitely affected by the electron-deficiency of the tin moieties induced by the fluorine substituents.

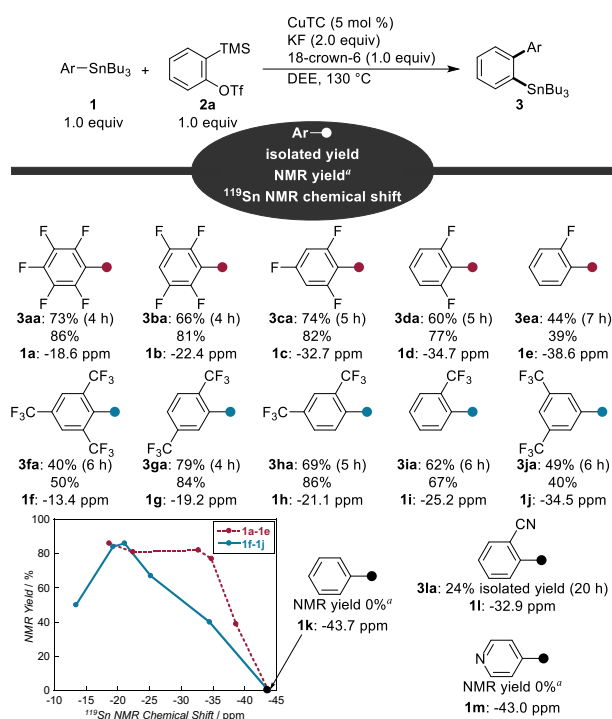


Fig. 2 Scope of arylstannanes for the synthesis of *ortho*-stannylbiaryls. Reaction performed at 0.10 mmol scale. ^a Yield was determined by ¹¹⁹Sn NMR analysis of the crude reaction mixture using tributyl(vinyl)stannane as an internal standard (reaction time: 4 h).

As depicted in Fig. 2, the tin-electron-deficiency (\approx tin-Lewis acidity) can be qualitatively estimated by ¹¹⁹Sn NMR chemical shift: it shows upfield shift as the number of fluorine decreases, demonstrating its reliability. The same tendency could be seen with trifluoromethyl-substituted phenylstannanes, and those with downfield shift afforded better yields of the arylstannylation products (**3ga–3ja**). The exceptional result of 2,4,6-tris(trifluoromethyl)phenylstannane (**1f**) may be attributable to the steric hindrance around the C(aryl)–Sn bond. In addition, 2-cyanophenylstannane (**1l**)¹³ was convertible into a 24% yield of **3la**, whereas the arylstannylation of 4-pyridylstannane (**1m**) did not proceed at all. Of note is that the reaction completely stopped at the single aryne insertion stage, irrespective of arylstannanes (**1**) employed, which implies that the tin-electron-deficiency of **3** is considerably reduced through the aryne insertion.

Variouly substituted *ortho*-stannylbiaryls were accessible by employing substituted arynes, and thus treatment of 3,6-dimethylbenzyne (from **2b**) with **1a** gave a 78% yield of **3ab** regardless of its steric congestion around the biaryl bond (Fig. 3). Other symmetrical arynes (from **2c–2e**) could also participate in the arylstannylation, and it should be noted that the reaction of unsymmetrical arynes (from **2f–2i**) proceeded with perfect regioselectivity, where the C(aryl)–C(aryl) bonds connected at the less sterically hindered sites.^{14,15} In addition, the exclusive formation of **3af** from a 3-methoxybenzyne precursor (**2'f**), a regioisomer of **2f**, has verified the intermediacy of an aryne in the arylstannylation.

Although the aryne insertion led to a decrease in the reactivity of **3**¹⁶ toward the arylstannylation as above, they turned out to be still involved in the reaction: treatment of **3aa**, **3af** or **3ag** with benzyne provided stannylteraryls (**4**) consisting of two different arynes in good yield (Fig. 4). The net sequential insertion was also applicable to 3,6-dimethylbenzyne to afford sterically-demanding **4afb**. As can be expected from the reactivity trend, no trace of tetraaryls via the arylstannylation of **4** was observable.

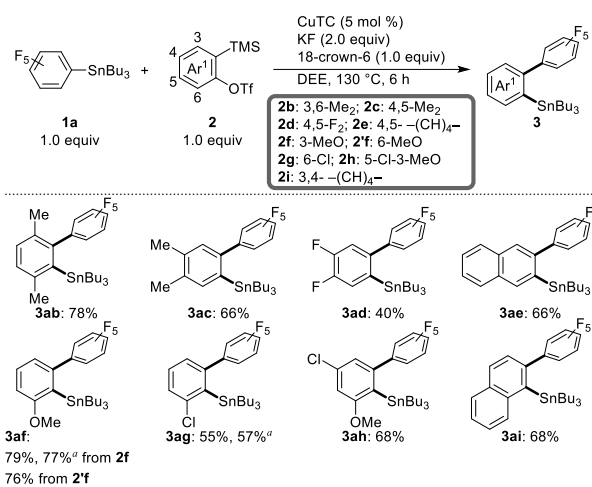


Fig. 3 Scope of arynes for the synthesis of *ortho*-stannylbiaryls. Reaction performed at 0.10 mmol scale. Isolated yields are shown. Regioisomeric ratio was determined by ¹H NMR analysis. ^a Reaction performed at 1.0 mmol scale.

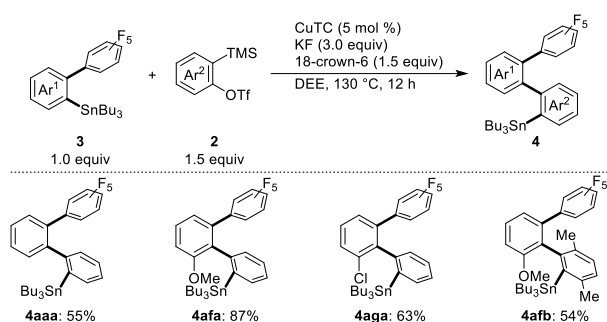


Fig. 4 Synthesis of stannylteraryls via sequential insertion of different arynes to tributyl(pentafluorophenyl)stannanes. Reaction performed at 0.10 mmol scale. Isolated yields are shown.

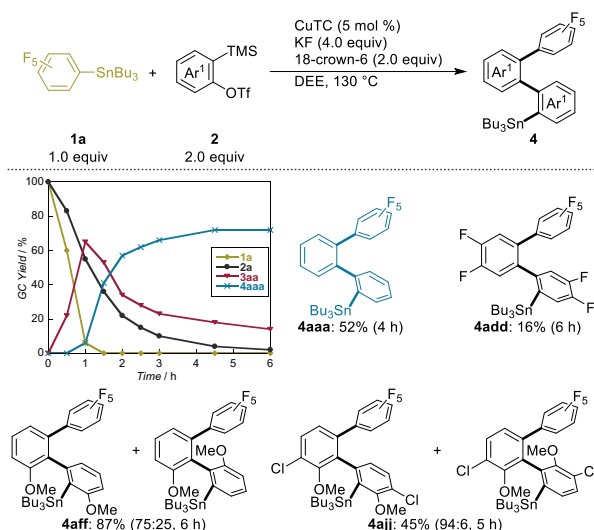


Fig. 5 A one-pot sequential insertion of the same arynes. Reaction performed at 0.10 mmol scale. Isolated yields are shown. Regioisomeric ratio was determined by ^1H NMR analysis.

The distinct reactivities between arylstannanes (**1**) and biarylstannanes (**3**) in the arylstannylation, which enables the sequential different aryne insertion, were confirmed by monitoring the reaction progress of one-pot sequential **2a** insertion. As shown in the Fig. 5 plot, **3aa** began to be consumed for generating **4aaa** after almost all of **1a** disappeared, giving 52% isolated yield of **4aaa**.¹⁷ The one-pot synthesis of stannylteraryls was also possible with 4,5-difluorobenzynes (from **2d**), although the yield became lower. In addition, unsymmetrical arynes (from **2f** or **2j**) underwent the one-pot sequential insertion to give a mixture of two regioisomers,¹⁵ where the second aryne was partially inserted in unusual orientation.

The present arylstannylation should be initiated by fluoride ion-assisted transmetalation between arylstannane **1** and Cu catalyst (Fig. 6, **Step 1** of **Cycle 1**). An aryne then accepts nucleophilic attack of the resulting arylcopper species (**1'**) to provide a biaryl copper species (**3'**) (**Step 2**), which is transformed into an *ortho*-stannylbiaryl (**3**) through capture by a tin fluoride (**Step 3**). After most of **1** is consumed, **cycle 2** becomes operative to convert **3** into a stannylteraryl (**4**).

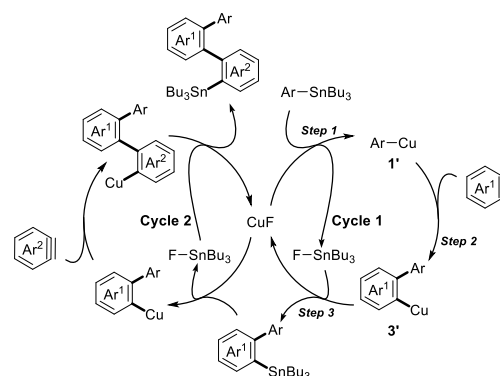
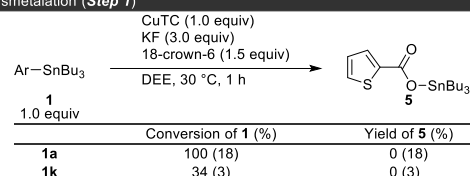
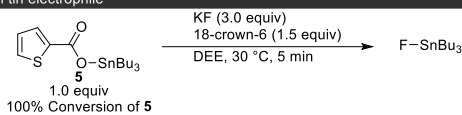


Fig. 6 A plausible catalytic cycle for copper-catalyzed arylstannylation.

A. Transmetalation (**Step 1**)



B. Actual tin electrophile



C. Capture of **1'k** with tin fluoride (**Step 3**)

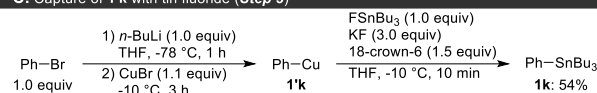


Fig. 7 Mechanistic studies on the proposed catalytic cycle. (A and B) Conversions and yields were determined by ^{119}Sn NMR analysis of the crude reaction mixture using tributyl(vinyl)stannane as an internal standard. Values in parentheses were obtained in the reaction without adding KF/18-crown-6. (C) Yield was determined by GC analysis.

To gain insight into the proposed catalytic cycle, we performed stoichiometric reactions on the elementary steps (**Steps 1** and **3**).¹⁸ Although the transmetalation (**Step 1**) turned out to take place by treating **1a** with CuTC, as judged by the formation of Bu_3SnTC (**5**), the presence of KF and 18-crown-6 remarkably accelerated this step (100% conv., Fig. 7A), indicating the pivotal role of a fluoride ion in the transmetalation.¹⁹ The contrasting results in the arylstannylation (**1a** vs. **1k**, Fig. 2) are attributable to different reactivities in the transmetalation: conversion of **1k** was considerably sluggish even in the presence of a fluoride ion (34% conv., Fig. 7A),²⁰ and the results reveal that tin-electron-deficiency directly affects the progress of the transmetalation. No observation of **5** in the fluoride-mediated reaction of **1a** with CuTC should imply that the tin moiety ended up being converted into Bu_3SnF .²¹ Besides, immediate formation of an insoluble solid (Bu_3SnF)²² in the reaction of **5** with KF/18-crown-6 strongly supports that the tin fluoride acts as an actual tin electrophile²³ in the catalytic cycle (Fig. 7B).²¹ Indeed, Bu_3SnF ²⁴ was captured by Ph-Cu (**1'k**) to give PhSnBu_3 (**1k**), thus proving the validity of **Step 3** (Fig. 7C).

Synthetic utility of the arylstannylation products has been demonstrated by converting the C(aryl)-Sn bond of **3aa**, which

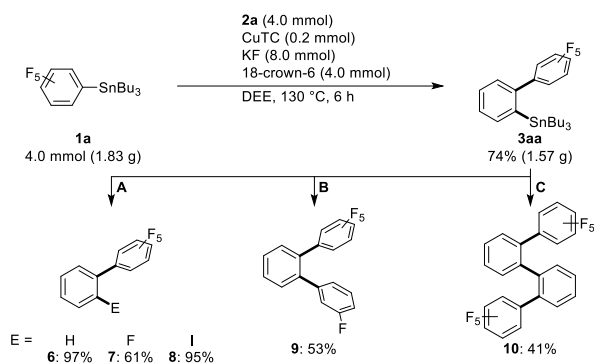


Fig. 8 Gram-scale arylstannylation and transformations of the resulting *ortho*-stannybiaryl. (A) E = H: HCl (10 equiv), THF, 25 °C, 3 h. E = F: F-TEDA (1.2 equiv), AgOTf (2.0 equiv), acetone, 25 °C, 30 min. E = I: I₂ (1.5 equiv), DCM, 25 °C, 30 min. (B) 1-fluoro-3-iodobenzene (1.8 equiv), Pd(PPh₃)₄ (10 mol %), CuCl (5.0 equiv), LiBr (6.0 equiv), DMF, 160 °C, 30 min (microwave). (C) CuCl (2.6 equiv), DMF, 25 °C, 6 h.

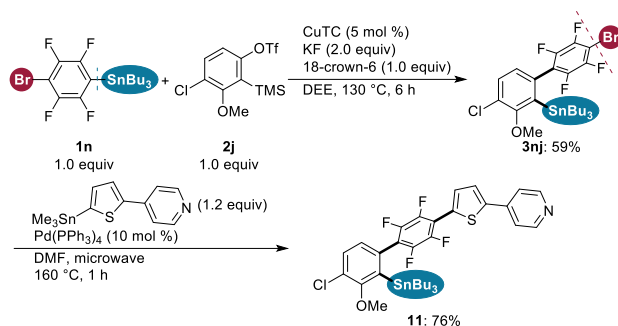


Fig. 9 Synthesis of π -extended arylstannane by chemoselective MKS coupling of an *ortho*-stannybiaryl generated from **1n**.

can be prepared in gram scale (1.57 g), into C(aryl)–F or C(aryl)–I bonds through electrophilic reactions with F-TEDA/AgOTf²⁵ or I₂ (Fig. 8). Quantitative protodestannylation and C–C bond-forming reactions (the MKS coupling and oxidative homocoupling), which furnished an *ortho*-teraryl (**9**) or an *ortho*-tetraaryl (**10**), were also achievable. Furthermore, the transmetalation (not oxidative addition)-based catalytic cycle allowed a C(aryl)–Br bond of **1n** to be compatible with the arylstannylation, affording multihalogenated *ortho*-stannybiaryl **3nj**. Finally, **3nj** could be transformed into a π -extended arylstannane (**11**) by chemoselective MKS coupling at the C(aryl)–Br bond (Fig. 9).

In conclusion, we have developed the arylstannylation of arynes, which provides direct access to diverse *ortho*-stannybiaryls and teraryls, under the copper catalysis method. The tin-electron-deficiency has been found to significantly affect the reaction progress, thus enabling different arynes to be sequentially inserted into C(aryl)–Sn bonds. Further studies on the unique copper catalysis toward carbostannylation of unsaturated carbon–carbon bonds are in progress.

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Conflicts of interest

There are no conflicts to declare.

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- 87% recovery of **1k** was observed by ¹¹⁹Sn NMR analysis of the crude reaction mixture.
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- The regioselective outcome can be rationally explained by the general tendency of arynes to accept nucleophilic attack at the more electron-deficient and the less sterically hindered sites. See: H. Yoshida, in *Comprehensive Organic Synthesis, Second Edition*, ed. P. Knochel and G. A. Molander, Elsevier, Amsterdam, 2014, Vol. 4, pp. 517–579.
- See ESI for details (Figure S7†).
- The tin-electron-deficiency of **3** may be underestimated by ¹¹⁹Sn NMR chemical shift; their upfield chemical shift (*ca.* -40 ppm), being comparable to that of **1k**, is probably attributable to shielding effect by the *ortho*-C₆F₅ moiety, which resulted in the smooth arylstannylation.
- The use of **2a** (3 equiv) at 200 °C did not give a stannytetraaryl. See ESI for details (Table S13†).
- Step 2** has been already reported. See ref. 5.
- It has been reported that a fluoride anion coordinates to a tin center of arylstannanes to give hypercoordinate tin species with enhanced reactivity towards the transmetalation in the MKS coupling in ethereal solvents. See: A. F. Littke, L. Schwarz and G. C. Fu, *J. Am. Chem. Soc.*, 2002, **124**, 6343.
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- Bu₃SnF is usually insoluble in organic solvents, however, it becomes soluble in the presence of an excess fluoride ion, thus acting as a tin electrophile. See: H. Yoshida, R. Yoshida and K. Takaki, *Angew. Chem., Int. Ed.*, 2013, **52**, 8629.
- Commercially available Bu₃SnF was used.
- A mixture of **7** (61% yield) and **6** (19% yield) was formed.