

Organic & Biomolecular Chemistry

Accepted Manuscript



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.



EDGE ARTICLE

Sn atom-economical approach toward arylstannanes: Ni-catalysed stannylation of aryl halides using Bu₃SnOMe†

Kimihiro Komeyama,* Ryota Asakura and Ken Takaki

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

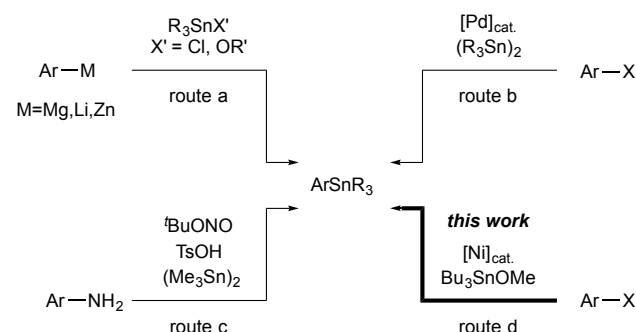
www.rsc.org/chemicalscience

Stannylation of carbon-halogen bonds is one of the most promising and straightforward approach for the preparation of organostannane compounds. Although a wide variety of methods are now available, all protocols require the use of highly nucleophilic organometals or wasteful stannyl sources like distannanes. Here, we report a new nickel-catalysed stannylation of aryl and alkenyl-halides using Bu₃SnOMe as stannyl source to afford aryl and vinyl-stannanes, respectively. This method enables the stannylation of not only bromides, but also of chlorides and triflates to furnish functionalized aryl and alkenyl-stannanes without a liberation of wasteful and toxic stannyl byproduct.

Arylstannanes are useful synthetic intermediates because of their versatility in the construction of the Aryl-C, ^[1]-NR₂, ^[2]-F, ^[3] and -OCF₃ ^[4] bonds. The most promising route to afford arylstannanes relies on the trapping of arylmetal species (Mg, Li, Zn) ^[3a,5] using trialkylstannyl electrophiles R₃SnX' (route a, Scheme 1). However, these protocols have some drawbacks: poor functional group tolerance and/or delicate conditions for the preparation of arylmetal species. In contrast, the Pd-catalysed stannylation of aryl halides (Scheme 1b) ^[6] and the recently proposed Sandmeyer-type reaction of anilines (Scheme 1c) ^[7] using hexaalkyl distannanes have been demonstrated as alternative procedures. Although both the above methods are useful and powerful for functionalized arylstannane synthesis, the liberation of highly toxic stannyl byproducts is unavoidable. These disadvantages drastically reduce the efficiency of organostannane chemistry in both academic and industrial pursuits.

On the other hand, a few transition metal-catalysed reactions involve nucleophilic stannylation processes using trialkylstannyl alkoxides ROSn(alkyl)₃ as terminal electrophiles. For instance, the interception of alkynylzinc ^[8] and alkenylcopper intermediates ^[9] generated in situ using stannyl alkoxides quickly transforms into the corresponding alkynyl or alkenyl stannane compounds, respectively. ^[10] However, these catalytic processes have never been applied to the stannylation of ubiquitous carbon(sp²)-halogen bonds because of their low reactivity for zinc and copper complexes. In this paper, we report a Ni-catalysed stannylation of aryl halides using Bu₃SnOMe in the presence of manganese powder (Scheme 1d). This stannylation process could be an ideal and

straightforward approach to afford aryl or vinyl stannanes from both organohalides and organotriflates. The proposed process possesses the following advantages: (1) available substrates, (2) a broad scope of functional groups, and (3) Sn atom-economy without the liberation of wasteful toxic inorganic stannyl residues.



Scheme 1 Representative synthetic method for arylstannanes.

Initially, we explored the suitable reaction conditions for the stannylation of aryl bromides **1a** and **1b** using stannyl electrophile as model substrates based on the previous work by Tsuji and Fujihara (Table 1).¹¹ When **1a** was treated with Bu₃SnOMe (1.2 equiv.) in the presence of NiBr₂ (10 mol%), 2,2'-bipyridine (bpy, 10 mol%), and Mn powder (2.0 equiv. treated with 20 mol% of chlorotrimethylsilane), arylstannane **2a** was afforded in 72% yield along with biaryl **3a** in 14% yield (entry 1).¹² The preformed [NiBr₂(bpy)] complex exhibited higher catalytic performance to afford **2a** in 91% yield (entry 2).¹³ 2,2'-Bipyridine ligand and Ni catalyst were crucial (entries 3–7). The replacement of Mn or **1a** with Zn or 4-iodoanisole, respectively, induced the homocoupling reaction (entries 8 and 9). In contrast, the optimized conditions (entry 2) were not sufficient for the stannylation of

Department of Applied Chemistry, Graduate School of Engineering, Hiroshima University, 1-4-1 Kagamiyama, Higashi-Hiroshima City, Hiroshima 739-8527, Japan. E-mail: kkome@hiroshima-u.ac.jp

† Electronic Supplementary Information (ESI) available: Additional data for the screening of reaction conditions, experimental procedures and characterization for new compounds are provided. See DOI: 10.1039/x0xx00000x

Table 1 Screening of reaction conditions in the stannylation of 4-methoxy bromobenzene (**1a**) and 4-trifluoromethyl bromobenzene (**1b**).

entry	1	[Ni] _{cat.}	ligand (x mol%)	yield / % ^a	
				2	3
1	1a	NiBr ₂	bpy (10)	72	14
2	1a	NiBr ₂ (bpy)	—	91 (85)	9
3	1a	NiBr ₂	—	0	0
4	1a	NiBr ₂	PPh ₃ (20)	21	7
5	1a	NiBr ₂	dppe (10)	0	0
6	1a	NiBr ₂	tbpy ^b (10)	10	70
7	1a	—	bpy (20)	0	0
8 ^c	1a	NiBr ₂ (bpy)	—	23	60
9 ^{d,e}	1a	NiBr ₂ (bpy)	—	60	39
10 ^f	1b	NiBr ₂ (bpy)	—	22	68
11 ^f	1b	NiBr ₂	PPh ₃ (20)	75	12
12 ^f	1b	NiBr ₂	PPh ₃ (30)	86	6
13 ^{f,g}	1b	NiBr ₂	PPh ₃ (30)	96 (90)	4

^a Determined by GC yield with tridecane as internal standard. Parenthesis value indicates isolated yield. ^b tbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine. ^c Zn was used instead of Mn. ^d 4-Iodoanisole was used instead of bromide **1a**. ^e 25 °C, 4 h. ^f 25 °C, 18 h. ^g Et₄Ni (20 mol%) was added.

electron-poor aryl bromides like **1b**; instead, the homocoupling mainly proceeded due to the high reactivity of low-valent Ni toward the aryl halides [14] and/or the poor nucleophilicity of the generated aryl nickel. [15] Fortunately, the low chemoselectivity was improved by replacing the bpy ligand with electron-donating PPh₃ (entry 10). Further improvement was achieved by increasing ligand loading (30 mol%) and by adding Et₄Ni [11,17] (entries 11–13). In this stannylation, other stannyl electrophiles such as Bu₃SnCl, Bu₃SnO^tBu, and Bu₃SnOAc also participated, leading to **2a** in 74%, 69%, and 54% yields, respectively (Table S1 in supporting information). Additionally, hexane, toluene, tetrahydrofuran, 1,4-dioxane, and acetonitrile were not suitable solvents, the most of substrates remained unchanged.

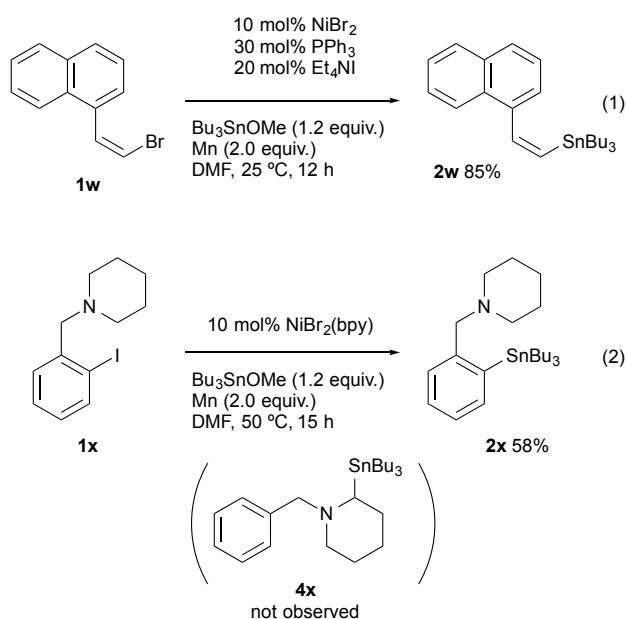
Table 2. Scope of aryl and vinyl halides

X = Br		
2c 66% (18 h) ^b	2d 72% (18 h) ^{a,c}	2e 87% (4 h) ^b 89% (4 h) ^{b,d}
2f 71% (18 h) ^b	2g 78% (18 h) ^b	2h 68% (18 h) ^{b,e}
2i 88% (4 h) ^b	2j 61% (90 h) ^a	2k 74% (24 h) ^a
2l 61% (4 h) ^a	2m 54% (18 h) ^{a,c}	2n 86% (18 h) ^b
2o 84% (12 h) ^b	2p 76% (18 h) ^b	2q 76% (18 h) ^b
2r 58% (13 h) ^b	2s 67% (36 h) ^b	
(<i>E</i>)- 2t 67% (18 h) ^a	(<i>Z</i>)- 2t 67% (36 h) ^b	
X = Cl, OTf		
2u 66% (18 h) ^b X = Cl	2o 84% (12 h) ^b X = OTf	2v 51% (12 h) ^b X = OTf

^a 10 mol% NiBr₂(bpy), 50 °C. ^b 10 mol% NiBr₂, 30 mol% PPh₃, 20 mol% Et₄Ni, 25 °C. ^c 1.5 equivalent of Bu₃SnOMe was used. ^d 2.05 gram of **2e** was obtained. ^e Xantophos (20 mol%) was used instead of PPh₃ (30 mol%). Reaction temperature: 40 °C.

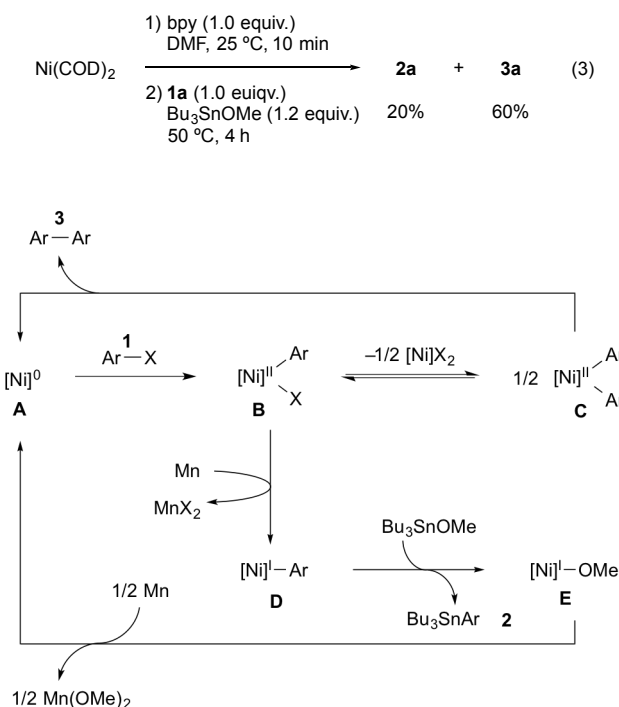
With optimized conditions in hand (entries 2 and 13, Table 1), we next investigated the substrate scope in the Ni-catalysed stannylation by employing various aryl or vinyl halides with Bu_3SnOMe (Table 2). Aryl bromides containing electron-donating (**1d**) and -withdrawing substituents (**1e–1g**) at the *para*-position were well tolerated, giving rise to the corresponding stannylated products (**2c–2g**) in good yields. In addition, the stannylation was successfully carried out on gram-scale synthesis, giving rise to **2e** in 2.05 gram (89% yield). For the efficient stannylation of 4-cyano bromobenzene (**1h**), bidentate phosphine ligands bearing large bite angles were effective (Table S2 in supporting information). *Ortho* and *meta*-substituents (**1i–1o**) also participated in the stannylation, leading to the corresponding stannylated products (**2i–2o**). Heteroaryl bromides (**1p–1r**) also underwent this transformation to afford the stannylation products in good-to-high yields. Slightly acidic N–H bond did not prevent the reaction and afforded 4-amino-2-fluorophenyl stannane (**2s**), which is an intermediate in torezolid synthesis.^[18] In addition, the stereochemistry of (*E*)- and (*Z*)-olefinic moieties (**1t**) were maintained during the stannylation. Furthermore, the present stannylation is active not only for bromides, but also for chloride **1u** and triflates **1o** and **1v**, yielding the corresponding stannylated products **2u**, **2o**, and **2v**, respectively.

A stereocontrol study was conducted using (*Z*)-1-(bromovinyl)naphthalene (**1w**), as shown in equation 1. The reaction of **1w** with Bu_3SnOMe exclusively yielded (*Z*)-vinyl stannane **2w** with complete retention of the stereo-integrity.^[19] In addition, it is known that the aryl radical possessing a (dialkylamino)methyl group at the *ortho*-position, derived from the halogen atom abstraction of 1-(2-iodobenzyl)piperidine (**1x**), rapidly undergoes 1,5-hydrogen atom transfer to afford an α -amino alkyl radical.^[20] This radical might be converted to alkyl stannane **4x** through the formation of alkyl nickel species via recombination between Ni and the alkyl radical.^[21] However, the reaction of **1x** provided simple arylstannane **2x** (eqn (2)). Furthermore, the addition of a hydrogen atom donor



	Mn /equiv.	2a /%	3a /%
1) Mn (0.9–2.3 equiv.) ① DMF, 25 °C, 30 min	0.9	9	70
$\text{NiBr}_2(\text{bpy})$	1.0	14	68
2) 1a (1.0 equiv.) ② Bu_3SnOMe (1.2 equiv.) ③ 50 °C, 4 h	1.1	20	60
	1.5	47	42
	2.3	90	5

Scheme 2. Stoichiometric reaction of $\text{NiBr}_2(\text{bpy})$ with **1a** (1.0 equiv.) and Bu_3SnOMe (1.2 equiv.) in the presence of Mn powder (x equiv.).



Scheme 3. Plausible reaction pathway for the Ni-catalysed stannylation of aryl halides.

like 9,10-dihydroanthracene^[22] into the reaction media did not fully block the stannylation; 45–62% yields of **2a** were obtained even if excess scavenger (2.0–3.0 equiv.) was present in the reaction media.^[23] These findings imply that the primary pathways for oxidative addition of Ni into organohalides **1** do not generate free organic radicals.

The stoichiometric reaction of $\text{NiBr}_2(\text{bpy})$ with **1a** and Bu_3SnOMe in the presence of various amounts of Mn powder (Scheme 2) provided some important information about the mechanism. As the loading of Mn was increased, the yield of stannylated product **2a** increased, while that of the homocoupling product **3a** decreased. Particularly note that the lower loading (0.9–1.1 equiv.) of Mn powder mainly produced the homocoupling product **3a**. A similar product distribution was observed in the reaction of $\text{Ni}(\text{COD})_2/\text{bpy}$ with **1a** and Bu_3SnOMe in the absence of Mn reductant (eqn (3)). These results could indicate that monovalent Ni is an active intermediate in the Ni-catalysed stannylation. Thus, the present stannylation could be initiated by the generation of $[\text{Ni}]^0$ complex A from the reduction of the initial $[\text{Ni}(\text{II})]$ with Mn

powder (Scheme 3). The oxidative addition of aryl halides (Ar-X: **1**) to **A** afford Ar-[Ni]^{II}-X **B**. Although the divalent Ni intermediate **B** might be slightly active in the interception of Bu₃SnOMe (Scheme 2 and eqn (3)), disproportionation of **B** would spontaneously occur to afford [Ni]^{II}X₂ and [Ni]^{II}Ar₂ **C**,^[14a,24] which would lead to the homocoupling product **3** and **A** via reductive elimination. In contrast, in the presence of excess Mn, **B** could be preferentially reduced to [Ni]^I-Ar **D**, which would be more active than **B** for interception because of the higher nucleophilicity of monovalent Ni.^[15,16] This would afford the stannylated product **2** as well as [Ni]^I-OMe **E**, followed by the regeneration of **A** with Mn.

Conclusions

In conclusion, we have demonstrated a simple and atom-economic al stannylation using stannyl electrophiles catalysed by Ni complexes in the presence of Mn reductant. This stannylation can be tolerated by a diverse set of functional groups on aryl halides and does not release wasteful stannyl residues. Preliminary mechanistic studies suggest that aryl Ni(I) species are intermediates in this transformation. Further mechanistic studies and synthetic applications of this transmetalation process of the C-Ni bond are underway.

Acknowledgements

This work was partially supported by a Grant-Aid for Scientific Research (KAKENHI) from the Ministry of Education, Culture, Sports, Science and Technology of Japan. K. K thanks for financial support from the Electronic Technology Research Foundation of Chugoku. We also acknowledge the Natural Science Center for Basic Research and Development (N-BARD) in Hiroshima University for HRMS analysis.

Notes and references

- (a) J. K. Stille, *Angew. Chem. Int. Ed.* 1986, **25**, 508; (b) M. Kosugi, K. Fugami, *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E. Negishi), Wiley, New York, 2002, p. 263.
- P. Y. S. Lam, G. Vincent, D. Bonne, C. G. Clark, *Tetrahedron Lett.* 2002, **43**, 3091.
- (a) T. Furuya, A. E. Strom, T. Ritter, *J. Am. Chem. Soc.* 2009, **131**, 1662; (b) Y. Ye, M. S. Sanford, *J. Am. Chem. Soc.* 2013, **135**, 4648.
- C. Huang, T. Liang, S. Harada, E. Lee, T. Ritter, *J. Am. Chem. Soc.* 2011, **133**, 13308.
- (a) L. Adam Shih-Yuan, D. Wen-Chin, *Tetrahedron Lett.* 1996, **37**, 495; (b) T. Hayashi, M. Ishigedani, *Tetrahedron* 2001, **57**, 2589; (c) P. Knochel, R. D. Singer, *Chem. Rev.* 1993, **93**, 2117; (e) C. Gosmini, J. Périchon, *Org. Biomol. Chem.* 2005, **3**, 216.
- (a) D. Azarian, S. S. Dua, C. Eaborn, D. R. Walton, *J. Orgmet. Chem.* 1976, **117**, C55; (b) H. Azizian, C. Eaborn, A. Pidcock, *J. Organomet. Chem.* 1981, **215**, 49.
- Di Qiu, L. Jin, S. Wang, S. Tang, X. Wang, F. Mo, Y. Zhang, J. Wang, *Angew. Chem. Int. Ed.* 2013, **52**, 11581.
- K. Kiyokawa, N. Tachikake, M. Yasuda, A. Baba, *Angew. Chem. Int. Ed.* 2011, **50**, 10393.
- (a) Y. Takemoto, H. Yoshida, K. Takaki, *Chem. Eur. J.* 2012, **18**, 14841; (b) T. Wakamatsu, K. Nagao, H. Ohmiya, M. Sawamura, *Angew. Chem. Int. Ed.* 2013, **52**, 11620.
- Interception of carbon-silver bond using other stannyl electrophiles was reported. See: J. Liu, X. Xie, Y. Liu, *Chem. Commun.* 2013, **49**, 11794.
- T. Fujihara, K. Nogi, T. Xu, J. Terao, Y. Tsuji, *J. Am. Chem. Soc.* 2012, **134**, 9106.
- A possibility that the biaryl **3a** was formed through the Stille coupling of **1a** with the generated **2a** was completely ruled out in the reaction of **1a** with PhSnBu₃ under the identical conditions. D. A. Powell, T. Maki, G. C. Fu, *J. Am. Chem. Soc.* 2005, **127**, 510.
- The reaction of 4-anisyl chloride under the identical conditions (Table 1, entry 2) afforded **2a** in 33% yield, along with **3a** in 32%.
- (a) T. T. Tsou, J. K. Kochi, *J. Am. Chem. Soc.* 1979, **101**, 6319; (b) V. P. Ananikov, *ACS Catal.* 2015, **5**, 1964.
- J.-X. Hu, H. Wu, C.-Y. Li, W.-J. Sheng, Y.-X. Jia, J.-R. Gao, *Chem. Eur. J.* 2011, **17**, 5234.
- (a) M. Zembayashi, K. Tamao, J.-I. Yoshida, M. Kumada, *Tetrahedron Lett.* 1977, **18**, 4089; (b) M. Iyoda, H. Otsuka, K. Sato, N. Nisato, M. Oda, *Bull. Chem. Soc. Jpn.* 1990, **63**, 80; (c) V. Percec, J.-Y. Bae, M. Zhao, D. H. Hill, *J. Org. Chem.* 1995, **60**, 176.
- W. B. Im, S. H. Choi, J.-Y. Park, S. H. Choi, J. Finn, S.-H. Yoon, *Eur. J. Med. Chem.* 2011, **46**, 1027.
- J. J. Hirner, S. A. Blum, *Organometallics* 2011, **30**, 1299.
- (a) V. Snieckus, J. C. Cuevas, C. P. Sloan, H. Liu, D. P. Curran, *J. Am. Chem. Soc.* 1990, **112**, 896; (b) M. Murakami, M. Hayashi, Y. Ito, *J. Org. Chem.* 1992, **57**, 793; (c) N. Yoshikai, A. Mieczkowski, A. Matsumoto, L. Ilies, E. Nakamura, *J. Am. Chem. Soc.* 2010, **132**, 5568.
- (a) H. Yin, C. Zhao, H. You, K. Lin, H. Gong, *Chem. Commun.* 2012, 48, 7034; (b) D. A. Everson, B. A. Jones, D. J. Weix, *J. Am. Chem. Soc.* 2012, **134**, 6146; (c) H. Xu, C. Zhao, Q. Qian, W. Deng, H. Gong, *Chem. Sci.* 2013, **4**, 4022; (d) Y. Peng, X.-B. Xu, J. Xiao, Y.-W. Wang, *Chem. Commun.* 2013, **50**, 472; (e) Z. Zuo, D. T. Ahneman, L. Chu, J. A. Terrett, A. G. Doyle, D. W. C. MacMillan, *Science* 2014, **345**, 437; (f) L. K. G. Ackerman, L. L. Anka-Lufford, M. Naodovic, D. J. Weix, *Chem. Sci.* 2014, **6**, 1115.
- (a) Ba L Tran, Bijie Li, M. Driess, J. F. Hartwig, *J. Am. Chem. Soc.* 2014, **136**, 2555; (b) S. K. Bose, K. Fucke, L. Liu, P. G. Steel, T. B. Marder, *Angew. Chem. Int. Ed.* 2014, **53**, 1799.
- Decreasing solubility of Bu₃SnOMe by addition of 9,10-dihydroanthracene would cause low yields. Indeed, as the amount of the scavenger increases (1.0 – 3.0 equiv.), the homocoupling reaction exclusively occurred to form **3a** in 16–31% yields. See Table S3 in supporting information.
- A. Nakamura, S. Otsuka, *Tetrahedron Letters* 1974, **15**, 463.