"Copper Effect" in Migita–Kosugi–Stille Coupling Revisited

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SUMMARY

"Copper effect" in Migita–Kosugi–Stille coupling (MKSC) has been well known as acceleration effect by a copper cocatalyst, which has thus far been ascribed to two different actions of copper depending on polarity of solvents, i.e., Sn/Cu transmetalation (in polar solvent such as DMF and NMP) and scavenging of ligands (in less polar ethereal solvent). In addition, the previous studies also reported that the Sn/Cu transmetalation does not occur in ethereal solvents. Herein, we report on reconsideration of the copper effect; MKSC is markedly accelerated based on the Sn/Cu transmetalation in ethereal solvents. In particular, perfluorophenyl- and heteroaryl-stannanes were found to undergo the Sn/Cu transmetalation with excellent site-selectivity in the presence of other Ar–Sn bonds under the ethereal conditions, leading to highly chemoselective, sequential MKSC without masking/unmasking process on a tin center. Moreover, we have also demonstrated that a combination of ^{119}Sn NMR chemical shifts (experimental) and computed fluoride ion affinity (FIA, theoretical) provides a quantitative criterion estimating tin-Lewis acidity that is strongly linked to activity toward the present MKSC.

INTRODUCTION

The cross-coupling reaction of organic electrophiles with organostannanes, the Migita–Kosugi–Stille coupling (MKSC), has proven to be one of the most reliable and versatile methods that enable various carbon frameworks of organic compounds to be constructed straightforwardly.[1–3] The characteristic feature of organostannanes is excellent stability toward moisture and oxygen, arising from their less polarized carbon–tin bonds, which allows them to be readily isolated by common methods including chromatography and distillation, and stored for a long period without degradation. On the other hand, organostannanes exhibit enough nucleophilicity in the cross-coupling process, and thus MKSC can be conducted under mild, usually neutral conditions with excellent chemoselectivity and functional group compatibility, leading to its numerous utilization for synthesis of bioactive molecules and natural products.[4–7] Notably, its superiority over Suzuki–Miyaura coupling has been well demonstrated in the use of heteroarylstannanes, which are frequently utilized for
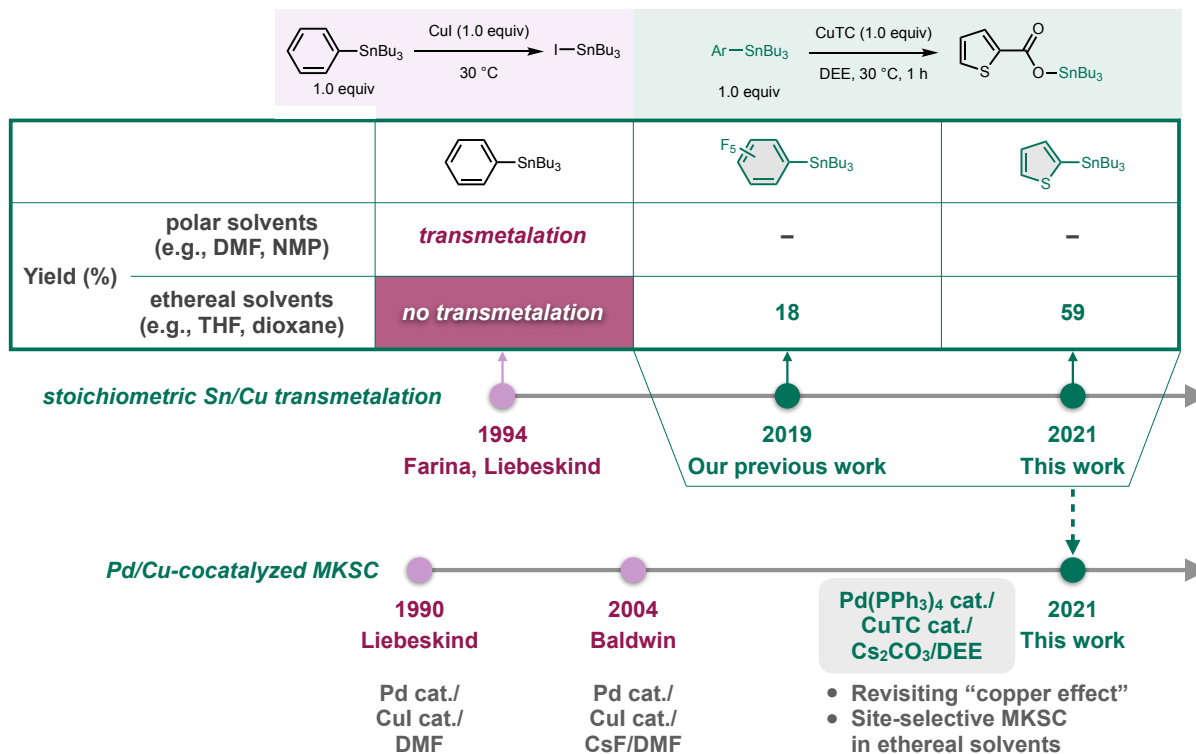
Figure 1. A timeline for stoichiometric Sn/Cu transmetalation and Pd/Cu-cocatalyzed MKSC

synthesizing bioactive molecules[8] and π-conjugated functional materials including dye-sensitized solar cells[9] and organic photovoltaics;[10,11] the boron-counterpart sometimes suffers from inefficiency owing to instability of heteroarylboranes under the reaction conditions. The versatility of arylstannanes has also been exemplified by tin–lithium exchange, being applicable to direct [11C]carbon dioxide fixation for positron emission tomography (PET) imaging study.[12] Hence, developing convenient and powerful ways of accessing arylstannanes, and uncovering their potential reactivities have continued to be an important subject in synthetic organic chemistry.

"Copper effect" in MKSC has been widely recognized as acceleration effect by adding a Cu(I) cocatalyst, which was first developed by Liebeskind in 1990.[13] Subsequently, Farina and Liebeskind reported a seminal work on the copper effect depending upon solvent polarity: in polar solvents such as DMF and NMP, Sn/Cu transmetalation occurs to give a more reactive organocopper intermediate (Figure 1), while a Cu(I) salt functions as a ligand scavenger in less polar ethereal solvents.[14] In addition, they also observed that the transmetalation between tributyl(phenyl)stannane and CuI did not occur in ethereal solvents, which was described as follows: "*No reaction was observed in THF or dioxane. Only highly polar solvents like NMP and DMF supported the reaction*".[14] The concept of the copper effect, especially with polar solvents (Sn/Cu transmetalation), was actually game-changing, and thus the scope of MKSC was greatly expanded by improved Pd/Cu cocatalysts[15–17] and copper-only catalysts,[15,18,19] the latter of which was recently used for PET imaging study via [11C]carbon dioxide fixation.[20] In 2004, Lee and Baldwin established a highly active system employing CsF as an additive under the Sn/Cu transmetalation conditions in DMF, which has continued to be the most popular option in MKSC.[7,21] In stark contrast to the extensive studies on the Pd/Cu-cocatalyzed
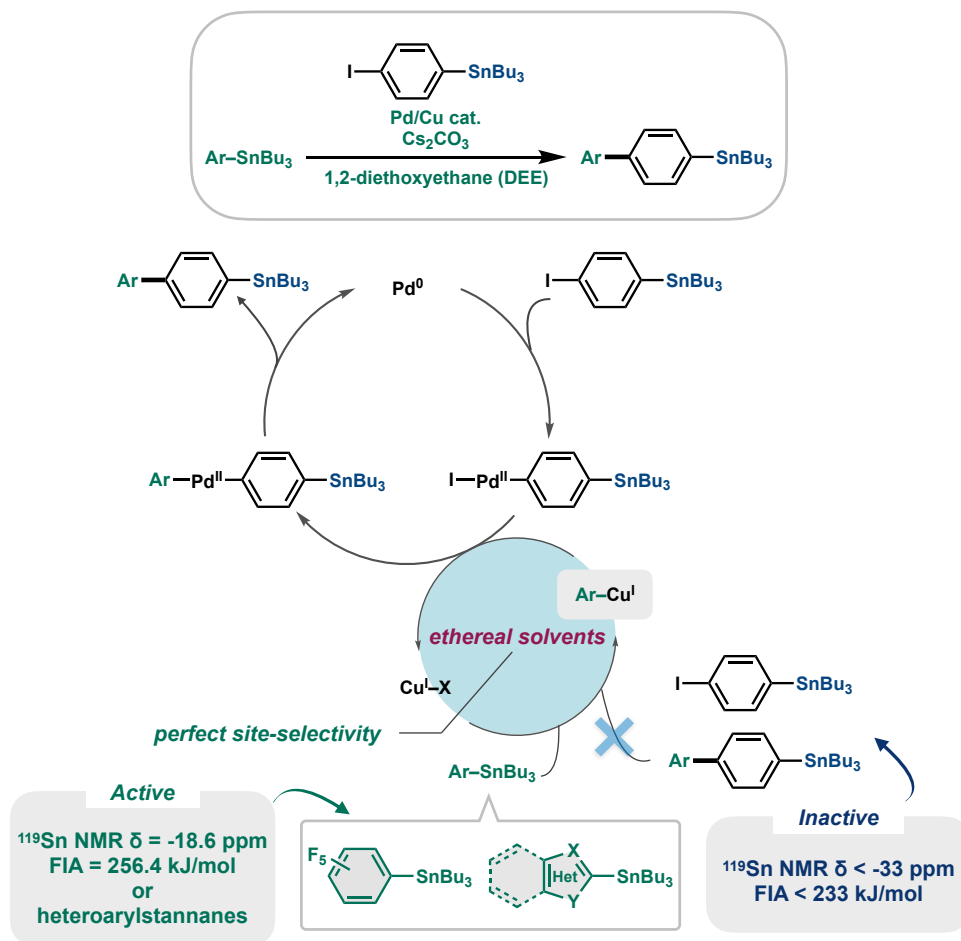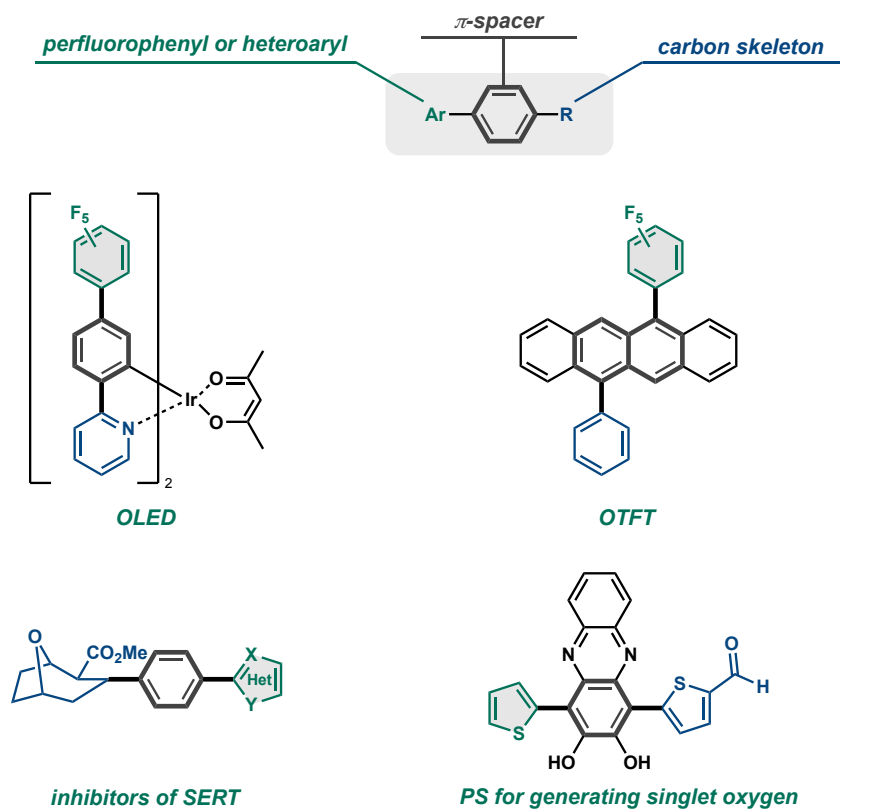
Figure 2. Pd/Cu-cocatalyzed site-selective MKSC in ethereal solvents

MKSC in polar solvents, those in ethereal solvents are totally underexplored, probably because the copper effect has been construed not in terms of the Sn/Cu transmetalation, but in terms of the ligand scavenging.[14,22] On the other hand, we have recently reported on copper-catalyzed arylstannylation of arynes, which proceeds via the Sn/Cu transmetalation in an ethereal solvent, 1,2-diethoxyethane (DEE).[23–25] This result in conjunction with advantages of ethereal solvents (e.g., unique media in cross-coupling reactions;[26] environmentally friendly characteristics as represented by biomass-derived 2-MeTHF;[27] suitability for cross-coupling-based polymer syntheses[28]) motivated us to explore fully the Pd/Cu-cocatalyzed MKSC in ethereal solvents without preconceived ideas.

Here, we report the Pd/Cu-cocatalyzed MKSC in ethereal solvents with revisiting the copper effect, where the Sn/Cu transmetaltion is the key to the acceleration. Of particular note is that the progress of the Sn/Cu transmetaltion is precisely controllable by tin-Lewis acidity and heteroatom-derived directing effect, which led to highly site-selective, sequential MKSC without the need for masking/unmasking process, usually employed in the boron-based cross-coupling (Figure 2).[29–31] The new MKSC strategy provides the direct and efficacious way of synthesizing various π-extended compounds having perfluorophenyl/heteroaryl– π-spacer–carbon skeleton, which are commonly found in such valuable functional molecules as organic light-emitting diodes (OLEDs),[32] inhibitors of serotonin transporter (SERT),[33] organic thin-film transistors (OTFTs),[34] and photosensitizers (PSs) for generating singlet oxygen (Figure 3).[35]

Valuable Compounds

π-*spacer*

perfluorophenyl or heteroaryl

carbon skeleton

Ar—[benzene ring]—R

OLED

OTFT

inhibitors of SERT

PS for generating singlet oxygen

Our Strategy

I—[benzene ring]—SnBu$_3$

site-selective MKSC

Ar–SnBu$_3$

Pd(PPh$_3$)$_4$, CuTC,
Cs$_2$CO$_3$, DEE

Ar—[benzene ring]—SnBu$_3$

R–X

MKSC

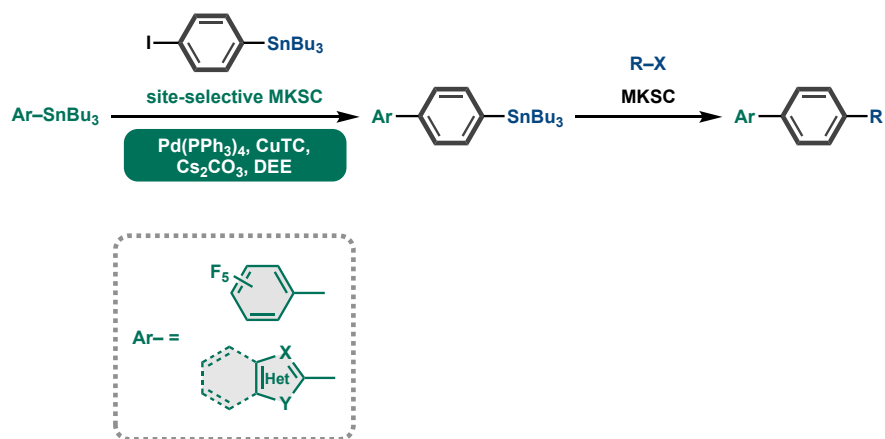Ar—[benzene ring]—R

Ar– =

Figure 3. Sequential site-selective MKSC for synthesizing valuable compounds

RESULTS AND DISCUSSION

We first conducted the reaction of tributyl(pentafluorophenyl)stannane (**1a**) and 4-iodotoluene (**2a**) in the presence of Pd(PPh₃)₄ (5 mol %) using various Cu(I) salts (10 mol %), bases, and solvents at 60 °C (see SI for full optimization details, Figure S5–S16), and found that the cross-coupling smoothly occurred by using copper(I) 2-thiophenecarboxylate (CuTC) and Cs₂CO₃ in DEE to give **3aa** in 91% yield (Figure 4, entry 1). Changing the Cu(I) salt from CuTC to CuI or CuCl resulted in considerable decrease in the yield, indicating the superior catalytic activity of CuTC with Cs₂CO₃ (Figure 4, entries 2 and 3). In sharp contrast, the reaction with CsF proceeded efficiently irrespective of a counter anion on the Cu(I) salt (Figure 4, entries 8–10), which may be attributable to slow (for Cs₂CO₃) and fast (for CsF) generation of trasmetalation-active CuOC(O)R [OC(O)R = TC, carbonate] and CuF[36,37] from CuX (X = I, Cl), respectively (trasmetalation-activity: CuTC > CuI, CuCl, see SI, Figure S17). DEE (and DME, see SI, Figure S7 and S8) turned out to be the best medium for the present MKSC, and thus the yield became lower in THF or toluene (Figure 4, entries 4, 5, 11, and 12). The efficient transformation could not be realized if even one of the Cu(I) salt, the palladium complex, and the base was lacking, demonstrating synergetic catalysis of the Cu(I) and the Pd, and a pivotal role of the base (Figure 4, entries 6, 7, and 13–16).
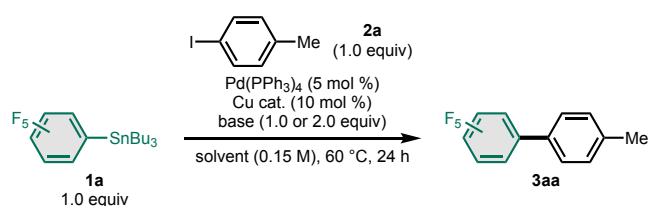
| Entry	Base	Solvent	Cu cat.	Yield (%)[a]
1	Cs₂CO₃	DEE	CuTC	91
2	Cs₂CO₃	DEE	CuI	24
3	Cs₂CO₃	DEE	CuCl	34
4	Cs₂CO₃	THF	CuTC	78
5	Cs₂CO₃	toluene	CuTC	21
6	Cs₂CO₃	DEE	none	0
7[b]	Cs₂CO₃	DEE	CuTC	0
8	CsF	DEE	CuTC	92
9	CsF	DEE	CuI	91
10	CsF	DEE	CuCl	90
11	CsF	THF	CuTC	88
12	CsF	toluene	CuTC	40
13	CsF	DEE	none	7
14[b]	CsF	DEE	CuTC	0
15	none	DEE	CuTC	20
16	none	DEE	none	0

Figure 4. Pd/Cu-cocatalyzed MKSC with pentafluorophenylstannane

Reaction conditions: **1a** (0.10 mmol), **2a** (0.10 mmol), Pd(PPh₃)₄ (5.0 mol %), Cu catalyst (10 mol %), base (Cs₂CO₃, 0.10 mmol; CsF, 0.20 mmol), solvent (0.67 mL), 60 °C, 24 h.

[a]Yields were determined by GC analysis of the crude reaction mixture calibrated against diethylene glycol dibutyl ether as an internal standard.

[b]The reaction was conducted without adding Pd(PPh₃)₄.

To examine an electronic effect of organostannanes on the reaction progress, we next carried out the reaction of 4-iodotoluene (**2a**) with tributyl(phenyl)stannane (**1f**) under the optimized conditions (Figure 4, entry 1 or 8); almost no cross-coupling product (**3fa**) was formed under our ethereal conditions, which clearly implies that increment of tin-Lewis acidity induced by the electron-withdrawing pentafluorophenyl group remarkably facilitates the process. Although the Lee and Baldwin conditions allowed even less Lewis acidic **1f** to undergo the cross-coupling, our conditions, largely affected by the tin-Lewis acidity, should be more suitable for site-selective reaction. Thus, treatment of **1a**, **1f**, and **2a** in the presence of Cs₂CO₃ in DEE exclusively furnished **3aa** without any formation of **3fa**, which verifies the excellent site-selectivity of the conditions (Figure 5, entry 5 and 6). A similar trend in the site-selectivity was also observed with other conditions (CsF in DEE, Cs₂CO₃ or CsF in DMF, Figure 5, entry 7–9), however the production of a small amount of **3fa** could not be suppressed. On the other hand, the reaction conducted only with the palladium catalyst in DMF gave a mixture of **3aa** (36%) and **3fa** (22%), demonstrating the synergetic Pd/Cu catalysis and the base are the key to the high site-selectivity as well as the activity (Figure 5, entry 10).
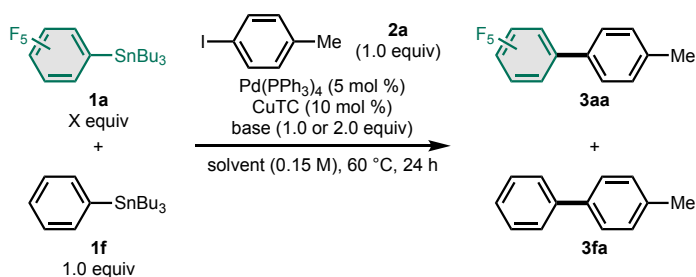
Entry	X	Solvent	Base	3aa/3fa (%)[a]
1	0	DEE	Cs₂CO₃	0/1
2	0	DEE	CsF	0/3
3	0	DMF	Cs₂CO₃	0/5
4	0	DMF	CsF	0/84
5	1.0	DEE	Cs₂CO₃	75/0
6[b]	1.0	**DEE**	**Cs₂CO₃**	**95(88)[c]/0**
7	1.0	DEE	CsF	93/2
8	1.0	DMF	Cs₂CO₃	87/3
9	1.0	DMF	CsF	87/4
10[d]	1.0	DMF	none	36/22

Figure 5. Site-selective MKSC with pentafluorophenylstannane and phenylstannane

Reaction conditions: **1a** (0.10 mmol), **1f** (0.10 mmol), **2a** (0.10 mmol), Pd(PPh₃)₄ (5.0 mol %), CuTC (10 mol %), base (Cs₂CO₃, 0.10 mmol; CsF, 0.20 mmol), solvent (0.67 mL), 60 °C, 24 h.

[a]Yields were determined by GC analysis of the crude reaction mixture calibrated against diethylene glycol dibutyl ether as an internal standard.

[b]The reaction was conducted with 0.15 mmol of Cs₂CO₃.

[c]Isolated yield is shown.

[d]The reaction was conducted at 100 °C without adding CuTC.

We previously reported on the copper-catalyzed arylstannylation of arynes in DEE, where arylstannanes of higher tin-Lewis acidity reacted faster via Sn/Cu transmetalation as a key step, and moreover tributyl(pentafluorophenyl)stannane (**1a**) actually underwent the stoichiometric transmetalation with CuTC.[23] These results in conjunction with the distinct difference in the reactivity between **1a** and **1f** in the present Pd/Cu-cocatalyzed MKSC imply that the transmetalation-based "copper effect" would be operative even in less polar ethereal solvents, being in stark contrast to the conventional notion of the copper behavior in MKSC. Then, our attention was focused on correlation between MKSC (≈ transmetalation) reactivity and tin-Lewis acidity, which was found to be estimated by the ^{119}Sn NMR chemical shift.[23,38] The ^{119}Sn NMR method worked well for the prediction of the reactivity toward the arylstannylation, and also electrophilicity has been generally determined by NMR chemical shift.[39] However, we needed additional method of determining tin-Lewis acidity, because the NMR evaluation sometimes mislead; Brønsted acidity of fluoroaromatic compounds does not correspond to ^{1}H NMR chemical shift (^{1}H NMR: C_6H_6, 7.41 ppm > C_6F_5H, 6.91 ppm *vs.* pKa: C_6H_6[40,41] > C_6F_5H[41,42]), and degree of shielding effect in ^{1}H NMR was reported to be different between a fluoroaromatic and a benzene ring, which might be the case in ^{119}Sn NMR.[43] In this context, we adopted computed fluoride ion affinity (FIA) using DFT calculations at the M06-2X/def2-SVP level, being utilized for gauging Lewis acidity of various elements theoretically,[44,45] and investigated its relationship with ^{119}Sn NMR chemical shift by use of fluorinated arylstannanes (**1a**–**1e**) (Figure 6). It should be noted that ^{119}Sn NMR chemical shifts and FIA values have proven to be in excellent linear relationship, which would provide a quantitative criterion determining tin-Lewis acidity by both experimental and theoretical approaches.

As depicted in Figure 5, the most Lewis acidic **1a** (δ = -18.6 ppm, FIA = 256.4 kJ/mol) efficiently underwent the site-selective MKSC to afford **3aa** in 95% yield, whereas the reaction with the second most Lewis acidic **1b** (δ = -22.4 ppm, FIA = 248.8 kJ/mol) became slow (24% yield) (Figure 6). The tin-Lewis acidity-dependent reactivity was further confirmed by employing other fluorinated arylstannanes: **1c**–**1e** of decreased tin-Lewis acidity were hardly involved in the MKSC. In each case, **3fa** derived from the least Lewis acidic tributyl(phenyl)stannane (**1f**) was not formed at all, thus verifying the reaction progress relies upon the tin-Lewis acidity that accelerates Sn/Cu transmetalation, as was the case in the arylstannylation.[23] In addition, we also performed competitive reaction between fluorinated arylstannanes to further clarify required difference in the tin-Lewis acidity for perfectly site-selective MKSC (Figure 7). Although the reaction by use of **1a** and **1b** resulted in the formation of a mixture of **3aa** and **3ba** (Figure 7, entry 1, **3aa**:**3ba** = 75:23), the perfect site-selectivity was achieved by difference of two fluorine substituents (**1a** *vs.* **1c**) to afford **3aa** exclusively (Figure 7, entry 2). These results clearly illustrate that the perfect site-selectivity in the MKSC with highly Lewis acidic **1a** would be guaranteed in the presence of other arylstannanes of less Lewis acidity determined by ^{119}Sn NMR chemical shift and/or FIA value (δ < -33 ppm, FIA < 233 kJ/mol).
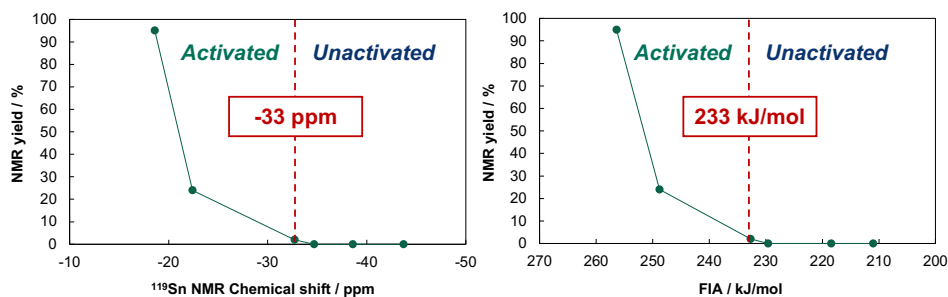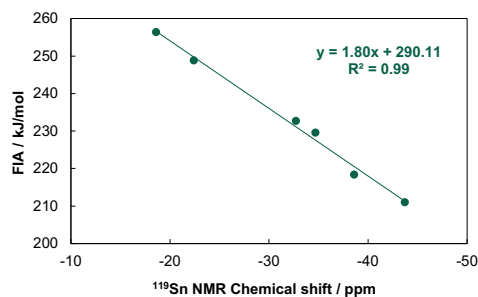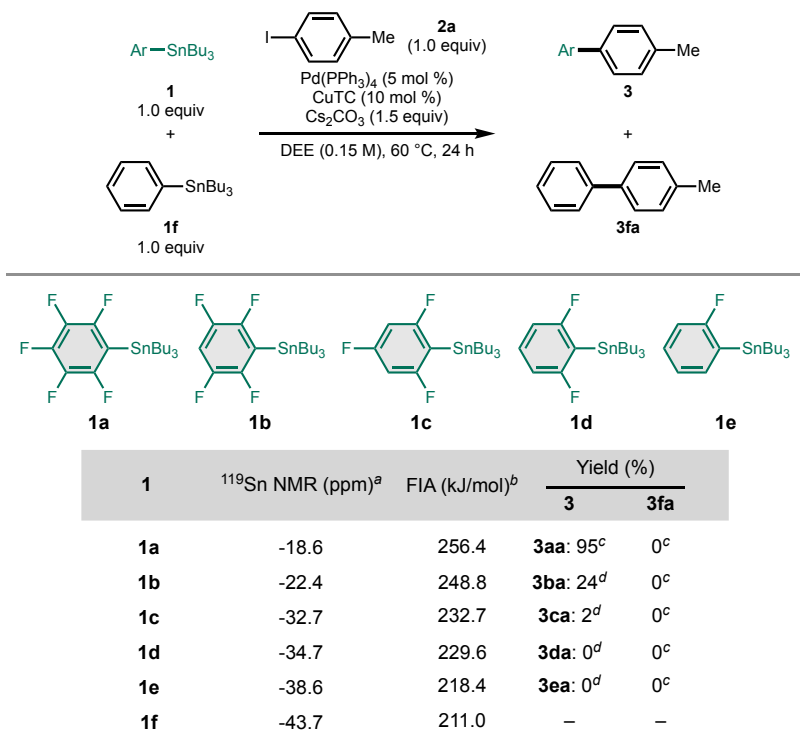
1	^{119}Sn NMR (ppm)[a]	FIA (kJ/mol)[b]	Yield (%)	
			3	3fa
1a	-18.6	256.4	3aa: 95[c]	0[c]
1b	-22.4	248.8	3ba: 24[d]	0[c]
1c	-32.7	232.7	3ca: 2[d]	0[c]
1d	-34.7	229.6	3da: 0[d]	0[c]
1e	-38.6	218.4	3ea: 0[d]	0[c]
1f	-43.7	211.0	–	–

and tin-Lewis acidity predicted by

(0.10 mmol), Pd(PPh$_3$)$_4$ (5.0 mol %), CuTC
, 24 h.
SnMe$_4$ as an external standard.
2-SVP level.
ude reaction mixture calibrated against

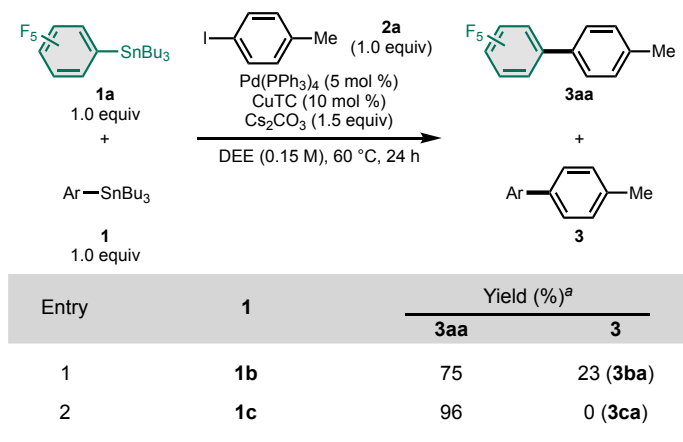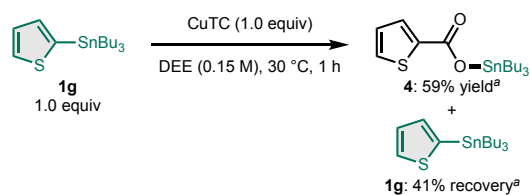of the crude reaction mixture using

Figure 7. Competitive MKSC by use of fluorinated arylstannanes

Reaction conditions: **1a** (0.10 mmol), **1b** or **1c** (0.10 mmol), **2a** (0.10 mmol), Pd(PPh$_3$)$_4$ (5.0 mol %), CuTC (10 mol %), Cs$_2$CO$_3$ (0.15 mmol), DEE (0.67 mL), 60 °C, 24 h.
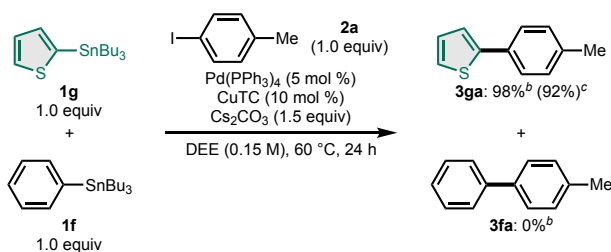
[a]Yields were determined by ^{19}F NMR analysis of the crude reaction mixture using pentafluorobenzene as an internal standard.

Besides the simple increment in tin-Lewis acidity induced by an electron-deficient aryl group, the transmetalation-based copper effect in DEE was found to be pronounced with 2-heteroarylstannanes. Thus, stoichiometric treatment of tributyl(2-thienyl)stannane (**1g**) with CuTC in DEE resulted in smooth Sn/Cu transmetalation with efficiency higher than that with **1a**, despite its lower predicted tin-Lewis acidity (^{119}Sn NMR chemical shift δ = -39.6 ppm, FIA = 227.4 kJ/mol) (Figure 8, A). The prominent facility would be ascribable to heteroatom-derived directing effect,[46,47] being another key factor affecting the Sn/Cu transmetalation, and this characteristic feature was again applied to the perfectly site-selective MKSC to afford a 92% yield of **3ga** in the competitive reaction with **1g** and **1f** (Figure 8, B). With the optimized Pd/Cu cocatalytic system endowed with the excellent site-selectivity in our hands, the substrate scope of the MKSC on aryl iodides was investigated (Figure 8, C); the reaction with **1a** or **1g** was applicable to a variety of aryl iodides bearing electron-donating (**2b**) or relatively base-sensitive electron-withdrawing groups (**2c–2e**) to provide the corresponding biaryls in high yields with demonstrating the high functional group compatibility. 4-Chloroiodobenzene (**2f**) underwent the reaction at the Ar−I bond over the Ar−Cl bond to provide **3gf** exclusively, and sterically demanding 2-iodotoluene (**2g**) and 1-iodonaphthalene (**2h**) were also smoothly convertible into the products (**3gg** and **3gh**). In contrast to the satisfactory reactivity of **1g**, tributyl(3-thienyl)stannane (**1g'**) did not react at all (**1g'**: ^{119}Sn NMR chemical shift δ = -49.8 ppm, FIA = 207.5 kJ/mol), which further demonstrated the pivotal role of the heteroatom-derived directing effect in the Sn/Cu transmetalation process.
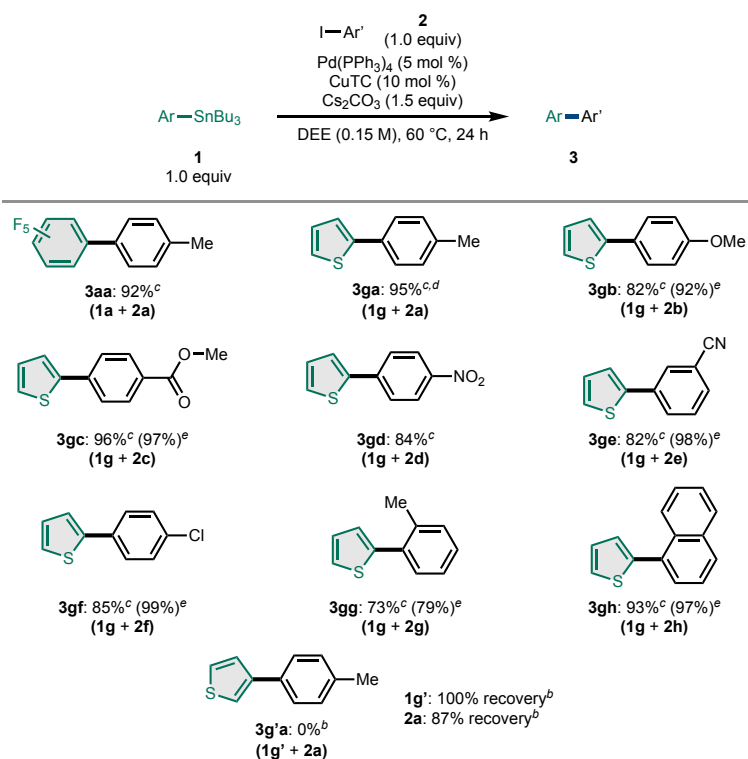
Figure 8. (A) Stoichiometric Sn/Cu transmetalation of 2-thienylstannane with CuTC in DEE. (B) Competitive MKSC with 2-thienylstannane and phenylstannane. (C) Scope on aryl iodides.

These reactions were performed on 0.10 mmol scale.

[a]Yields were determined by ^{119}Sn NMR analysis of the crude reaction mixture using tributyl(vinyl)stannane as an internal standard.

[b]Yields were determined by GC analysis of the crude reaction mixture calibrated against diethylene glycol dibutyl ether as an internal standard.

[c]Isolated yields are shown.

[d]The reaction was performed on 0.50 mmol scale.

[e]Yields were determined by ^{1}H NMR analysis of the crude reaction mixture using anisole as an internal standard.

para-Stannylbiaryls having heteroaromatic rings are of high synthetic value, because they are convertible into important bioactive compounds that serve as inhibitors of SERT. Although their previous synthesis with 4-bromoiodobenzene branched at the first step, and thus required many steps for accessing the target compounds (Figure 9),[33] our site-selective MKSC enabled the laborious steps to be cut down. Thus, various *para*-stannylbiaryls (**6a**, **6g**–**6j**) became directly accessible by the MKSC-based shotgun-synthesis, where arylstannanes (**1a**, **1g**–**1j**) were coupled with tributyl(4-iodophenyl)stannane (**5**), available from 1,4-diiodobenzene on large scale (31.5 mmol scale), without damaging the Ar–Sn bond of **5**. As was the case of **1g**, predicted tin-Lewis acidity of other heteroarylstannanes (**1h**–**1j**) were relatively low (^{119}Sn NMR chemical shift δ = -63.4 to -51.8 ppm, FIA = 212.0 to 245.9 kJ/mol), which also substantiates the heteroatom-driven Sn/Cu transmetalation. The low tin-Lewis acidity of **5** (δ = -38.5 ppm, FIA = 232.2 kJ/mol) and the resulting *para*-stannylbiaryls (δ = -42.1 to -40.7 ppm, FIA = 209.0 to 233.3 kJ/mol) as well as the absence of an α-heteroatom led to the excellent site-selectivity, and the synthetic versatility of this process was demonstrated by synthesis of a ligand for OLEDs (**7**)[32] through the sequential MKSC with **1a**, **5**, and intermediary-formed **6a**, which could be prepared on a gram scale (1.45 g) (Figure 10).

Finally, we rigorously investigated the difference in site-selectivity between our conditions and the Baldwin conditions by the MKSC of **5** with **1a**. As shown in Figure 11, **6a** was exclusively produced under our conditions, whereas the reaction under the Baldwin conditions was contaminated by stannylteraryl **8** (6% yield) with a decreased yield of **6a** (66%), demonstrating unambiguously the superiority of our ethereal solvent (DEE)-based system in the site-selective MKSC.
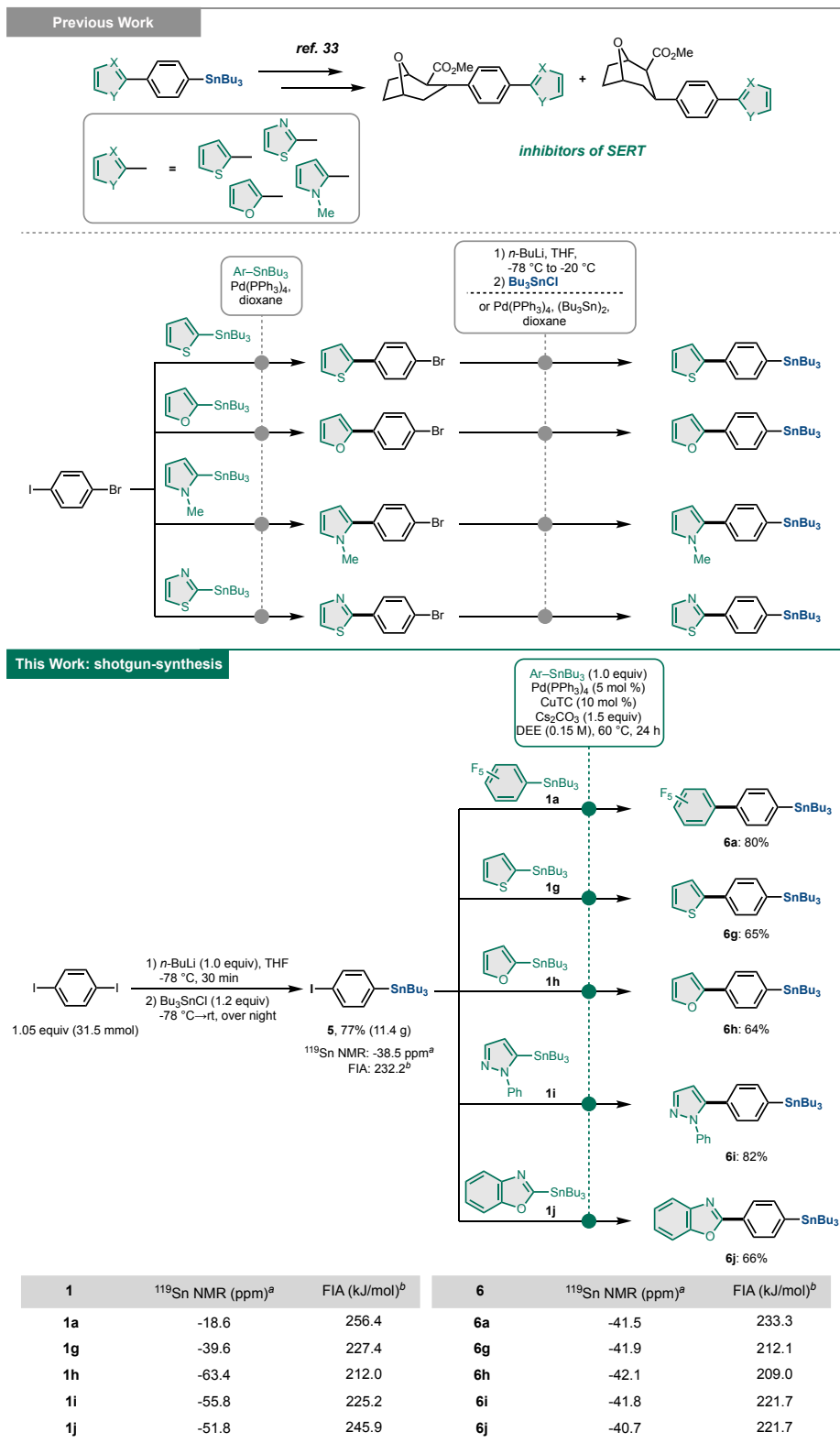
Figure 9. Shotgun-synthesis of stannylbiaryls via site-selective MKSC

MKSC reactions were performed on 0.10 mmol scale. Isolated yields are shown.

[a]^{119}Sn NMR spectra (solvent: CDCl$_3$) were taken using SnMe$_4$ as an external standard.

[b]DFT calculations were carried out at the M06-2X/def2-SVP level.

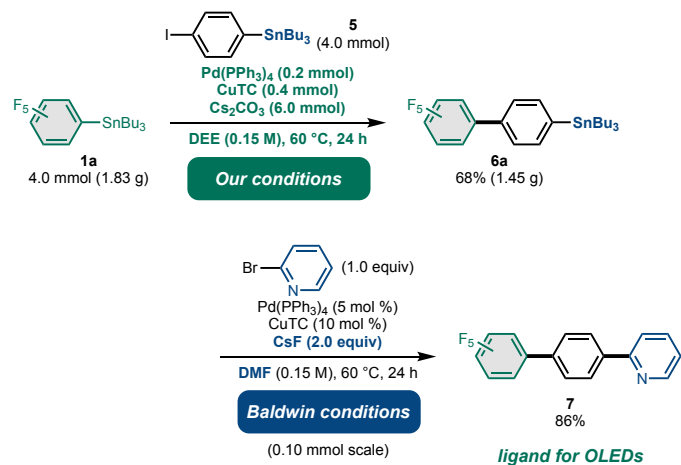| 1	^{119}Sn NMR (ppm)[a]	FIA (kJ/mol)[b]	6	^{119}Sn NMR (ppm)[a]	FIA (kJ/mol)[b]
1a	-18.6	256.4	6a	-41.5	233.3
1g	-39.6	227.4	6g	-41.9	212.1
1h	-63.4	212.0	6h	-42.1	209.0
1i	-55.8	225.2	6i	-41.8	221.7
1j	-51.8	245.9	6j	-40.7	221.7

Figure 10. Synthesis of a ligand for OLEDs by sequential site-selective MKSC
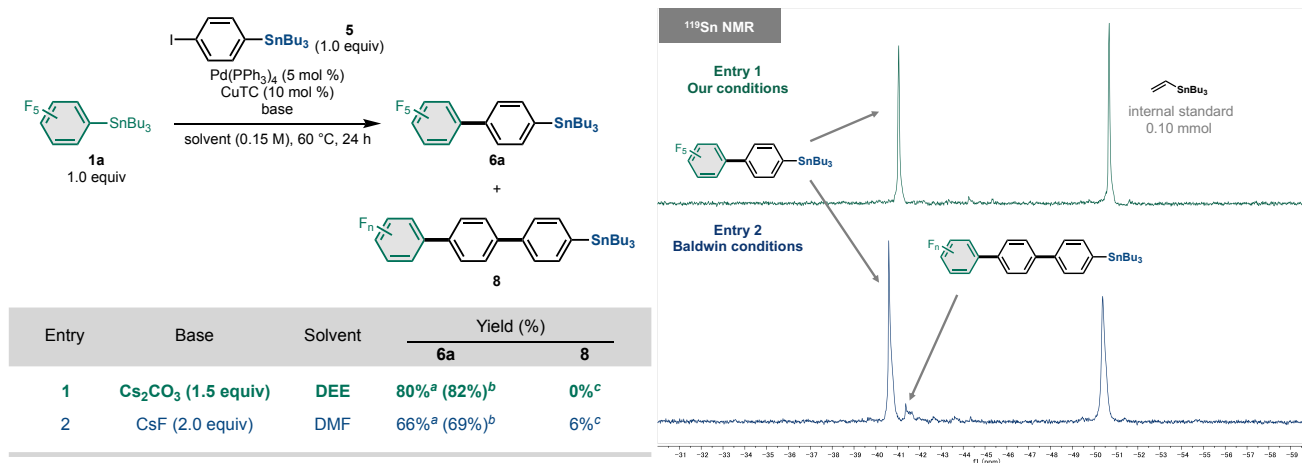
Isolated yields are shown.

Figure 11. Rigorous discrimination of SnBu₃ moieties

These reactions were performed on 0.10 mmol scale.

[a]Isolated yields are shown.

[b]Yields were determined by GC analysis of the crude reaction mixture calibrated against diethylene glycol dibutyl ether as an internal standard.

[c]Yields were determined by ¹¹⁹Sn NMR analysis of the crude reaction mixture using tributyl(vinyl)stannane as an internal standard.

Conclusions

We have develpoed the new, potent system for MKSC based on Pd/Cu (CuTC) cocatalyst, a base (Cs$_2$CO$_3$), and an ethereal solvent (DEE). The present MKSC turned out to proceed through Sn/Cu transmetalation, whose progress was decisively governed by tin-Lewis acidity and heteroatom-derived directing effect. The unique characteristic allowed pentafluorophenylstannane and heteroarylstannanes to undergo the MKSC with (4-iodophenyl)stannane with perfect site-selectivity, leading to the shotgun-synthesis of diverse *para*-stannylbiaryls, which are useful intermediates for synthesizing inhibitors of SERT and a ligand for OLEDs. Furthermore, we have also demonstrated that a combination of ^{119}Sn NMR chemical shifts (experimental) and computed FIA (theoretical) provides a quantitative criterion estimating tin-Lewis acidity. The results would definitely update the widely accepted concept of how a copper catalyst functions in the MKSC (copper effect), and provide a promising clue to develop new tin-based reactions involving the Sn/Cu transmetalation as a key step.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact
Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Hiroto Yoshida (yhiroto@hiroshima-u.ac.jp).

Materials availability
This study did not generate new unique reagents.

Data and code availability
This study did not generate any datasets.

Full experimental procedures are provided in the Supplemental information.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at

ACKNOWLEDGMENTS

AUTHOR CONTRIBUTIONS

H.T. and H.Y. conceived the concept and wrote the manuscript. H.T. conducted all experiments and DFT calculations. M.N. provided advice for DFT calculations. H.Y. directed the project.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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