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Preparation of 2,2-difluoro-1-trialkylsilylethenylstannanes and their cross-coupling reactions

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ABSTRACT

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1,1-Difluoroalkenes are valuable fluoroorganic compounds which exhibit chemical reactivities toward nucleophiles and thus can be utilized as useful synthetic intermediates for the preparation of monofluorinated organic molecules.¹⁻⁴ They are also potential mechanism-based inhibitors^{5,6} and have been known to behave as a bioisostere for the carbonyl group.⁷ Therefore, the synthesis of 1,1-difluoroalkenes is an important aspect of organofluorine chemistry and thus numerous methods for the preparation of 1,1-difluoroalkenes have been reported in the previous literatures.^{8–10} 2,2-Difluoroethenylstannanes could be remarkable precursors of 1,1-difluoroalkenes because they can undergo the Stille type of cross-coupling reaction with aryl, akenyl, and alkynyl halides. Although several methods for the preparation of 2,2-difluoroethenylstannane reagents having proton, bromine, alkoxy, and phenyl groups at 1-position and their cross-coupling reactions have been developed in last one decade,¹¹⁻¹⁸ these types of reagents were utilized to introduce only one substituent at tributylstannyl site via cross-coupling reaction. Recently, we developed the method for the preparation of 2,2-difluoro-1-tributylstannylethenyl p-toluenesulfonate and (2,2-difluoroethenylidene)bis(tributylstannane) which have two coupling partners such as the nucleophilic tributylstannyl or electrophilic tosylate group at the same carbon and underwent the cross-coupling reactions to give 1,1-difluoroalkenes.^{19,20} However, these two reagents still have some drawbacks such as low reactivity of the tosylate group as a coupling partner and low selectivity for the unsymmetrical coupling reaction of bis(tributylstannane). In the course of our studies on the preparation of new type of 2,2-difluoroethenylstannane to

Reaction of **2** with bis(tributyltin) in the presence of 3 mol % $Pd_2(dba)_3$, 6 mol % XPhos, and 30 equiv of LiBr in wet and air bubbled THF at reflux for 8 h afforded the desired products **3** in 73–74% yields. The cross-coupling reaction of **3a** with aryl iodides in the presence of 10 mol % $Pd(PPh_3)_4$ and 10 mol % Cul afforded the coupled products **4a–p** in 47–90% yields. The coupling reaction of **3b** with various alkynyl bromides having aryl-, alkyl, or trialkylsilyl group also afforded the corresponding 1,3-enynes **5a–g** in 61–77% yields.

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overcome these drawbacks, we are interested in the preparation of 2,2-difluoro-1-trialkylsilylethenylstannanes because the tributylstannyl group can be utilized for the cross-coupling reaction to give 1-substituted 2,2-difluoroethenylsilanes which were known to be valuable synthetic intermediates to give monofluoroalkenes in recent years.^{21–25} Resultant 1-substituted 2,2-difluoroethenylsilanes will be also potential synthetic intermediates to provide the variety of 1,1-difluoroalkenes via transformation of the trialkylsilyl group. Herein, we report an efficient method for 2,2-difluoro-1-trialkylsilylethenylstannanes and their cross-coupling reactions.

First of all, we synthesized 2,2-difluoro-1-trimethylsilylethenyl *p*-toluenesulfonate (**2a**) in 95% yield from the reaction of 2,2,2-tri-fluoroethyl *p*-toluenesulfonate (**1**) with LDA (2 equiv) in THF at -78 °C, followed by treatment with trimethylsilyl chloride (1 equiv). Similarly, 2,2-difluoro-1-triethylsilylethenyl *p*-toluene-sulfonate (**2b**) was also prepared in 96% yield from the treatment with triethylsilyl chloride.

$$CF_{3}CH_{2}OTs \xrightarrow{1. LDA (2 equiv)/THF, -78 \circ C} F \xrightarrow{C} F$$
1
$$1 \xrightarrow{I} F \xrightarrow{I} F$$
2a, R = Me (95%)
2b, R = EI (96%)

Although the direct cross-coupling reaction of **2a** with phenylstannane or phenylboronic acid was carried out in the catalytic condition, the coupled product **3a** was not obtained. Therefore, we attempted the stannylation reaction of **2** with bis(tributyltin) in the presence of Pd catalyst, ligand, and lithium salt to introduce a stannanyl group at the tosylate site. When **2a** was reacted with bis(tributyltin)





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in the presence of 10 mol % Pd(PPh₃)₄ and 30 equiv of LiBr in dry THF at reflux for 8 h, a trace amount of the desired product 3a was observed in GC-MS spectrum. However, the use of wet and air bubbled THF in the same reaction resulted in the formation of 3a in 24% yield (entry 2). The longer reaction time and the use of low equiv of LiBr caused to decrease the yield of 3a (entries 3 and 4). The same reaction was performed in the presence of 10 mol % Pd(PPh₃)₂Cl₂ and 6 mol % XPhos²⁶ as a ligand to give **3a** in 35% yield (entry 5). The use of Pd(CH₃CN)₂Cl₂ instead of Pd(PPh₃)₂Cl₂ in this reaction caused to increase the yield of 3a up to 48% yield. When this reaction was carried out in the presence of 10 mol % Pd₂(dba)₃ and 6 mol % XPhos under the same reaction condition, 3a was obtained in 60% vield. After monitoring the reaction by changing the mol % of $Pd_2(dba)_3$ and XPhos, we found that the use of 3 mol % Pd₂(dba)₃ and 6 mol % X-Phos in this reaction provided the highest vield (73%) of **3a**. Optimized reaction condition for the stannylation of **2a** is summarized in Table 1. Similarly, the stannylation reaction of 2b with bis(tributyltin) in the presence of 3 mol % Pd₂(dba)₃, 6 mol % XPhos, and 30 equiv of LiBr in wet and air bubbled THF at reflux for 8 h afforded the desired product 3b in 74% yield.

We attempted the palladium-catalyzed cross-coupling reaction of **3a** with a variety of aryl iodides to introduce an aromatic group at the stannane site. Initially, the coupling reaction between **3a** (1.0 equiv) and 4-iodobiphenyl (1.0 equiv) in the presence of 10 mol % Pd(PPh₃)₄ and 10 mol % CuI in DMF at 80 °C for 10 h provided the coupled product 4a in 90% yield. When this reaction was carried at room temperature, very slow reaction was occurred and thus the reaction was not completed even after stirring for 24 h and gave the low yield (43%) of 4a based on the conversion of starting material. The coupling reaction between 3a and iodobiphenyl did not occur without 10 mol % CuI under the same reaction condition. The use of other solvents such as THF, ether, benzene. and toluene in this coupling reaction did not provide the satisfied result. The use of bromobiphenvl instead of iodobiphenvl as a coupling partner under the same reaction condition did not provide the desired product 4a at all. The coupling reactions of **3a** with various aryl iodides having proton, fluoro, chloro, bromo, methyl, methoxy, trifluoromethyl, and nitro on the meta or paraposition of the benzene ring afforded the coupled products **4b**-**p** in 47-90% yields which are summarized in Table 2. Aryl iodides with electron-releasing and electron-withdrawing groups in the

Table 1

Optimization reaction condition for the stannylation of 2a

$ \begin{array}{c} F \\ F \\ SiMe_3 \end{array} + \begin{array}{c} (Bu_3Sn)_2 \\ (1.0 \text{ equiv}) \end{array} \begin{array}{c} Pd \text{ catalyst (X mol %)/XPhos (Y mol %)} \\ LiBr (Z equiv), THF, reflux, th \\ 3a \end{array} \begin{array}{c} F \\ SiMe_3 \\ 3a \end{array} $								
Entry	Pd catalyst	X (mal%)	Y (m al %)	Z	t (h)	Yield ^{a,b}		
		(mol %)	(mol %)	(equiv)	(n)	(%)		
1 ^c	$Pd(PPh_3)_4$	10	0	30	8	Trace		
2	$Pd(PPh_3)_4$	10	0	30	8	24		
3	$Pd(PPh_3)_4$	10	0	10	8	10		
4	$Pd(PPh_3)_4$	10	0	30	24	5		
5	$Pd(PPh_3)_2Cl_2$	10	6	30	8	35		
6	$Pd(CH_3CN)_2Cl_2$	10	6	30	8	48		
7	Pd ₂ (dba) ₃	10	6	30	8	60		
8	Pd ₂ (dba) ₃	6	6	30	8	68		
9	Pd ₂ (dba) ₃	3	6	30	8	73		

^a Isolated yield.

 $^{\rm b}\,$ The reactions were performed in wet (0.025 mg of H_2O in 1 mL THF) air bubbled THF.

^c The reactions were carried in dry THF.

para-position of the aromatic ring were coupled well under the optimized reaction condition, whereas aryl iodides with electronreleasing and electron-withdrawing groups in the meta-position of the aromatic ring underwent the coupling reaction to produce the corresponding cross-coupled product in relatively low yields. The coupling reaction with aryl iodides having a substituent such as methoxy or chloro group in the ortho-position of the benzene ring resulted in a complex reaction mixture and failed to produce the desired product. Similarly, the cross-coupling reaction of 3b with iodobiphenyl as a standard coupling partner under the optimized reaction condition also afforded the corresponding cross-coupled product 4s in 88% yield. In spite of synthetically useful compound in recent years,²²⁻²⁴ synthesis of the coupled products **4** has been quite limited in the previous literature^{27,28} except for a recent report, in which **4** were prepared from the Suzuki-Mivaura reactions of 2.2-difluoro-1-iodoethenvltrialkylsilane. synthesized from 2.2.2-trifluoroethyl iodide, with arylboronic acids.25

We also attempted the palladium-catalyzed cross-coupling reaction of **3b** with alkynyl iodides to produce 1,1-difluoro-2-triethylsilyl-1,3-enynes 5. When 3b was reacted with phenylethynyl iodide in the presence of 10 mol % of Pd(PPh₃)₄ and 10 mol % of CuI in DMF at 80 °C for 1 h, the starting material 3b was completely consumed, but only dimerized product of phenylethynyl iodide, 1,4-diphenyl-1,3-butadiyne, was obtained in 85% yield and no desired product 5a was observed. The reaction was also carried out at room temperature and 50 °C, but the dimerized product was always obtained. This result indicated that palladium-catalyzed dimerization process of alkynyl iodide was much faster than palladium-catalyzed cross-coupling reaction of 3b with alkynyl iodide. To establish a method for the preparation of 1,1-difluoro-2-triethylsilyl-1,3-enynes 5, we attempted the palladium-catalyzed cross-coupling reaction of **3b** with phenylethynyl bromide which may be less reactive than phenylethynyl iodide in the catalytic process of the dimerization reaction. The coupling reaction between **3b** and phenylethynyl bromide in the presence of 10 mol % of Pd(PPh₃)₄ and 10 mol % of

 Table 2

 Cross-coupling reaction of 3a with aryl iodides



Compound no.	R	<i>t</i> (h)	Yield ^a (%)
4a	<i>p</i> -С ₆ Н ₅	10	90
4b	Н	16	70
4c	p-F	16	78
4d	p-Cl	14	86
4e	p-Br	16	79
4f	p-OCH ₃	20	72
4g	$p-CH_3$	20	71
4h	$p-NO_2$	14	89
4i	p-CF ₃	16	85
4j	<i>m</i> -F	16	50
4k	m-Cl	14	54
41	m-Br	16	57
4m	m-OCH ₃	20	51
4n	m-CH ₃	20	47
40	$m-NO_2$	14	60
4p	m-CF ₃	16	53
4q	o-OCH ₃	20	b
4r	o-Cl	14	b

^a Isolated yield.

^b No product was obtained.

Table 3

Cross-coupling reaction of 3b with alkynyl bromides



^a Isolated yield.

CuI in DMF at 80 °C for 3 h afforded the coupled product **5a** in 47% yield along with the dimerized product of alkynyl bromide. This result indicated that phenylethynylpalladium (II) bromide intermediate formed from the oxidative addition process between phenylethynyl bromide and Pd(PPh₃)₄ underwent the transmetallation with **3b** much faster than the dimerization with phenylethynyl bromide. When this reaction was performed in THF instead of DMF, the coupled product **5a** was obtained in 61% vield. Arvl-, alkvl-, and trialkylsilyl-substituted ethynyl bromides also underwent coupling reactions with **3b** under a similar condition to give the coupled products **5b**-g in good yields which are summarized in Table 3.

In summary, we have developed a method for the novel 1, 1-difluoro-2-trialkylsilylethenylstannane **3** as a new type of 2,2difluoroethenylstannane reagent by the stannylation of 2,2-difluoro-1-trialkylsilylethenyl p-toluenesulfonate 2. Novel stannane reagent 3 underwent the palladium-catalyzed cross-coupling reaction with aryl iodides to give 2,2-difluoro-1-arylethenylsilane 4. Similarly, alkynylation reaction of **3** with alkynyl bromides under the same reaction condition also provided the coupled products, 2,2-difluoro-1,3-enynes 5. Alternatively, 2,2-difluoro-1,3-enynes 5 was also prepared from the palladium-catalyzed cross-coupling reaction between 2,2-difluoro-1-trialkylsilylethenyl iodide 6 and alkynyltributylstannane reagents. The further synthetic utilities of **3** and **5** will be described in the future Letters.

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Supplementary data

Supplementary data (experimental procedures and ¹H, ¹³C and ¹⁹F NMR spectra for **2a-b**, **3a-b**, **4a-p**, **5a-g**) associated with this article can be found, in the online version, at http://dx.doi.org/ 10.1016/j.tetlet.2013.12.071.



In order to examine the cross-coupling reaction via reverse reactive counterpart, we prepared 2,2-difluoro-1-trialkylsilylethenyl iodides **6a-b** in 70-73% yields from the reaction of **3** with iodine (2 equiv) in THF at -30 °C followed by warming to room temperature. Recently, Paquin et al. also prepared **6a-b** via an one-pot two step reaction from the 2,2,2-trifluoroethyl iodide.²⁵ The palladiumcatalyzed cross-coupling reaction of **6b** with phenylethynyltributylstannane in the presence of 10 mol % of Pd(PPh₃)₄ and 10 mol % of CuI in THF at reflux for 2 h provided the desired product 5a in 85% yield and no dimerized product was observed. Similarly, the reaction of **6b** with *n*-butyl- or trimethylsilyl-substituted ethynyltributylstannane also afforded the corresponding 1,3-enynes 5d or 5f in 95% and 75% yields, respectively. We also performed the Sonogashira reaction of **6b** with phenylethyne in the presence of PdCl₂(PPh₃)₂, CuI, and triethylamine in DMF at 80 °C for 3 h, but the desired product 5a was isolated in only 31% yield.



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