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Preparation of (2,2-difluoroethenylidene)bis(tributylstannane) and arylation reaction: efficient approach to 1,1-diaryl-2,2-difluoroethenes

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ABSTRACT

Reaction of 2,2-difluoro-1-tributylstannylethenyl *p*-toluenesulfonate (**1**) with bis(tributyltin) in the presence of 5 mol % $Pd(PPh_3)_4$ and 30 equiv LiBr in THF at reflux temperature for 7 h afforded (2,2-difluoroethenylidene)bis(tributylstannane) (**2**) in a 70% yield. Coupling reaction of **2** with aryl iodides in the presence of 5 mol % $Pd(PPh_3)_4$ and 5 mol % CuI in DMF at 80 °C for 3–4 h provided the coupled products **3** in 59–85% yields.

2,2-Disubstituted 1,1-difluoroethenes are an important class of fluoroorganic compounds with unique chemical[1] and biological properties.[2] They undergo an addition–elimination reaction toward nucleophiles[3] to give the corresponding 1,2,2-trisubstituted 1-fluoroethenes, in which 2,2-disubstituted 1-fluoroethenes are potential mechanism-based inhibitors,[4] and are known to act as a bioisostere for the disubstituted ketones.[5] Among these compounds, 1,1-diaryl-2,2-difluoroethenes are of special interest, due to their potential utility as enzyme inhibitors and pesticides.[6] The synthesis of 1,1-diaryl-2,2-difluoroethenes can be achieved by the Wittig-type reaction, the use of 2,2-difluoroethenylmetal reagents as building blocks and other methods. However, the Wittig-type reaction was not suitable due to the poor reactivity of the diaryl ketones toward the difluoromethylene ylide.[7] Other method also gave a specific 1,1-difluoro-2,2-diphenylethene.[8] The use of 2,2-difluoethenylmetal reagents provided one straightforward route to 1,1-diaryl-2,2-difluoroethenes. Burton et al. reported a general and efficient method for the synthesis of 1,1-diaryl-2,2-difluoroethenes, in which α-halo-β,β-difluorostyrenes formed by the coupling reaction of the corresponding α-halo-β,β-difluoroethenylzinc reagents with aryl iodides were functionalized at the halogen site via Suzuki–Miyaura coupling reactions.[9] 1,1-Diaryl-2,2-difluoroethenes can be also prepared from the Pd(0)/CuI-catalyzed coupling reaction of β,β-difluoro-α-phenylvinylstannane with aryl iodides.[10] Recently, consecutive cross-coupling reactions of 2,2-difluoro-1-tributylstannylethenyl *p*-toluenesulfonate afforded 1,1-diaryl-2,2-difluoroethenes. This method has a couple of advantages as compared to the other methods, such as relatively simple procedure and easy handling of reagents. However, this method still has some drawbacks such as the lack of generality due to the use of arylstannane reagents as a coupling partner.[11] To overcome this disadvantage, we decided to introduce two tributylstannanyl groups at the same vinylidene carbon and such a compound has not been reported, although synthesis of (*E*)-(1,2-difluoroethenylidene)bis(tributylstannane)[12] and its synthetic application[13] have been previously studied. Herein, we first report the method for the preparation of (2,2-difluoroethenylidene)bis(tributylstannane) and its arylation reaction. (2,2-Difluoroethenylidene)bis (tributylstannane) (**2**) could be a remarkable precursor of 2,2-diaryl-1,1-difluoroethenes (**3**) because it has two functionally same coupling partners at the same position such as the nucleophilic tributylstannyl groups.

2,2-Difluoro-1-tributylstannylethenyl *p*-toluenesulfonate (**1**) was easily prepared in a 90% yield from the reaction of 2,2,2-trifluoroethyl *p*-toluenesulfonate with 2 equiv of LDA in THF at −78 °C, followed by treatment with tributylstannyl chloride.[11] Then, we attempted the stannanylation reaction of **1** with bis(tributyltin) in the presence of catalytic amount of $Pd(PPh_3)_4$ and excess of LiBr to introduce a stannanyl group at the tosylate site. When **1** was reacted with bis(tributyltin) in the presence of 5 mol % $Pd(PPh_3)_4$ and 3 equiv of LiCl in THF at reflux temperature for 24 h, the desired product **2** was obtained along with reduction product **4** (GC ratio of **2**:**4** = 25:75). It is postulated that the formation of **4** could be derived from the protonation of vinyl palladium (II) complex, possible intermediate in this stannylation reaction, via quenching with water. The same reaction was performed in the presence of 3 equiv of LiBr instead of LiCl to give **2** in higher

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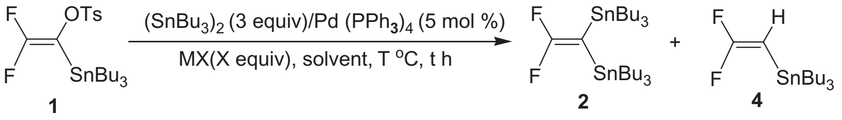
Table 1
Optimization of 2,2-difluoro-1-tributylstannylethenyl *p*-toluenesulfonate (**1**) with bis(tributyltin)



Entry	Solvent	MX	*X*	*T* (°C)	*t* (h)	GC ratio (%)		Yield[a] (%)
						2	**4**	
1	THF	LiCl	3	Reflux	24	25	75	45
2	THF	LiBr	3	Reflux	24	37	63	69
3	THF	LiBr	10	Reflux	24	52	48	74
4	THF	LiBr	15	Reflux	24	67	33	76
5	THF	LiBr	25	Reflux	7	90	10	79
6[b]	THF	LiBr	30	Reflux	7	100	0	85
7[c]	THF	LiBr	30	Reflux	48	100	0	40
8	Dioxane	LiBr	10	Reflux	48	5	95	55
9	DMF	LiBr	3	100	72	0	100	46

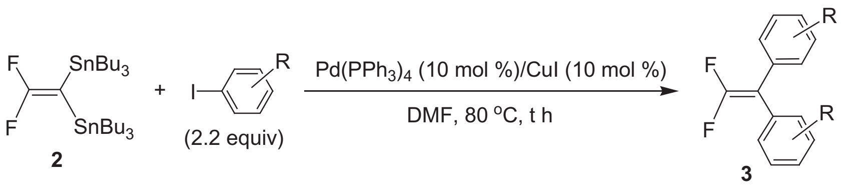
[a] Total GC yield of **2** and **4**.
[b] Reaction gave the product in a 70% isolated yield.
[c] LiBr (5 equiv) was added every 5 h and the reaction gave the product **2** in a 28% isolated yield along with several unidentified products.

GC ratio. The use of high equiv of LiBr in the same reaction resulted in the formation of **2** in higher GC ratio. After monitoring the reaction under a different solvent, different equiv of LiBr, and reaction time (Table 1), we found that the use of THF at reflux temperature for 7 h in the presence of 30 equiv of LiBr caused to provide only **2** which was obtained in a 70% isolated yield (entry 6). Although addition of LiBr (5 equiv) in every 5 h resulted in the formation of only **2**, **2** was obtained in only a 28% isolated yield. The use of DMF or dioxane as a solvent in this reaction afforded the reduction product **4** exclusively.

The coupling reaction between **2** (1.0 equiv) and iodobenzene (1.0 equiv) in the presence of 10 mol % of $Pd(PPh_3)_4$ and 10 mol % CuI in DMF at 80 °C for 3 h afforded the only di-coupled product **3** instead of mono-coupled one **4** and approximately 50% of starting material **2** was recovered. This result indicates that the second coupling process continues to be fast and thus mono-coupled product **4** cannot be tolerated for the second coupling reaction under the reaction condition. Therefore, we turned our focus to prepare the di-coupled products **3**. When **2** was reacted with 2.2 equiv of iodobenzene in the presence of 10 mol % of $Pd(PPh_3)_4$ and 10 mol % CuI in DMF at 80 °C for 3 h, 1,1-difluoro-2,2-diphenylethene (**3a**) was obtained in a 70% isolated yield. The reaction of **2** with bromobenzene under the same reaction condition was sluggish and gave a low yield of **3a**. The coupling reactions between **3** and aryl iodides having fluoro, chloro, bromo, methoxy, methyl, trifluoromethyl, and nitro on the *meta* or *para*-position of benzene ring afforded the di-coupled products **3b–m** in 59–85% yields. Aryl iodides having *ortho*-substituent (CH_3, OCH_3, Cl) gave a trace amount of di-coupled products **3n–o**, in which coupling process could be affected by steric hindrance. The coupling reactions of **2** with aryl iodides are summarized in Table 2.

Heteroaryl iodides (2.2 equiv) such as 2-iodothiophene and 3-iodothiophene also underwent coupling reactions with **2** under a similar condition to give the di-coupled products **3p** and **3q** in 55% and 61% yields, respectively. However, coupling reaction of **2** with 2-iodopyridine under the same reaction did not provide the desired product. When **2** was reacted with *p*-diiodobenzene (2.2 equiv) at room temperature in DMF for 3 h, di-coupled product

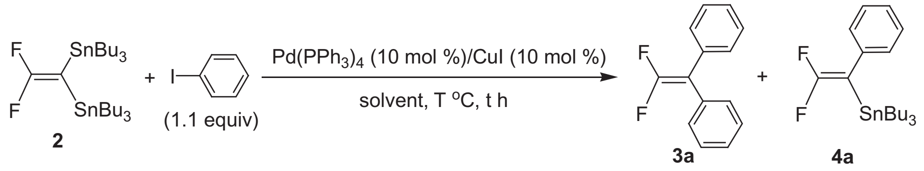
Table 2
Preparation of 2,2-difluoro-1,1-diarylethenes (**3**)



Compound no.	R	*t* (h)	Yield[a] (%)
3a	H	3	70
3b	*p*-F	3	70
3c	*p*-Cl	3	75
3d	*p*-Br	4	85
3e	*p*-OCH_3	4	62
3f	*p*-CH_3	4	59
3g	*p*-NO_2	4	80
3h	*m*-F	3	74
3i	*m*-Cl	4	71
3j	*m*-Br	3	80
3k	*m*-OCH_3	4	70
3l	*m*-CH_3	4	65
3m	*m*-CF_3	4	62
3n	*o*-OCH_3	4	—[b]
3o	*o*-CH_3	4	—[b]
3p	*o*-Cl	4	—[b]

[a] Isolated yield.
[b] Trace amount of product was obtained.

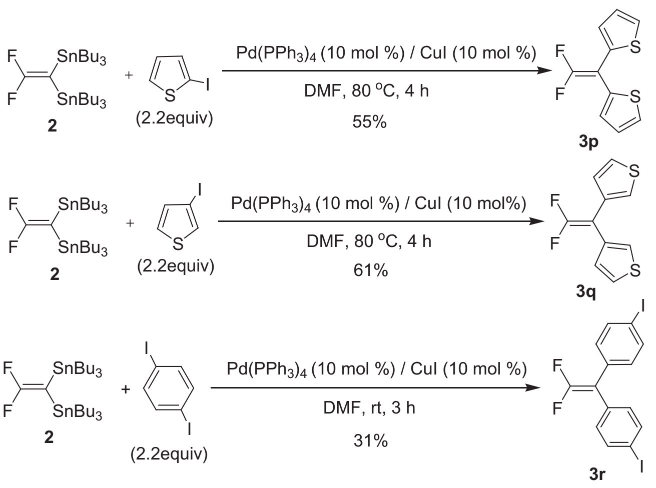
Table 3
Mono-arylation reaction of **2** with iodobenzene



Entry	Solvent	T (°C)	t (h)	Ratio[a] (%)			Yield[b] (%)
				2	**3a**	**4a**	
1	THF:DMF (10:1)	reflux	0.5	62	28	10	68
2	THF:DMF (10:1)	reflux	1	28	35	37	65
3	THF:DMF (20:1)	reflux	1	63	5	32	70
4	THF:DMF (20:1)	reflux	3	28	35	37	66
5	THF:DMF (50:1)	reflux	1	76	4	20	78
6	THF	reflux	15	70	0	30	90
7	THF	reflux	24	60	0	40	89
8	THF	reflux	48	35	18	47	84

[a] Ratio was determined by the integration of ^{19}F NMR spectrum.
[b] NMR yield of **3a** and **4a** based on the conversion of **2**.

3r was obtained in a 31% yield, but poly(arylenevinylene) was not observed at all. The use of excess of **2** (2 equiv) in this reaction provided a messy reaction mixture which cannot be separated.

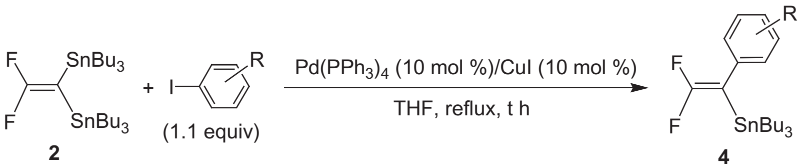


We attempted this coupling reaction at various temperatures such as 50, 25, 0, −20 and −40 °C, to provide the mono-coupled product. However, these conditions still gave a mixture of mono- and di-coupled products and made a slow reaction. Then, we used the mixture of THF and DMF as a solvent to obtain the mono-coupled product, but the mixture of coupling products were obtained regardless of the ratio of two solvents. The use of THF instead of DMF as a solvent under the same reaction condition except for the reaction time made a mono-coupled product **4** even though the reaction was not completed. Therefore, reaction of **2** with iodobenzene (1.1 equiv) in the presence of 10 mol % $Pd(PPh_3)_4$ and 10 mol % CuI in THF at reflux temperature for 24 h made 40% conversion of the starting material to the mono-coupled product **4a**. The longer reaction time (48 h) improved the conversion rate of the starting material up to 65% (Table 3), but di-coupled product **3a** was observed with mono-coupled product **4a** (**3a**:**4a** = 18:47).

Although reaction was not completed (entry 7 in Table 3), an optimized reaction condition (reflux in THF for 24 h) was applied to prepare several mono-coupled products **4b–f** via reaction between **2** and aryl iodides having hydrogen, chloro, methoxy, nitro, and trifluoromethyl on the *meta* or *para*-position of the benzene ring. The coupling reactions provided the good yields (65–78%) of **4** (Table 4). These mono-coupled products **4** can be utilized to prepare the symmetrical and unsymmetrical 1,1-diaryl-2,2-difluoroethenes **3** via the method developed at our laboratory.[10]

In summary, we have developed a general and efficient method for the synthesis of 2,2-diaryl-1,1-difluoroethenes from the mono- and di-coupling reactions of (2,2-difluoroethenylidene)bis(tributylstannane) (**2**). Mono-coupling reaction of **2** with aryl iodides was achieved by the use of THF as a solvent at the reflux temperature under the Stille-coupling reaction condition and the use of DMF at 80 °C under the same reaction condition afforded the only

Table 4
Preparation of 2,2-difluoro-1-arylethenylstannane **4**



Compound no.	R	t (h)	Conversion of **2** (%)	Yield[a] (%)
4a	H	24	40	78
4b	*p*-Cl	24	38	67
4c	*m*-OCH_3	24	50	68
4d	*p*-OCH_3	24	52	75
4e	*m*-CF_3	24	35	71
4f	*p*-NO_2	24	32	65

[a] Isolated yield based on the conversion of starting material.

di-coupled products. This method has several advantages such as satisfaction of generality, relatively simple procedure, and easy handling of reagents.

Acknowledgment

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Supplementary data

Supplementary data (experimental procedures and ^{1}H, ^{13}C and ^{19}F NMR spectra data for **2**, **3a**–**3r**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.127.

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