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A novel method for the synthesis of 2,2-diaryl-1,1-difluoroethenes

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Abstract

β,β-Difluoro-α-phenylvinylstannane **3** was prepared in 60% yield from the reaction of β,β-difluoro-α-phenylvinylsulfone **2** with tributyltin hydride in refluxing benzene for 5 h. The cross-coupling reaction of **3** with aryl iodides bearing substituents such as proton, fluoro, chloro, bromo, methoxy, methyl, trifluoromethyl, and nitro on *ortho*, *meta*, *para* positions of the benzene ring in the presence of 10 mol % $Pd(PPh_3)_4$/10 mol % CuI afforded the corresponding 2,2-diaryl-1,1-difluoroethenes **4** in 22–82% yields.

1,1-Difluoroolefins have attracted much attention because of their unique chemical,[1] and biological properties.[2] They exhibit chemical reactivities toward nucleophiles[3,4] and thus can be utilized as useful synthetic intermediates for the preparation of fluorinated organic molecules.[5] They are also an important class of potential mechanism-based inhibitors[6] and have been known to behave as a bioisostere for carbonyl group.[7] Although numerous methods for the preparation of 1,1-difluoroolefins have been well documented in the previous literatures,[8,9] methods for the preparation of 2,2-diaryl-1,1-difluoroethenes have been quite limited because the Wittig reaction for the preparation of 2,2-diaryl-1,1-difluoroethenes was not suitable due to the poor reactivity of the diaryl ketones toward the difluoromethylene ylide and also diaryl ketones are not easily available. The modified Wittig reactions using (diethylphosphinyl)difluoromethyllithium[10] or difluoromethyl diphenylphosphine oxide[11] afforded the only 2,2-diphenyl-1,1-difluoroethene. Nowak and Robins have used $(CF_3)_2Hg/NaI/R_3P$ to generate difluoromethylene ylide in situ that was reacted with diphenyl ketone to give 2,2-diphenyl-1,1-difluoroethene.[12] Recently, Burton et al. reported the first preparation of α-halo-β,β-difluorostyrene reagent that was functionalized at the halogen site with arylboronic acids under Pd(0)-catalyzed Suzuki–Miyaura coupling reactions to give 2,2-diaryl-1,1-difluoroethenes.[13] However, the previous methods have some drawbacks such as lack of generality[10–12] because of less ready availability of arylboronic acids.[13] One promising approach to 2,2-diaryl-1,1-difluoroethenes is to utilize β,β-difluoro-α-arylvinylmetal reagents because of their unique property of the carbon–carbon bond formation via carbon–metal bond. To the best of our knowledge, the only β,β-difluoro-α-phenylvinylzinc reagent has been reported as precursor to provide 2,2-diaryl-1,1-difluoroethenes.[13] However, this reagent is stable only in solution and less thermostable, and thus has some limitation for the coupling reaction with aryl iodides. Therefore, the development of thermostable and isolable β,β-difluoro-α-arylvinylmetal reagent is needed to overcome this problem. The introduction of carbon–stannane functionality into this metal reagent will provide a stable β,β-difluoro-α-arylvinylstannane which will be a promising precursor to give 2,2-diaryl-1,1-difluoroethenes. Although there have been but a couple of reports of β,β-difluorovinylstannane which bears carbamoyloxy[14] or MEMO[15] at α-position, our attention has focused on the preparation of β,β-difluoro-α-phenylvinylstannane, which can be utilized to prepare unsymmetrically 2,2-diaryl-1,1-difluoroethenes. Herein, we wish to report the first preparation of novel β,β-difluoro-α-phenylvinylstannane and its arylation reaction to give 2,2-diaryl-1,1-difluoroethenes.

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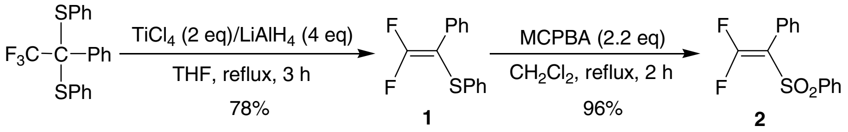
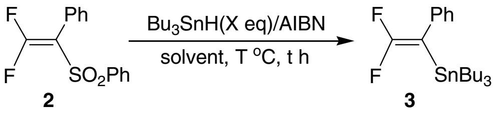
β,β-Difluoro-α-phenylvinylsulfone will be a potential starting material for the preparation of β,β-difluoro-α-phenylvinylstannane because of the successful transformation of α-fluorovinylsulfone to α-fluorovinylstannane in the previous literature,[16,17] However, this transformation should be different from that of β-fluorovinylsulfone to β-fluorovinylstannane because β-fluorovinyl anion formed as a reaction intermediate[18] during the reaction can easily undergo the β-defluorination reaction. Therefore, the transformation of β,β-difluoro-α-phenylvinylsulfone to β,β-difluoro-α-phenylvinylstannane should be carefully controlled not to bring about the β-defluorination reaction. Precursor of β,β-difluoro-α-phenylvinylsulfone, β,β-difluoro-α-phenylvinylsulfide **1**, was prepared in 78% yield from 1,1-bis(phenylthio)-2,2,2-trifluoroethylbenzene.[19] The oxidation of **1** with MCPBA (2.2 equiv) in refluxing CH_2Cl_2 for 2 h gave the β,β-difluoro-α-phenylvinylsulfone **2** in 96% isolated yield.[20]



First, we examined the stannanylation of **2** with Bu_3SnH to give the corresponding β,β-difluoro-α-phenylvinylstannane **3**. When **2** was reacted with Bu_3SnH (1.0 equiv) in refluxing benzene for 5 h, trace amount of the desired product **3** was observed. The same reaction was performed with 3.0 equiv of Bu_3SnH in refluxing benzene for 5 h to give the desired product **3** in 32% isolated yield. The optimized reaction condition was achieved using 4.0 equiv of Bu_3SnH, in which **3**[21] was obtained in 60% isolated yield. The longer reaction time (12 h) did not increase the yield of **3**, rather decreased the yield down to 45%. The use of 5.0 equiv of Bu_3SnH under the same reaction condition caused to decrease the yield (41%) of **3**. The use of other solvents such as ether, THF, and toluene did not provide better results. The results of these reactions are summarized in Table 1.

Table 1
Stannanylation of β,β-difluoro-α-phenylvinylsulfone **2**



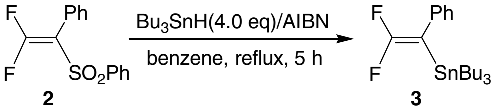
Entry	Solvent	*X* (equiv)	*T* (°C)	*t* (h)	Yield[a,b] (%)
1	Benzene	1.0	Reflux	5	—[c]
2	Benzene	3.0	Reflux	5	32
3	Benzene	4.0	Reflux	5	60
4	Benzene	4.0	Reflux	12	45
5	Benzene	5.0	Reflux	5	41
6	Benzene	6.0	Reflux	5	27
7	THF	4.0	Reflux	5	Trace
8	Toluene	4.0	100	5	23

[a] Isolated yield.
[b] All reactions were carried out in 0.045 M solution.
[c] Trace amount was observed.

The concentration of **2** in the reaction mixture is also very important to maximize the yield of **3**, in which the best result was obtained in 0.045 M solution (Table 2). The lower yields were obtained in either lower concentration or higher concentration than 0.045 M. It seems to me that the formation of β,β-difluoro-α-phenylvinylstannane might be maximized in this concentration by the recombination of β,β-difluoro-α-phenylvinyl anion and tributyltin cation as an ion pair intermediate,[18] instead of β-defluorination.

We attempted the palladium-catalyzed cross-coupling reaction of the β,β-difluoro-α-phenylvinylstannane **3** with a variety of aryl iodides to introduce an aromatic group at the stannane site. Initially, **3** was reacted with iodobenzene in the presence of 10 mol % $Pd(PPh_3)_4$/10 mol % CuI in DMF at room temperature for 24 h, but no desired product **4a** was obtained and the starting material was recovered from the reaction mixture. The reaction was then performed in the presence of 10 mol % $Pd(PPh_3)_4$/10 mol % CuI in DMF at 50 °C for 9 h to give **4a** in 65% isolated yield. The treatment of **3** with iodobenzene in the presence of 10 mol % $Pd(PPh_3)_4$/10 mol % CuI in DMF at 80 °C for 5 h resulted in the formation of **4a** in 80% isolated yield. However, the coupling reaction between **3** and iodobenzene 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 reaction of **3** with *p*-bromobenzene under the optimized reaction condition afforded **4a** in only 22% yield. Similar reactions were then carried out with aryl iodides having substituents such as fluoro, chloro, bromo, methyl, methoxy, nitro, and trifluoromethyl at *ortho*, *meta*, and *para* positions of the benzene ring under the optimized reaction condition. The reactions of **3** with aryl iodides having chloro, methyl, methoxy,

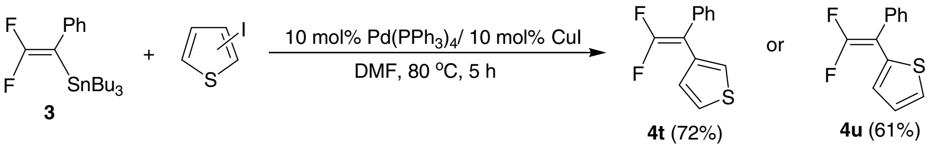
Table 2
Stannanylation of β,β-difluoro-α-phenylvinylsulfone **2** under different concentrations



Entry	Concentration (M)	Yield[a] (%)
1	0.018	—[b]
2	0.035	43
3	0.045	60
4	0.070	40
5	0.100	15

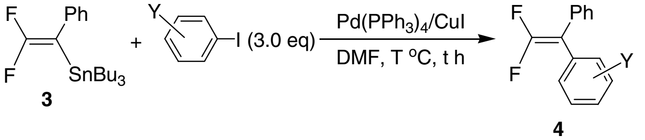
[a] Isolated yield.
[b] Trace amount of the product was obtained and most of the starting material was recovered.

nitro, trifluoromethyl on the benzene ring afforded the corresponding difluoroalkenes **4d–j**, **4l–o**, **4r** in 22–82% isolated yields. Prolonged reaction time (9 h) was needed in the reactions of **3** with aryl iodides having fluoro- and bromo-substituents on the benzene ring and the corresponding difluoroalkenes **4b**,**c**, **4k** were obtained in 50–80% yields. *o*-Fluoroiodobenzene and *o*-bromoiodobenzene provided **4p** and **4q** in less than 5% yields from this reaction. Especially, the reaction of **3** with *p*-diiodobenzene under the same reaction condition afforded a double coupling product **4s** in 20% yield as well as the formation of **4f** in 38% yield. The results of these reactions are summarized in Table 3. 3-Iodo- and 2-iodothiophene also underwent the cross-coupling reaction with **3** to give the corresponding 2,2-diaryl-1,1-difluoroethene **4t** and **4u** in 72% and 61% yields, respectively. However, the reaction of **3** with 2-iodopyrazine at the same reaction condition provided a messy reaction mixture.



Although the role of CuI in the coupling reaction of **3** with aryl iodides is not clear, it seems likely that CuI facilitates the transmetalation process of vinlystannane to vinylcopper[22] and thus speeds the cross-coupling in the presence of Pd catalyst. One experimental result showed that the total decomposition of **3** was observed from the reaction of **3** with the same equivalent of CuI only, which indicates that vinylcopper was formed. The lower yields with *ortho*-substituted aryl iodides can be explained by the steric and electronic effects of *ortho*-substituted aryl iodides toward the vinylpalladium intermediate.

Table 3
Cross-coupling reactions of **3** with aryl iodides



Compound no.	Y	*T* (°C)	*t* (h)	Yield[a] (%)
4a	H	25	24	NR[b]
4a	H	50	9	65
4a	H	80	5	80
4b	*p*-F	80	9	50
4c	*p*-Br	80	9	73
4d	*p*-Cl	80	5	61
4f	*p*-I	80	5	38[c]
4g	*p*-OCH_3	80	5	79
4h	*p*-CH_3	80	5	80
4i	*p*-CF_3	80	5	82
4j	*p*-NO_2	80	5	47
4k	*m*-Br	80	5	80
4l	*m*-CH_3	80	5	71
4m	*m*-CF_3	80	5	76
4n	*m*-NO_2	80	5	48
4o	*o*-CH_3	80	5	37
4p	*o*-F	80	9	<5
4q	*o*-Br	80	9	<5
4r	2,4-Cl	80	5	22

[a] Isolated yield.
[b] No reaction.
[c] Double coupling product **4s** was obtained in 20% yield.

A typical reaction procedure for the preparation of **4h** is as follows: A 15 mL two-neck round-bottom flask equipped with a magnetic stirrer bar, glass stopper, and reflux condenser connected to an argon source was charged with **3** (0.116 g, 0.27 mmol), *p*-iodotoluene (0.177 g, 0.81 mmol), $Pd(PPh_3)_4$ (10 mol %), CuI (10 mol %), and 6 mL of DMF. After the reaction mixture was heated at 80 °C for 5 h, the reaction mixture was cooled to room temperature and then quenched with water. The reaction mixture was extracted with ether twice, washed with 5% KF and brine, dried over anhydrous $MgSO_4$, and chromatographed on SiO_2 column. Elution with a mixture of *n*-hexane and ethyl acetate (20:1) provided **4h** (0.050 g, 98% GC purity) in 80% yield. **4h**: oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.29 (m, 2H), 7.28–7.25 (m, 2H), 7.14–7.11 (m, 5H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7 (t, $J = 293$ Hz), 129.6, 129.5, 129.1, 128.6, 128.4, 127.5, 96.1 (t, $J = 31$ Hz), 21.1; ^{19}F NMR (376 MHz, $CDCl_3$, internal standard $CFCl_3$) δ −88.68 (d, $J = 33.9$ Hz, 1F), −88.87 (d, $J = 33.9$ Hz, 1F); MS, *m*/*z* (relative intensity) 230 (M^+, 60), 214 (10), 209 (16), 179 (100), 169 (67), 165 (12), 89 (12). Anal. Calcd for $C_{15}H_{12}F_2$: C, 78.25; H, 5.25. Found: C, 77.93; H, 5.18.

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21. The mixture of **2** (0.50 g, 1.79 mmol), tributyltin hydride (1.92 mL, 7.15 mmol), catalytic amount of AIBN, and 40 mL of benzene was heated to reflux for 5 h and then cooled to room temperature followed by quenching with saturated NaCl solution. The mixture was extracted with ether twice, dried over anhydrous $MgSO_4$, and chromatographed on SiO_2 column. Elution with *n*-hexane provided **3** (0.461 g, 96% GC purity) in 60% yield. **3**: oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.44 (m, 1H), 7.28–7.22 (m, 2H), 7.14–7.11 (m, 1H), 7.06–7.01 (m, 2H), 1,57–1.44 (m, 6H), 1.36–1.24 (m, 6H), 1.08–0.97 (m, 6H), 0.90–0.82 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8 (t, $J = 249$ Hz), 128.6, 128.3, 128.0, 127.7, 125.9, 85.7 (dd, $J = 52$, 13 Hz), 28.9, 27.4, 13.6, 10.6; ^{19}F NMR (376 MHz, $CDCl_3$, internal standard $CFCl_3$) δ −74.37 (d, $J = 41.4$ Hz, 1F), −77.72 (d, $J = 41.4$ Hz, 1F); MS, *m*/*z* (relative intensity) 373 ($M^+ - 56$, 45), 371 (34), 369 (20), 253 (100), 251 (76), 249 (76), 247 (46), 177 (20), 175 (13), 139 (18), 137 (12). Anal. Calcd for $C_{20}H_{32}F_2Sn$: C, 55.97; H, 7.52. Found: C, 55.54; H, 7.38.
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