Preparation of 2,2-Difluoro-1-arylethenylstannane as a Precursor of 1,1-Diaryl-2,2-difluoroethenes

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gem-Difluoroolefins have attracted much attention because they show chemical reactivities toward nucleophiles and are useful intermediate for the synthesis of fluorinated organic compounds via addition-elimination reaction. They are also important class of potential mechanism-based inhibitors and have been known to behave as a bioisostere for carbonyl group. The synthesis of gem-difluoroolefins can be mainly achieved by two generalized methods such as Wittig and related reaction, and metalation and related chemistry. However, Wittig methodology was not suitable for the preparation of 1,1-diaryl-2,2-difluoroethenes because of the poor reactivity of the diaryl ketones. One straightforward route to 1,1-diaryl-2,2-difluoroethenes is to use 2,2-difluoroethenylmetal reagents. Among these reagents, one of the promising precursors to gem-difluoroolefins is 2,2-difluoroethenylstannane reagents which can be utilized as cross-coupling reaction at stannylic site. Although numerous methods for the preparation of 2,2-difluoroethenylmetal reagents have been well documented in the previous literature, methods for the preparation of 2,2-difluoroethenylstannane reagents have been quite limited, in which 1,1-diaryl-2,2-difluoroethenes can be easily prepared by the Stille cross-coupling reaction. Percy et al. reported a method for the synthesis of 2,2-difluoro-1-tributylstannylethenyl diethylcarbamate from the reaction of 2,2-difluoro-1-lithio-ethenyl diethylcarbamate with tributylstannyl chloride. 2,2-Difluoro-1-tributylstannylethenyl ethers were prepared in a similar manner and their cross-coupling with aryl iodides, followed by cleavage of ether linkage provided difluoro-methyl ketones. Burton et al. synthesized 2,2-difluoroethenylstannane from the reaction of 2,2-difluoroethyl-triethylsilane with tributylstannyl chloride in the presence of KF. He also prepared 2,2-difuoro-1-bromoethenylstannane from the reaction of 1,1-dibromo-2,2-difluoroethene with tributyltin chloride in the presence of Zn metal. We reported a method for the preparation of 2,2-difluoro-1-phenylethenylstannane from the stannylation of sulfonil group in 2,2-difluoro-1-phenylethenylsulfone and its arylation to give 1,1-diaryl-2,2-difluoroethenes. Alkenylation and alkylation of 2,2-difluoro-1-phenylethenylstannane provided the corresponding 1,1-difuoro-1,3-butadienes and 1,1-difuoro-1,3-eneynes. Recently, efficient synthesis of 2,2-diaryl-1,1-difluoroethenes can be achieved by consecutive cross-coupling reactions of 2,2-difluoro-1-tributylstannylethenyl p-toluenesulfonate. However, a general preparation of 1-aryl-2,2-difluoroethenylstannane which is a better coupling partner of arylation as compared to 1-aryl-2,2-difluoroethenyltosylate has not been reported in the previous literature. Herein, we wish to report a general method for the preparation of 1-aryl-2,2-difluoroethenylstannane which should be a nice precursor to 1,1-diaryl-2,2-difluoroethenes.

2,2-Difluoro-1-tributylstannylethenyl p-toluenesulfonate (1) was easily prepared in 90% yield from the reaction of 2,2,2-trifluoroethyl p-toluenesulfonate with 2.8 equiv of LDA in THF at –78 °C, followed by treatment with tributylstannyl chloride. Then, the cross-coupling reaction of 1 with aryl iodides in the presence of 10 mol % Pd(PPh$_3$)$_2$Cl and 10 mol % Cul in DMF at 80 °C for 10-20 hours afforded the 2,2-difluoro-1-arylethenyl p-toluenesulfonate 2 in moderate to excellent yields.

We attempted the stannylation of tosylate functional group of 2. When 2,2-difluoro-1-phenylethenyl p-toluenesulfonate (2a) was reacted with 1.2 equiv of hexabutyldistannane in the presence of 5 mol % of Pd(PPh$_3$)$_2$Cl and 5 equiv of LiCl in DMF at 100 °C for 6 h, the desired product 3a was observed in a trace amount and starting material was recovered. The longer reaction time and increase of LiCl up to 30 equivalent afforded the similar result. The reaction was performed in the presence of 5 equiv of LiBr instead of LiCl to give 3a in 45% yield, in which the reaction completed in 8 hours. The dramatically increased yield (60% yield) of 3a was achieved by the use of 10 equiv of LiBr in this reaction. However, when the higher equiv of LiBr was used in the reaction, the yield of 3a decreased. Increase of Pd(PPh$_3$)$_2$Cl to 10 mol % did not cause to increase the yield of 3a. Reaction of 2a with 1.2 equiv of hexabutylstannane in the presence of 5 mol % of Pd(PPh$_3$)$_2$Cl and 10 equiv of LiBr in THF at reflux temperature for 8 hours afforded the desired product 3a in a trace amount and most of starting material was recovered. Reaction did not improve even though 30 equiv of LiBr was used in this reaction. The use of a mixture of PdCl$_2$(PPh$_3$)$_2$ and X-Phos as a ligand in the reaction also did not give the observation of 3a. After monitoring of the reaction under the different solvent, different equiv of LiBr and catalyst (Table 1), we found that the use of 5 mol % of Pd(PPh$_3$)$_2$Cl and 10 equiv of LiBr in DMF at 100 °C for 8 hours provided 3a in 60% isolated yield.

Optimized reaction condition was applied to prepare a
variety of 2,2-difluoro-1-arylethenylstannane 3b-n via reaction between hexabutyldistannane and 2 having fluor, chloro, bromo, methoxy, methyl, trifluoromethyl and nitro on the benzene ring. Except for the 2,2-difluoro-1-arylethenyl p-toluenesulfonate having electron-donating group (CH$_3$, OCH$_3$) on the benzene ring attached to double bond, the desired products 3 were obtained in 58-67% isolated yields (Table 2). The longer reaction time (14 hours) was required for the reaction with 2,2-difluoro-1-arylethenyl p-toluenesulfonate having electron-donating group or ortho-substituent, with relatively low yields (31-45%).

A typical reaction procedure for the preparation of 3e 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 LiBr (0.869 g, 10 equiv) and 5 mol % Pd(PPh$_3$)$_4$ and then a solution of hexabutyldistannane (0.696 g, 1.2 equiv) in 3 mL of DMF was added by dropwise to the mixture. Then, DMF (2 mL) solution of 2a (0.340 g, 1 mmol) was added. After the reaction mixture was heated at 100 °C for 24 hours, 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 3e (0.188 g) in 41% yield. 3e: oil; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.91-6.89 (d, $J = 8.8$ Hz, 2H), 6.76-6.74 (d, $J = 8.8$ Hz, 2H), 3.69 (s, 3H), 1.45-1.36 (m, 6H), 1.26-1.18 (m, 6H), 0.92-0.88 (m, 6H), 0.84-0.77 (m, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 153.3 (dd, $J = 314$, 271 Hz), 129.6, 128.5, 114.2, 113.8, 84.9 (dd, $J = 51$, 13 Hz), 55.1, 28.2, 27.2, 13.6, 10.5; $^{19}$F NMR (376 MHz, CDCl$_3$, internal standard CFCl$_3$) δ $-$74.95 (d, $J = 41.4$ Hz, 1F), $-$78.11 (d, $J = 41.4$ Hz, 1F); MS, m/z (relative intensity) 460 (M$^+$+1, 1), 403 (20), 253 (100), 177 (39), 139 (31), 57 (18). Anal. Calcd for C$_2$H$_3$F$_2$OSn: C, 54.93; H, 7.46. Found: C, 54.71; H, 7.40.

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References