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Mg(0)-promoted debromometalation of *gem*-difluoropropargyl bromides

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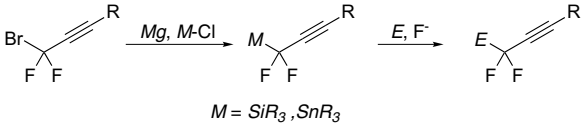
Abstract—Mg(0)/Me_3SiCl was found to be effective for the preparation of difluoropropargylsilanes. This method, using Me_3SnCl, produced the corresponding propargylstannane.

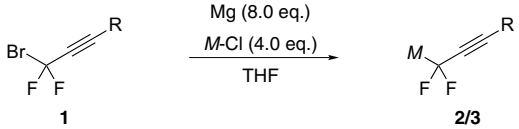
There is a growing interest in developing difluorinated building blocks for the synthesis of *gem*-difluoromethylene-containing compounds because of their interesting biological activities, such as the anticancer agent gemcitabine,[1] HIV-1 protease inhibitors,[2] phosphotyrosine (*p*Tyr) mimetics,[3] and fluorinated sugars.[4] A silylated and/or stannylated *gem*-difluoropropargyl synthon, RC≡C–CF_2Si(Sn), could be a key synthetic intermediate in the synthesis of *gem*-difluoromethylene containing C-3 synthons because of the rich chemistry of acetylenes. The non-fluorinated propargylsilanes or stannanes are stable species,[5] and have been converted into biological active compounds, or have served as precursor of allenes.[6] In stark contrast, there are only a handful of reports on the generation of *gem*-difluoropropargyl organometallic complexes.[7] In this letter, we report a practical synthesis of *gem*-difluoropropargylsilane and *gem*-difluoropropargylstannane using Mg(0)-promoted reductive debromometalation[8] of 3-bromo-3,3-difluoropropyne as a key reaction (Eq. 1).



(1)

As shown in Table 1, the procedure for the selective formation of **2** works well for a diverse group of aromatic and aliphatic alkynes. No allenyl organometallics were detected.[9] Neither over-reduction nor C–F bond cleavage were observed. In the case of aromatic alkynes, the reactions were completed within 30 min at 0 °C in THF (entries 1–4). Also, an aliphatic alkyne reacts smoothly to give the corresponding silylated difluoroalkyne at 0 °C in THF (entry 5), as compared with aliphatic ketones and imines (C–F bond cleavage of aliphatic trifluoromethyl ketone and imine) which required DMF as a solvent and high temperature.[8a,g] Moreover,

Table 1. Mg(0)-promoted debromometalation of bromodifluoroalkyne **1**[a]



Entry	R	M–Cl	Conditions	% Yield of **2**/**3**[b]
1	*p*-MeP_6H_4	TMSCl	0 °C, 30 min	81 (**2a**)
2	*o*-MeC_6H_4	TMSCl	0 °C, 30 min	77 (**2b**)
3	*p*-$MeOC_6H_4$	TMSCl	0 °C, 30 min	90 (**2c**)
4	Ph	TMSCl	0 °C, 30 min	51 (**2d**)
5	Hex	TMSCl	0 °C, 30 min	63 (**2e**)
6	TIPS	TMSCl	0 °C, 30 min	82 (**2f**)
7	TES	TMSCl	0 °C, 30 min	93 (**2g**)
8	Ph	Me_3SnCl	0 °C, 1 h	75 (**3**)

[a] The reaction was carried out by the procedure shown in Ref. 10.
[b] Isolated yield. All compounds gave satisfactory spectral data.

Keywords: Magnesium; *gem*-Difluoromethylene; Propargylsilane; Propargylstannane.
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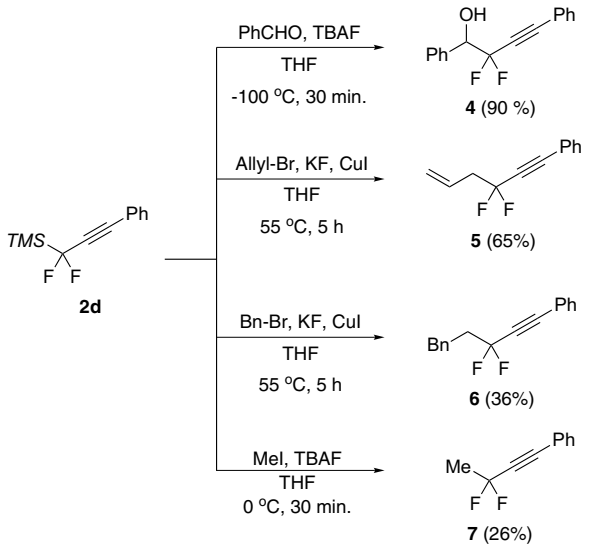

Scheme 1.

silylated alkynes **1f**,**g** generally gave good yields (entries 6 and 7). Using the same protocol, **1** reacted with trimethylstannyl chloride to give the stannane **3** in 75% yield (entry 8).

Difluorotrimethylsilylmethyl **2** is a promising building block because it is readily available, can be stored for long periods of time, and it is highly reactive in the presence of a fluoride anion.[11] To explore the reactivity of 3,3-difluoro-3-trimethylsilyl alkyne, **2d** was subjected to a fluoride anion promoted C–C bond formation with electrophiles such as aldehydes and halides (Scheme 1). The reaction of **2d** with benzaldehyde proceeded smoothly to give **4** in excellent yield. Allylation and benzylation of **2d** in the presence of KF and CuI gave **5** and **6** in good to moderate yields. Also, methylation of **2d** in the presence of TBAF succeeded to give **7** albeit in low yield.

In conclusion, the selective metalation of bromodifluoropropargyl **1**, using Mg/Me_3SiCl or Me_3SnCl, allowed access to difluoropropargylsilanes **2** and difluoropropargylstannane **3** in good yields. The former reacted with various electrophiles in the presence of fluoride anion to give the corresponding difluoromethylene compounds. Further utilization of difluoropropargylsilanes and/or -stannanes are in progress in our laboratory.

Acknowledgements

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10. A typical reaction procedure is as follows: To the mixture of Mg (194 mg, 8.0 mmol) and chlorotrimethylsilane (0.51 mL, 4.0 mmol) in dry THF (10 mL), 3-bromo-3,3-difluoro-1-(4-methylphenyl)propyne **1a** (238 mg, 1.0 mmol) was added dropwise at 0 °C under an argon atmosphere. The reaction mixture was stirred for 30 min. at 0 °C. The residual Mg was removed by decantation, and the THF solution was washed with H_2O (5 mL). The aqueous layer was extracted with hexane (5 mL × 2) and the combined organic layers were dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by silica gel treated with Et_3N/hexane = 1/9 column chromatography (hexane) to afford **2a** as an orange oil (187 mg, 81%); IR (neat) 2225 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.29 (s, 9H), 2.37 (s, 3H), 7.16 (d, J = 6.5 Hz, 2H), 7.38 (d, J = 7.5 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ −4.9, 21.5, 81.6 (t, J = 30.8 Hz), 91.4 (t, J = 8.7 Hz), 111.7, 120.6 (t, J = 253 Hz), 129.2, 131.9, 140.0; ^{19}F NMR (470 MHz, $CDCl_3$, C_6F_6 as an internal standard) δ 56.8 (s, 2F); GC/MS (CI) m/z (%) 239 ($M+1^+$, 14), 223 (27), 219 (100).
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