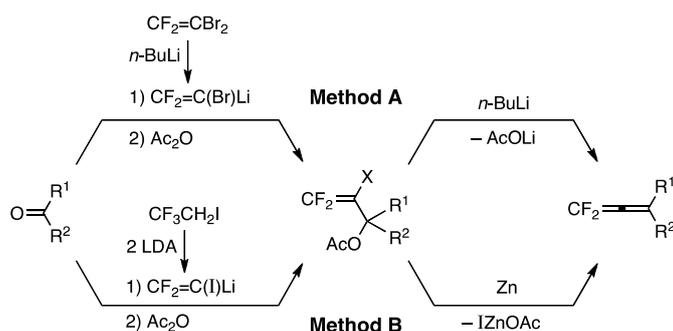


Facile Synthesis of Substituted 1,1-Difluoroallenes via C=O Difluorovinylideneation

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Abstract: Two methods for difluorovinylideneation of carbonyl compounds have been developed to synthesize 1,1-difluoroallenes bearing various substituents. The Reaction of 1-bromo-2,2-difluorovinyl lithium, generated from 1,1-dibromo-2,2-difluoroethylene and butyllithium, with aldehydes or ketones and subsequent acetylation with acetic anhydride gave 2-bromo-3,3-difluoroallylic acetates. Elimination of these acetates with butyllithium afforded 1,1-difluoroallenes in high yield (method A). 3,3-Difluoro-2-iodoallylic acetates were similarly prepared from aldehydes or ketones on treatment with 2,2-difluoro-1-iodovinyl lithium, generated from 1,1,1-trifluoro-2-iodoethane and LDA, followed by acetylation. These acetates readily underwent elimination with zinc metal to afford 1,1-difluoroallenes in high yield (method B).



Scheme 1 Synthesis of 1,1-difluoroallenes by difluorovinylideneation of aldehydes or ketones

Introduction

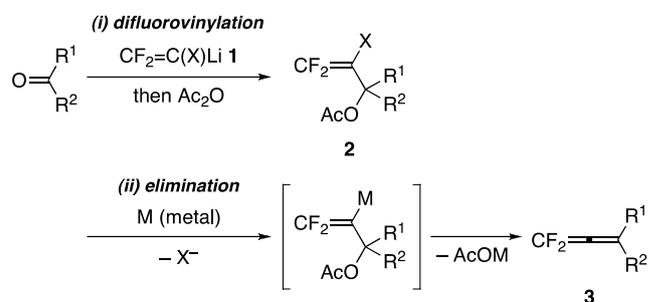
1,1-Difluoroallenes are highly attractive synthetic intermediates because of their fluorine substituents and cumulative double bonds. In addition, 1,1-difluoroallenes can serve as promising pharmaceuticals because some of non-fluorinated allenes have been used for therapeutic purposes.¹ To date, however, the synthetic method for 1,1-difluoroallenes bearing substituents has not been completely explored.²⁻⁴

We have recently reported a facile method for the synthesis of substituted 1,1-difluoroallenes via difluorovinylideneation of carbonyl compounds (Scheme 1).⁵ A wide variety of difluoroallenes were efficiently synthesized by our methods.

Our synthesis consists of two steps (Scheme 2): (i) the reaction of aldehydes or ketones with 2,2-difluoro-1-haloallyllithium **1** and subsequent acetylation gives 3,3-difluoro-2-haloallylic acetates **2**. (ii) Metallation of **2** with an appropriate reducing agent causes elimination of the halide ion (X^-) and the acetate ion to furnish the desired 1,1-difluoroallenes **3**. Depending on the reagents **Method A. Synthesis of 1,1-difluoroallenes from 1,1-dibromo-2,2-difluoroethylene (the first generation synthesis)**^{5a}

Initially, 1,1-dibromo-2,2-difluoroethylene ($CF_2=CBr_2$) was used as a difluorovinylideneation agent. 1,1-Dibromo-2,2-difluoroethylene was lithiated with 1 equiv of butyllithium at $-100^\circ C$. Aldehydes or ketones were treated with the formed vinylolithium and then with acetic anhydride. Next, the isolated 3,3-difluoro-2-bromoallylic acetates **2A** ($X = Br$) were next lithiated with butyllithium in hexane. Elimination of lithium acetate occurred to afford 1,1-difluoroallenes **3**.

used for the difluorovinylideneation (the first step) and the elimination (the second step), two methods are available, namely, method A and B. Method B should have wide applications because it includes a readily available starting material and facilitates the synthesis of difluoroallenes bearing functionalities that are sensitive to butyllithium.

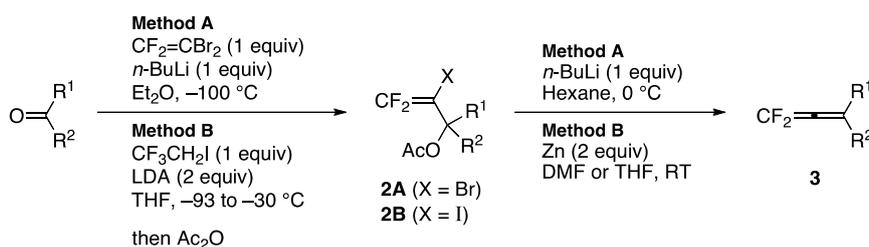


Scheme 2 Difluorovinylideneation–elimination sequence in difluoroallene synthesis

Note that controlling the temperature in the vinylation with dibromodifluoroethylene is crucial. The first lithiation at a temperature higher than $-100^\circ C$ led to undesired 1,2-elimination of LiF from the intermediate 1-bromo-2,2-difluorovinylolithium. The second lithiation of allylic acetates **2A** must be performed in hexane to realize the elimination in high yield.

The formed 1,1-difluoroallenes are purified by standard column chromatography (SiO_2). The isolated difluoroallenes can be stored in a refrigerator ($0^\circ C$) for at least one month or longer.

Table 1 Synthesis of 1,1-difluoroallenes from 1,1-dibromo-2,2-difluoroethylene or 1,1,1-trifluoro-2-iodoethane



Entry	Carbonyl Compound	Difluoroallene		Yield (%) (Method A)		Yield (%) (Method B)	
				2A	3	2B	3
1			Ar = Ph	93 (2Aa)	87 (3a)	82 (2Ba)	86 (3a)
2			Ar = 1-Naph	84 (2Ab)	73 (3b) ^a	83 (2Bb)	82 (3b)
3				—	—	84 (2Bc)	87 (3c)
4				83 (2Ad)	85 (3d)	81 (2Bd)	95 (3d)

PRACTICAL SYNTHETIC PROCEDURES

5			86 (2Ae)	84 (3e)	87 (2Be)	92 (3e)	
6			85 (2Af)	84 (3f)	—	—	
7			85 (2Ag)	83 (3g)			
8			R = H	—	—	83 (2Bh)	93 (3h)
9			R = Me	87 (2Ai)	82 (3i)	—	—
10			R = OMe	87 (2Aj)	81 (3j)	—	—
11			R = (CH ₂) ₂ Ph	84 (2Ak) ^b	90 (3k)	—	—
12			R = Me	—	—	80 (2Bl) ^b	86 (3l)
13			80 (2Am) ^b	85 (3m) ^a	—	—	

^a ¹⁹F NMR yield based on PhCF₃. ^b Acetylation was performed by isopropenyl acetate/TsOH.

Method B. Synthesis of 1,1-difluoroallenes from 1,1,1-trifluoro-2-iodoethane (the second generation synthesis)^{5b}

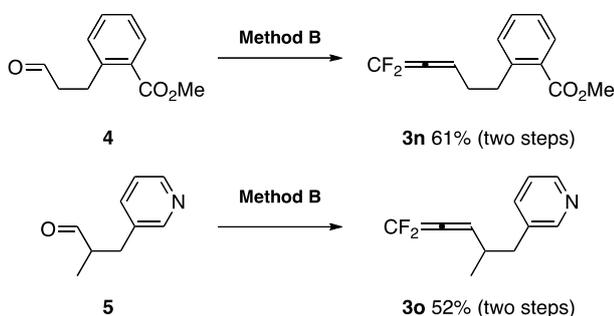
1,1-Dibromo-2,2-difluoroethylene, used in our first generation synthesis, is an expensive, potential ozone-depleting substance and is now difficult to purchase because of the ban on its industrial manufacture. In addition, highly reactive butyllithium is required in both metallation steps of alkenyl bromides.

The second generation synthesis of 1,1-difluoroallenes is realized using 1,1,1-trifluoro-2-iodoethane ($\text{CF}_3\text{CH}_2\text{I}$) as a difluorovinylating agent.⁶ This material is readily available because it is manufactured industrially for use as refrigerants or fluorinated intermediates. 1,1,1-Trifluoro-2-iodoethane is treated with 2 equiv of LDA to generate 2,2-difluoro-1-iodovinyl lithium. Aldehydes or ketones react with the iodovinyl lithium, and then the formed alkoxides are trapped with acetic anhydride in the one-pot synthesis. The isolated 3,3-difluoro-2-iodoallylic acetates **2B** ($\text{X} = \text{I}$) are reduced with zinc metal (2 equiv). Elimination proceeds smoothly in DMF or THF at room temperature, and the desired 1,1-difluoroallenes are obtained in high yield.

Reaction Scope

Yields of the synthesized acetates **2** and 1,1-difluoroallenes **3** by the methods A and B are summarized in Table 1. The efficiency of the two methods is almost comparable. A wide variety of monosubstituted difluoroallenes are obtained from aldehydes. The synthesis of disubstituted difluoroallenes is also accomplished by the difluorovinylideneation of ketones.

Method B particularly enables the synthesis of difluoroallenes bearing functionalities that are sensitive to butyllithium. Aldehydes **4**, bearing an ester moiety, and **5**, bearing a pyridine ring, are transformed to the corresponding difluoroallenes **3n** and **3o** in 61% and 52% yield, respectively.



Scheme 3 Synthesis of 1,1-difluoroallenes with an ester moiety and a pyridine ring

Summary

Difluorovinylating of aldehydes or ketones is readily realized with 1-bromo-2,2-difluorovinyl lithium (method A) or 2,2-difluoro-1-iodovinyl lithium (method B),

followed by acetylation to give 2-bromo-3,3-difluoroallylic acetates or 3,3-difluoro-2-iodoallylic acetates, respectively. The formed allylic acetates undergo facile elimination on treatment with butyllithium (method A) or zinc metal (method B) to afford 1,1-difluoroallenes in high yield. Method B starts from readily available $\text{CF}_3\text{CH}_2\text{I}$, and allows the synthesis of difluoroallenes bearing functionalities that are sensitive to butyllithium.

NMR spectra were recorded on Bruker AVANCE-500 or Bruker AVANCE-400 in CDCl_3 . Chemical shift values were given in ppm relative to internal SiMe_4 (for ^1H NMR: δ 0.00), CDCl_3 (for ^{13}C NMR: δ 77.0), and C_6F_6 (for ^{19}F NMR: δ 0.0). Mass spectra (EI-TOF or ESI-TOF) were measured on JEOL JMS-T100GCv or JMS-T100CS. IR spectra were recorded by ATR (attenuated total reflectance) method on a Horiba FT-720.

Column chromatography and preparative thin layer chromatography (preparative TLC) were conducted on silica gel (Silica Gel 60 N, Kanto Chemical Co., Inc. for column chromatography and Wakogel B-5F, Wako Pure Chemical Industries for PTLC, respectively).

All reactions were conducted under argon. THF, DMF, hexane, and diethyl ether were dried by passing over a column of activated alumina followed by a column of Q-5 scavenger (Engelhard). Pentane was distilled from calcium hydride.

Typical procedure for method A (Table 1, Entry 1).

To a solution of 1,1-dibromo-2,2-difluoroethylene (444 mg, 2.0 mmol) in Et_2O (16 mL) was added an Et_2O solution (2.0 mL) of butyllithium (1.28 mL, 1.60 M in hexane, 2.0 mmol) at -100°C under argon. After stirring for 15 min at the same temperature, 3-phenylpropanal (0.28 mL, 2.0 mmol) was added. The mixture was stirred for an additional 15 min. After acetic anhydride (0.19 mL, 2.0 mmol) was added, the mixture was allowed to warm to 0°C over 2 h. The reaction was quenched with saturated NH_4Cl aq., and the products were extracted with Et_2O . The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4 . After removal of the solvents under reduced pressure, the residue was purified by column chromatography (SiO_2 , hexane–AcOEt, 20:1) to give **2Aa** as a colorless liquid (593 mg, 93%). Butyllithium (2.6 mL, 1.60 M in hexane, 0.23 mmol) was added to a solution of **2Aa** (60 mg, 0.19 mmol) in hexane (2.6 mL) at 0°C under argon. After stirring for 1 min at the same temperature, the reaction was quenched with NH_4Cl aq., and the products were extracted with Et_2O . The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4 . After removal of the solvent under reduced pressure, the residue was purified by column chromatography (SiO_2 , pentane) to give **3a** (29 mg, 87%) as a colorless liquid.

Typical procedure for method B (Table 1, Entry 1).

To a solution of diisopropylamine (2.8 mL, 20 mmol) in THF (10 mL) was added butyllithium (12.0 mL, 1.67 M in hexane, 20.0 mmol) over 10 min at 0°C under argon. The resulting solution was allowed to stir for an additional 15 min, and then cooled to -93°C in a cold hexane bath. To the cold LDA solution was added a THF (5 mL) solution of $\text{CF}_3\text{CH}_2\text{I}$ (2.10 g, 10.0 mmol) over 10 min, keeping the temperature between -93°C and -85°C . After stirring for 20 min at the same temperature, a THF (5 mL)

solution of 3-phenylpropanal (1.34 g, 10.0 mmol) was added over 5 min, keeping the temperature between $-93\text{ }^{\circ}\text{C}$ and $-85\text{ }^{\circ}\text{C}$. The mixture was stirred for an additional 30 min, then warmed to $-30\text{ }^{\circ}\text{C}$ over 90 min. After acetic anhydride (1.23 g, 12.0 mmol) was added, the mixture was allowed to warm to $0\text{ }^{\circ}\text{C}$ over 2 h. The reaction was quenched with saturated NH_4Cl aq., and the products were extracted with Et_2O . The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 . After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–AcOEt, 20:1). The acetate **2Ba** was obtained as a colorless liquid (3.01 g, 82%). To a suspension of zinc powder (131 mg, 2.00 mmol) in DMF (3 mL) was added a DMF (2 mL) solution of **2Ba** (366 mg, 1.00 mmol) at room temperature under argon. After stirring for 3 h, the resulting mixture was filtered to remove the excess zinc and then diluted with Et_2O and brine. The products were extracted with Et_2O . The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4 . After removal of the solvent under reduced pressure, the residue was purified by column chromatography (SiO_2 , pentane). Difluoroallene **3a** was obtained as a colorless liquid (155 mg, 86%).

2-Bromo-1,1-difluoro-5-phenylpent-1-en-3-yl acetate (2Aa)

IR: 3028, 2949, 1747, 1731, 1282, 1221, 1026, 700 cm^{-1} .

^1H NMR: δ 1.98–2.08 (1H, m; CH_2), 2.07 (3H, s; CH_3CO), 2.11–2.17 (1H, m; CH_2), 2.58–2.62 (2H, m; CH_2), 5.44 (1H, dddd, $J = 7.3, 7.3\text{ Hz}$, $J_{\text{HF}} = 2.1, 2.1\text{ Hz}$; CH), 7.17 (2H, dd, $J = 7.8, 0.8\text{ Hz}$; ArH), 7.21 (1H, tt, $J = 7.8, 0.8\text{ Hz}$; ArH), 7.29 (2H, dd, $J = 7.8, 7.8\text{ Hz}$; ArH).

^{13}C NMR: δ 20.8, 31.1, 34.1, 68.3 (d, $J_{\text{CF}} = 3\text{ Hz}$), 81.0 (dd, $J_{\text{CF}} = 35, 21\text{ Hz}$), 126.3, 128.2, 128.6, 140.2, 154.2 (dd, $J_{\text{CF}} = 294, 289\text{ Hz}$), 169.7.

^{19}F NMR: δ 80.7 (1F, br d, $J_{\text{FF}} = 27\text{ Hz}$), 82.3 (1F, br d, $J_{\text{FF}} = 27\text{ Hz}$).

Anal. Calcd for $\text{C}_{13}\text{H}_{13}\text{BrF}_2\text{O}_2$: C, 48.92; H, 4.11. Found: C, 49.14; H, 4.34.

1,1-Difluoro-2-iodo-5-phenylpent-1-en-3-yl acetate (2Ba)

IR: 3028, 2954, 1743, 1716, 1267, 1219, 1024, 698 cm^{-1} .

^1H NMR: δ 1.87–1.93 (1H, m), 2.05–2.17 (1H, m), 2.07 (3H, s), 2.58 (2H, t, $J = 7.2\text{ Hz}$), 4.98 (1H, t, $J = 7.2\text{ Hz}$), 7.17–7.22 (3H, m), 7.29 (2H, dd, $J = 7.3, 7.6\text{ Hz}$).

^{13}C NMR: δ 20.9, 30.9, 36.0, 53.8 (dd, $J_{\text{CF}} = 25, 26\text{ Hz}$), 68.9 (d, $J_{\text{CF}} = 3\text{ Hz}$), 126.2, 128.2, 128.5, 140.2, 154.0 (dd, $J_{\text{CF}} = 286, 286\text{ Hz}$), 169.6.

^{19}F NMR: δ 89.2 (1F, d, $J_{\text{FF}} = 22\text{ Hz}$), 90.2 (1F, d, $J_{\text{FF}} = 22\text{ Hz}$).

HRMS (ESI+) calcd for $\text{C}_{13}\text{H}_{13}\text{F}_2\text{IO}_2\text{Na}$ [$\text{M} + \text{Na}$] $^+$ 388.9826, found 388.9830.

1,1-Difluoro-5-phenylpenta-1,2-diene (3a)

IR: 3030, 2927, 2856, 2011, 1462, 1192, 744, 698 cm^{-1} .

^1H NMR: δ 2.53–2.61 (2H, m; CH_2), 2.81 (2H, t, $J = 7.5\text{ Hz}$; CH_2), 6.47 (1H, tt, $J = 6.1\text{ Hz}$, $J_{\text{HF}} = 2.4\text{ Hz}$; =CH), 7.17–7.22 (3H, m; ArH), 7.30 (2H, dd, $J = 7.3, 7.3\text{ Hz}$; ArH).

^{13}C NMR: δ 33.8, 33.8, 121.4 (t, $J_{\text{CF}} = 6\text{ Hz}$), 126.2, 128.4, 128.5, 140.6, 152.8 (t, $J_{\text{CF}} = 261\text{ Hz}$), 170.1 (t, $J_{\text{CF}} = 36\text{ Hz}$).

^{19}F NMR: δ 59.9 (td, $J_{\text{FH}} = 5, 2\text{ Hz}$).

Anal. Calcd for $\text{C}_{11}\text{H}_{10}\text{F}_2$: C, 73.32; H, 5.59. Found: C, 73.16; H, 5.77.

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