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Facile Synthesis of 1,1-Difluoroallenes via the Difluorovinylidenation of Aldehydes and Ketones

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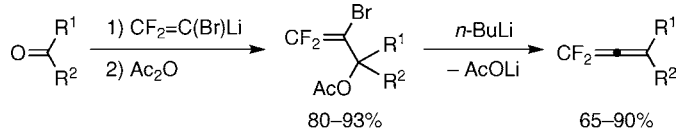
ABSTRACT



2-Bromo-3,3-difluoroallylic acetates were readily prepared by the reaction of carbonyl compounds with 1-bromo-2,2-difluorovinyllithium, generated from 1,1-dibromo-2,2-difluoroethylene, followed by acetylation. On treatment with butyllithium, the bromoacetates underwent selective 1,2-elimination of lithium acetate to afford mono- and disubstituted 1,1-difluoroallenes in high yields.

1,1-Difluoroallenes exhibit a wide range of reactivity. They react with various unsaturated compounds to give cycloaddition products: Diels−Alder[1a] and [3+2][1b−d] cycloaddition reactions with 1,3-dienes and 1,3-dipoles take place on the internal, nonfluorinated alkene moiety to give the corresponding products.[1e,f] The [2+2] cycloaddition reactions with alkenes and alkynes occur on the terminal, fluorinated alkene moiety to give cyclobutane[2a] and cyclobutene[2b] derivatives. 1,1-Difluoroallenes also serve as substrates for nucleophilic reactions. Not only nucleophilic substitution on the terminal alkene moiety[3a] but nucleophilic addition to the internal alkene moiety[3b] has been reported in the literature. Furthermore, the palladium-catalyzed coupling reaction of difluorohomoallenyl bromide with organoboronic acids takes place to give substituted butadienes.[4] Thus, 1,1-difluoroallenes are potentially useful building blocks for the construction of fluorinated molecules.

In addition, nonfluorinated allenes are found in the structures of many natural and non-natural biologically active compounds, and some of these have been used for therapeutic purposes.[5] The synthesis of their fluorinated analogues could lead to the development of pharmaceuticals with improved activity.

Despite their synthetic and practical importance, only a limited number of synthetic methods for accessing 1,1-

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(10) Thermal stability of allenes compared to the constitutionally isomeric terminal acetylenes might contribute in part to selective elimination of LiOE. For instance, 1,2-butadiene is more stable than 1-butyne by 2.9 kJ/mol: Pedley, J. B.; Naylor, R. D.; Kirby, S. P., Ed. *Thermochemical Data of Organic Compounds*; Chapman and Hall: London, UK; 1977.

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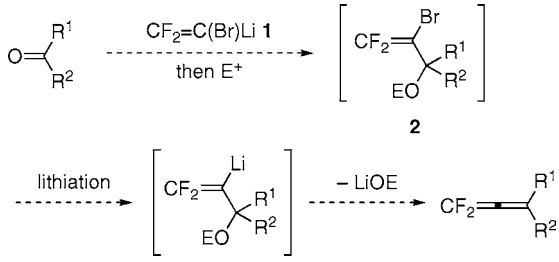
difluoroallenes have been reported.[6] 1-Trifluoromethyl-substituted alkenyllithium compounds, which are prepared from 2-bromo-1,1,1-trifluoro-2-alkene[1a] or trifluoromethyl-substituted hydrazones,[7] afford 1,1-difluoroallenes via the 1,2-elimination of lithium fluoride. 1,1-Difluoropropargylindium species, generated from the corresponding propargyl bromides, react with formaldehyde to give 1,1-difluoroallenes bearing a hydroxymethyl moiety.[8] These propargyl bromides also react with Grignard reagents in the presence of a copper catalyst to give 1,1-difluoroallenes.[3a] Notwithstanding these past contributions, general methods that can provide a wide range of 1,1-difluoroallenes are still needed.[9]

In this Letter, we describe a new route to 1,1-difluoroallenes starting from carbonyl compounds. Our strategy to access 1,1-difluoroallenes is via the difluorovinylidenation of carbonyl compounds, as shown in Scheme 1. Aldehydes and ketones are treated with

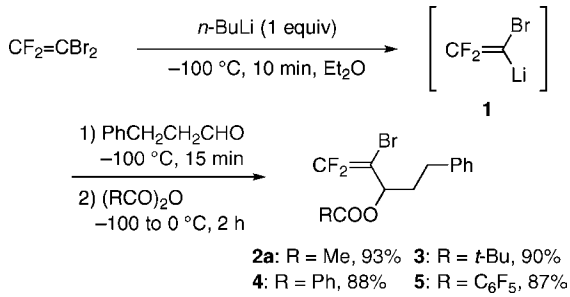
Scheme 1. Strategy for Accessing 1,1-Difluoroallenes



1-bromo-2,2-difluorovinyllithium **1**, which is expected to be prepared from 1,1-dibromo-2,2-difluoroethylene. The resulting alkoxides are modified on their oxygen atom, and 2-bromo-3,3-difluoroallylic precursors **2** are obtained. Lithiation of **2** would cause the 1,2-elimination of LiOE, affording the targeting 1,1-difluoroallenes. Although the elimination of lithium fluoride can also take place, the proper choice of the leaving group (OE) would promote the selective 1,2-elimination of LiOE.[10]

The lithiation of 1,1-dibromo-2,2-difluoroethylene was successfully performed by treatment with 1 equiv of butyllithium at −100 °C (Scheme 2).[11] The generated vinyllithium

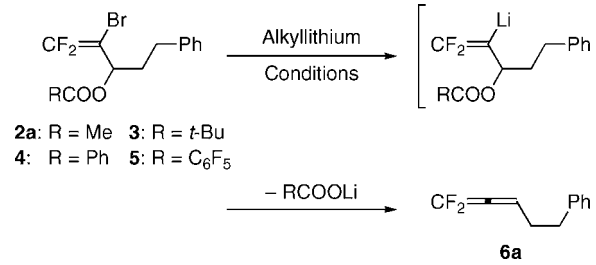
Scheme 2. Preparation of Precursors



1 reacted with 3-phenylpropanal, and subsequent acetylation with acetic anhydride gave 2-bromo-3,3-difluoroallylic acetate **2a** in a 93% yield. The corresponding pivalate **3**, benzoate **4**, and pentafluorobenzoate **5** were also prepared by using the same procedure.

The esters prepared above, **2a**, **3**, **4**, and **5**, were subjected to the elimination reaction (Table 1). Treatment of the

Table 1. Optimization of the Reaction Conditions



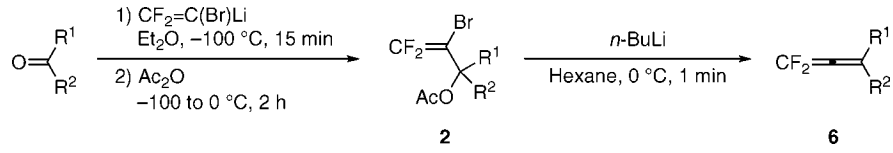
entry	substrate	alkyllithium (equiv)	conditions	**6a**, %
1	**2a**	*t*-BuLi (2)	pentane−Et_2O (1:1), −130 °C, 2 h	56
2	**3**	*t*-BuLi (2)	pentane−Et_2O (1:1), −130 °C, 2 h	48
3	**4**	*t*-BuLi (2)	pentane−Et_2O (1:1), −130 °C, 2 h	49
4	**5**	*t*-BuLi (2)	pentane−Et_2O (1:1), −130 °C, 2 h	56
5	**2a**	*t*-BuLi (1)	pentane−Et_2O, −130 °C, 2 h	67
6	**2a**	*t*-BuLi (2)	hexane, 0 °C, 0.5 h	67
7	**2a**	*t*-BuLi (1)	hexane, 0 °C, 0.5 h	38
8	**2a**	*s*-BuLi (1)	hexane, 0 °C, 0.5 h	72
9	**2a**	*n*-BuLi (1)	hexane, 0 °C, 0.5 h	82
10	**2a**	MeLi (1)	hexane, 0 °C, 0.5 h	54
11	**2a**	*n*-BuLi (1)	hexane, 0 °C, 1 min	87

precursors with *tert*-butyllithium (2 equiv) at −130 °C gave the desired 1,1-difluoroallene **6a** in 48−56% yields (entries 1−4). Acetate **2a** was found to be the most suitable from chemical and economical viewpoints.

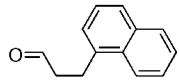
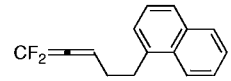
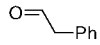
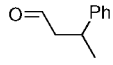
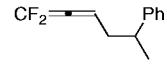
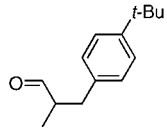
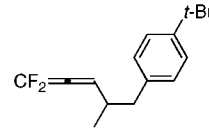
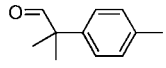
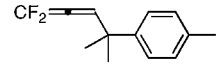
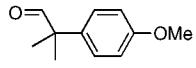
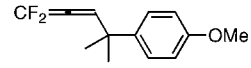
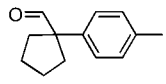
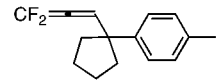
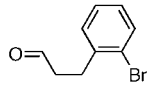
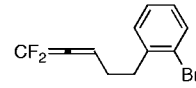
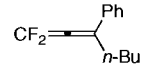
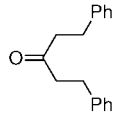
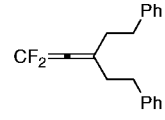
Further optimization of the conditions revealed that the elimination proceeded efficiently in hexane with butyllithium (1 equiv, entry 9), whereas employing an equimolar amount of *tert*-butyllithium gave a higher yield of **6a** (entry 5), suggesting a competitive decomposition of **6a**. The use of hexane as a solvent increased the yield of **6a** to 67% (entry 6). It is known that a nonpolar solvent brings about a higher degree of aggregation of alkyllithium reagents. The formation of higher aggregates with a low reactivity could suppress undesired side reactions.[12] *sec*-Butyllithium and butyllithum increased the yield of **6a** further to 72% and 82%, respectively (entries 8 and 9), whereas methyllithium was ineffective (entry 10). When

(11) A trace amount of fluoroethyne was sometimes observed in the reaction mixture (^{19}F NMR analysis), which suggests that elimination of lithium fluoride from vinyllithium **1** took place partially. However, this elimination was negligible when the lithiation was carried out under −100 °C. For the report on fluoro(silyl)ethyne, see: Hanamoto, T.; Koga, Y.; Kawanami, T.; Furuno, H.; Inanaga, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3582.

Table 2. Synthesis of 1,1-Difluoroallenes



2 **6**

entry	carbonyl compound	yield of **2** (%)	1,1-difluoroallene **6**	yield of **6** (%)
1		**2a**, 93		**6a**, 87
2		**2b**, 84		**6b**, 65 (73)[a]
3		**2c**, 85		**6c**, 83
4		**2d**, 83		**6d**, 85
5		**2e**, 86		**6e**, 84
6		**2f**, 87		**6f**, 82
7		**2g**, 87		**6g**, 81
8		**2h**, 83		**6h**, 82
9		**2i**, 85		**6i**, 84
10		**2j**, 80[b]		**6j**, 72 (85)[a]
11		**2k**, 84[b]		**6k**, 90

[a] ^{19}F NMR yield based on $PhCF_3$. [b] Acetylation was performed with isopropenyl acetate/TsOH. See the Supporting Information for details.

butyllithium was used, the reaction reached completion within 1 min, yielding **6a** in an 87% yield (entry 11).[13]

A variety of 1,1-difluoroallenes were synthesized under optimized conditions (Table 2).[14] Not only less hindered 1,1-difluoroallenes, but also sterically hindered 1,1-difluoroallenes were obtained from aldehyde-derived allylic acetates **2a**−**i** (entries 1−9). It is noteworthy that the lithium−bromine exchange of acetate **2i** occurred selectively on the bromoalkene moiety to afford the bromophenyl-substituted allene **6i** in an 84% yield (entry 9). Acetates, prepared from ketones also underwent elimination, and 3,3-disubstituted allenes were obtained in high yields (entries 10 and 11).[15]

(12) Yokoo, T.; Shinokubo, H.; Oshima, K.; Utimoto, K. *Synlett* **1994**, 645.

(13) ^{19}F NMR analysis revealed that 3-fluoropropargylic acetate was not generated.

In summary, we have developed a new method for the synthesis of 1,1-difluoroallenes. Difluorovinylidenation of aldehydes and ketones realized a general, expedient synthesis of 1,1-difluoroallenes.

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Supporting Information Available: Experimental details and characterization data of **2**−**6** and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) **Typical procedure:** 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 the solution was stirred for 15 min at the same temperature, 3-phenylpropanal (0.28 mL, 2.0 mmol) was added. The mixture was then 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 **2a** 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 **2a** (60 mg, 0.19 mmol) in hexane (2.6 mL) at 0 °C under argon. After the mixture was stirred 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 **6a** (29 mg, 87%) as a colorless liquid.

(15) On attempted reactions of 2-naphthaldehyde and 4-phenylbenzaldehyde, the ^{19}F NMR analysis of the reaction mixtures suggested the generation of the corresponding aromatic difluoroallenes. We, however, failed to isolate the products, probably due to their instability.