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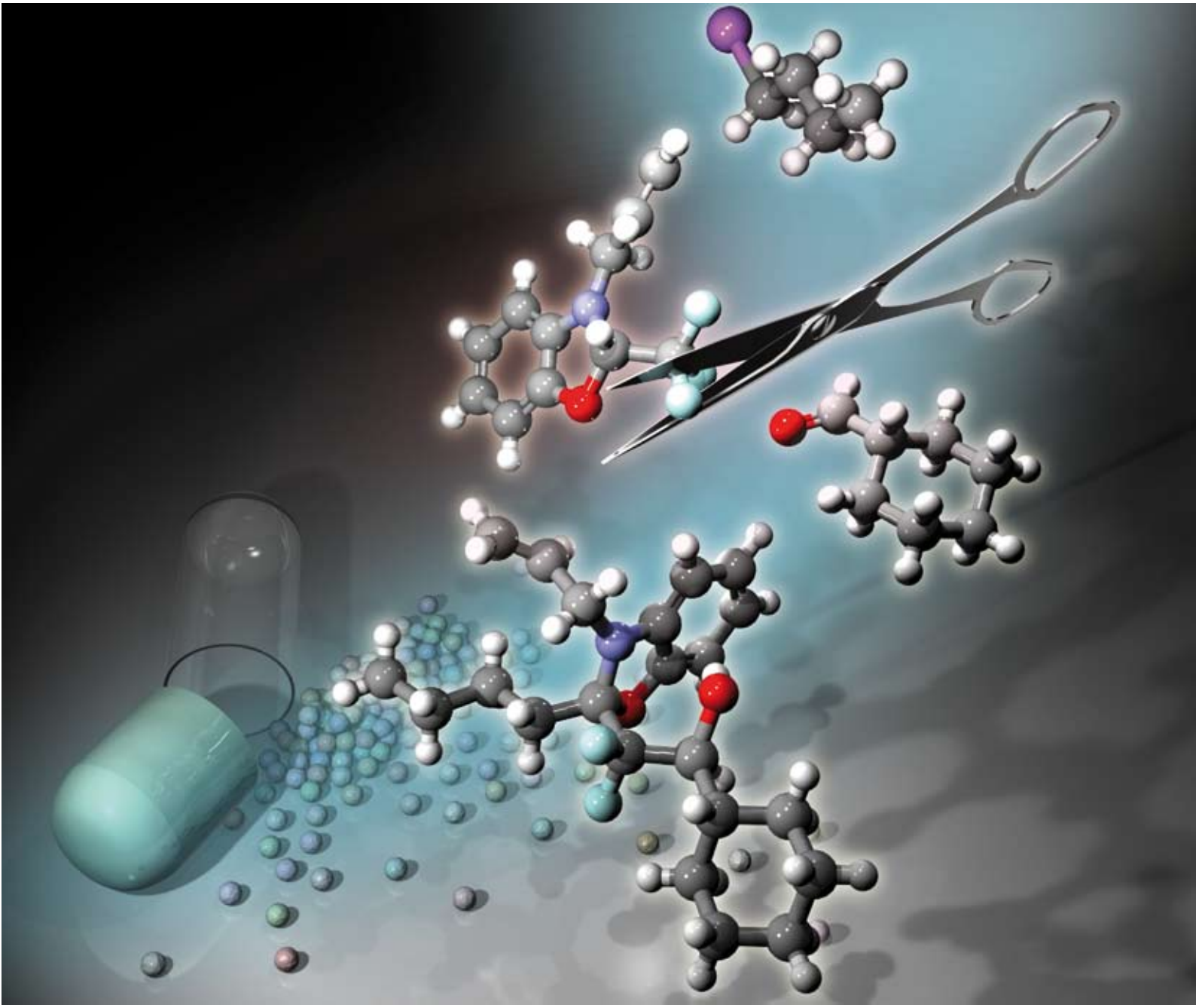

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Novel defluorinative alkylation of trifluoroacetaldehyde *N*,*O*-acetal derivatives and its application to multi-component reaction†

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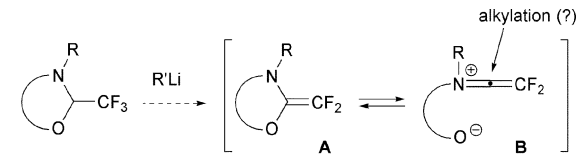
The reaction of trifluoroacetaldehyde *N*,*O*-acetal derivatives with 2 molar equivalents of alkyllithium reagents proceeded *via* β-elimination of fluoride followed by alkyl transfer from excess alkyllithium to the generated ketene *N*,*O*-acetal intermediate at the β-carbon of fluorine groups.

In the fields of medicinal and bioorganic chemistry, unique properties of organofluorine compounds are well known.[1] Especially, since difluoromethyl and difluoromethylene groups perform as bioisosteric structures for hydroxymethylene group[2] or ethereal oxygen,[3] these functionalities are widely found in the structure of biologically active molecules. The α,α-difluoroketone structure also performs as a transition state mimic against several peptidases, such as HIV protease,[4] elastase,[5] renin,[6] and human heart chymase.[7]

For these reasons, the development of effective synthetic strategies for difluoromethylene compounds has been one of the top concerns in organofluorine chemistry for a long time.[8–10] Among a number of difluoromethylene syntheses, functionalization of trifluoromethyl compounds through mono-defluorination is highly useful, because a wide range of CF_3-containing molecules can be obtained from commercial source or by simple preparation. For examples, Xu and co-workers reported that the treatment of trifluoroacetyltriphenylsilane with alkyllithiums results in the formation of 2,2-difluoroenol silyl ethers through 1,2-alkylation of silylketone moiety, the Brook rearrangement of the resultant lithium alkoxide intermediates followed by β-elimination of fluoride ion.[11,12] Uneyama and co-workers also reported the effective synthesis of 2,2-difluoroenol silyl ethers through electrochemical or Mg(0)-mediated reductions of trifluoromethylketones.[13] However, the further functionalization of 2,2-difluoroenol silyl ethers by the Mukaiyama aldol and related reactions has a disadvantage from a viewpoint of the atom economy. In addition, somewhat troublesome purification or isolation procedure of fluorinated enol silyl ethers is often required to use these as fluorine-containing building blocks.[14,15]

Recently, our research interest has been focused on the synthetic utility of polyfluorinated aldehyde hemiacetals such as trifluoroacetaldehyde ethyl hemiacetal (TFAE),[16] which is a commercially available material. As the second project, we designed the defluorinative alkylation of trifluoroacetaldehyde *N*,*O*-acetals (eqn (1)), which are easily prepared from amino alcohols and TFAE. That is, the treatment of these substrates with more than 2 molar equivalents of strongly basic alkyllithium reagents probably results in the elimination of fluoride to give difluoroketene *N*,*O*-acetal intermediates **A**.[17] If an equilibrium between highly polarized ketene *N*,*O*-acetal form **A** and zwitterionic ketene iminium form **B** exists, the following alkylation by excess alkyllithium would be expected to proceed at the β-carbon of fluorine groups. In contrast, it is known that the similar defluorinative alkylation of trifluoroacetaldehyde aminals selectively proceeds at the α-carbon of fluorine groups (eqn (2)).[18] In this paper, we disclose this unusual regioselectivity in the defluorinative alkylation of trifluoroacetaldehyde *N*,*O*-acetals. Furthermore, as a synthetic application of the present defluorinative alkylation, novel multi-component reaction of trifluoroacetaldehyde *N*,*O*-acetals, alkyllithiums and carbonyl compounds was developed.



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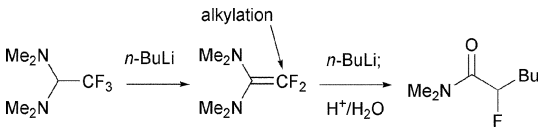

(2)

To confirm the regioselectivity of the defluorinative alkylation reaction, we examined the reaction of trifluoroacetaldehyde *N*,*O*-acetal **1** with 2.4 molar equivalents of various alkyllithium reagents in Et_2O. Selected results are summarized in Table 1. The reaction of *N*-allyl substrate **1a** and *n*-butyllithium (*n*-BuLi) completed within 3 h at −78 °C to give defluorinative alkylation product **2aa** as a sole regioisomer in 83% yield (entry 1). **2aa** was slightly unstable on silica gel, although rapid purification by the short silica gel pad resulted in the reasonable isolated yield of **2aa**. Since the reaction of **1a** and methyllithium under similar conditions resulted in the poor conversion due to low solubility of methyllithium in Et_2O, synthetically useful yield of **2ab** was realized by the reaction at −24 °C in Et_2O–THF (2 : 1) mixed solvent (entry 2; 81% yield). Cyclopropyllithium is also used as good

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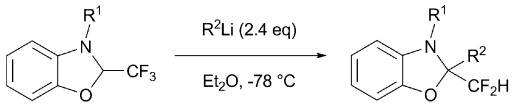
† Electronic supplementary information (ESI) available: Details of experiments, NMR data of all new compounds, and crystal structure of **2ca** (CCDC 702162) and *anti*-**3h** (CCDC 702163). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b817599c

Table 1 Defluorinative alkylation of *N*,*O*-acetals **1**



1 **2**

Entry	**1**	R^1	R^2Li	*t*/h	**2**	Yield[a] (%)
1	**1a**	Allyl	*n*-BuLi	3	**2aa**	83
2[b]	**1a**	Allyl	MeLi	4	**2ab**	81
3	**1a**	Allyl	*c*-C_3H_5Li	4	**2ac**	74
4[c]	**1b**	*n*-Pr	*n*-BuLi	4	**2ba**	58
5	**1c**	Bn	*n*-BuLi	5	**2ca**	73

[a] Isolated yield. [b] Reaction was carried out in Et_2O-THF (2 : 1) at −24 °C. [c] 29% of difluoromethyl ketone was formed (based on ^{19}F NMR).

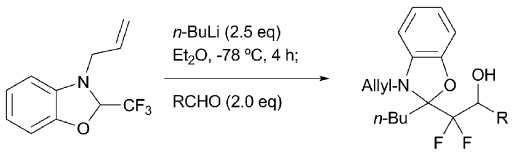
alkyl donor for this reaction to result in clean formation of defluorinative cyclopropylation product **2ac** (entry 3; 74% yield). In contrast, the use of less basic organolithium reagents such as phenyllithium and allyllithium resulted in no reaction (not shown). These results suggest that the deprotonation at CF_3-substituted methine position is the initiation step for the present reaction. Furthermore, we examined the effects of *N*-substituent of substrate **1**. Under similar conditions, the reaction of *N*-propyl substrate **1b** with 2 molar equivalents of *n*-BuLi gave alkylated product **2ba** in 58% with the formation of the corresponding ketone in 29% yield. The reaction of *N*-benzylated *N*,*O*-acetal **1c** with *n*-BuLi also provided alkylated product **2ca** in 73% yield.

Since the hydrogen of difluoromethyl group in the defluorinative alkylation product **2** was delivered by aqueous workup,[19] we examined the treatment of the *in situ* generated reactive intermediate with various aldehydes (Table 2). After the reaction of **1a** with 2.5 molar equivalents of *n*-BuLi for 4 h at −78 °C, the reaction mixture was treated with 2.0 molar equivalents of benzaldehyde to give difluoromethylenyl carbinol **3a** in 85% yield as a mixture of diastereomers in a ratio of 1 : 1.5 (entry 1). In the reaction with 4-substituted benzaldehyde derivatives, little or no substituent effects were observed giving rise to the corresponding carbinol products in excellent yield with low diastereoselectivity (entries 2,3). Heteroaromatic aldehydes and cinnamaldehyde were also used as examples of electrophiles to give the corresponding 1,2-adducts in excellent yield (entries 4–6). Interestingly, in the reaction with 2-pyridinecarbaldehyde, acceleration of the reaction rate and moderate diastereoselectivity were observed. Thus, after the reaction for only 15 min, pyridyl carbinol product **3e** was obtained in 87% yield as a mixture of diastereomers in a ratio of 3.4 : 1 (entry 5). This finding possibly indicates that the coordination of basic nitrogen of pyridine ring to the lithium center of the reactive intermediate effected the increase in both reaction rate and diastereoselectivity. In contrast to aromatic or α,β-unsaturated aldehydes, aliphatic aldehydes such as 3-phenylpropionaldehde and cyclohexanecarbaldehyde showed low reactivity, therefore, higher reaction temperature and prolonged reaction time were required to complete the reaction (entries 7, 8). For example, the reaction with cyclohexanecarbaldehyde proceeded at 0 °C for 8 h to give **3h** in 81% yield with excellent *anti* selectivity (*anti*/*syn* = 10.5 : 1). The stereochemistry of **3h** was determined by an X-ray crystallographic analysis of the major isomer (see ESI†).

Although it is known that 2,2-difluoroketene silyl acetals did not smoothly react with ketones under several conditions, we found that defluorinative butylation of **1a** with *n*-BuLi followed by the reaction with various ketones proceeded smoothly at 0 °C or at room temperature to give the difluoromethylated tertiary alcohol products in excellent yield (Table 3). For example, after the treatment of **1a** with 2.5 molar equivalents of *n*-BuLi at −78 °C for 4 h, the reaction with cyclohexanone provided tertiary alcohol **4a** in 84% yield (entry 1). Under the similar conditions, the reaction with acetone gave an excellent result (89% yield, entry 2). Furthermore, acetophenone was found to be a nice electrophile and **4c** was obtained in 79% yield as a mixture of diastereomers in a ratio of 1.8 : 1 (entry 3).

Concerning the present reaction, we propose the reaction mechanism as shown in Scheme 1. First, the β-elimination of *N*,*O*-acetal **1** by 1 molar equivalent of alkyllithium reagent gives difluoroketene *N*,*O*-acetal intermediate **C**.[20] Regioselective alkylation of **C** by excess alkyllithium reagents is possibly induced by the coordination of *N*,*O*-acetal oxygen to the lithium center to give lithium phenoxide **E** *via* zwitterion **D**. Since it is known that α-fluorinated methyllithium species without the stabilization by electron withdrawing groups rapidly decompose at low temperature through the α-elimination of LiF, lithium phenoxide **E** should be a reactive species in the present C–C bond formation.[21] That is, in the presence of carbonyl

Table 2 Multi-component reaction of **1a**, *n*-BuLi and aldehydes

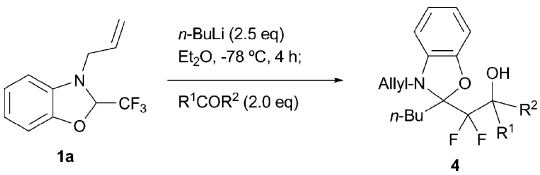


1a **3**

Entry	R	*T*/°C	*t*/h	**3**	Yield[a] (%)	Dr[b]
1	Ph	−78	0.5	**3a**	85	1 : 1.5
2	4-$MeOC_6H_4$	−78	0.5	**3b**	79	1 : 1.5
3	4-$CF_3C_6H_4$	−78	0.5	**3c**	85	1 : 1.7
4	2-Furyl	−78	1	**3d**	87	1.2 : 1
5	2-Pyridyl	−78	0.25	**3e**	87	3.4 : 1
6	CH=CHPh	−78	1	**3f**	87	1 : 1.2
7	CH_2CH_2Ph	−24	3	**3g**	76	11 : 1
8	*c*-C_6H_{11}	0	8	**3h**	81	11 : 1[c]

[a] Isolated yield. [b] Based on ^{19}F NMR. [c] *anti*/*syn* selectivity.

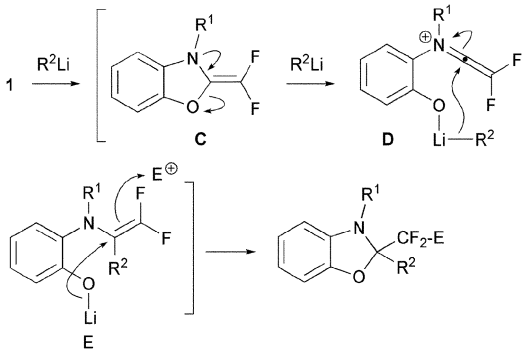
Table 3 Multi-component reaction of **1a**, *n*-BuLi and ketones



1a **4**

Entry	R^1	R^2	*T*/°C	*t*/h	**4**	Yield[a] (%)
1	$-CH_2(CH_2)_3CH_2-$		0	6	**4a**	84
2	Me	Me	rt	9	**4b**	89
3	Ph	Me	rt	9	**4c**	79[b]

[a] Isolated yield. [b] Dr = 1.8 : 1



Scheme 1 Proposed reaction mechanism.

compounds, the intramolecular nucleophilic attack by the phenoxide moiety of **E** to the polarized difluoroenamine moiety and the simultaneous C–C bond formation with carbonyl compounds smoothly provide the corresponding carbinol products. In the reaction of difluoroketene aminal, which has a symmetric structure, and *n*-BuLi reported by Dolbier and coworkers (eqn (2)),[18] similar equilibria between the ketene aminal form and zwitterionic form should not exist due to insufficient ability of dimethylamino group as a leaving group. For this reason, the reaction of difluoroketene aminal and *n*-BuLi proceeded an *via* addition–elimination mechanism.

In summary, we found that the treatment of trifluoroacetaldehyde *N*,*O*-acetal derivatives with 2 molar equivalents of alkyllithium provides difluoromethyl ketone *N*,*O*-acetal products in excellent yield with complete regioselectivity. The observed regioselectivity is opposite to that in the similar reaction of aminal derivatives. This result suggests the unique properties and the synthetic utilities of asymmetric *N*,*O*-acetal derivatives. As a further extension of this regioselective defluorinative alkylation, novel multi-component reaction of trifluoromethylated *N*,*O*-acetals, alkyllithiums and carbonyl compounds was also developed. This multi-component reaction provides an effective and convergent construction method for β-hydroxy-α,α-difluoroketone derivatives. Further study on the synthetic utility and the mechanistic insight is under progress in our laboratory.

The authors gratefully acknowledge Mr. Hideyuki Mimura and Dr. Kosuke Kawada (TOSOH F-TECH Inc.) for supplying TFAE.

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19 By D_2O quench of the reaction mixture of **1a** and *n*-BuLi, deuterium introduction at difluoromethinic position of **2aa** was observed.

20 Reaction of 1a with an equimolar amount of *n*-BuLi gave **2aa** in 38% yield with the recovery of **1a** in 41%.

21 We examined the thermal stability of intermediate **E** by stepwise reaction of **1a**, *n*-BuLi and benzaldehyde. After simple evaporation at room temperature of the reaction mixture of **1a** and *n*-BuLi, treatment of the resultant residue with benzaldehyde in Et_2O gave **3a** without significant decrease in the product yield. This finding strongly indicates that intermediate **E** is stable at least at room temperature.

