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A rapid and convergent synthesis of α,α-difluoro-β-hydroxyketones through regiospecific defluorinative alkylation reaction

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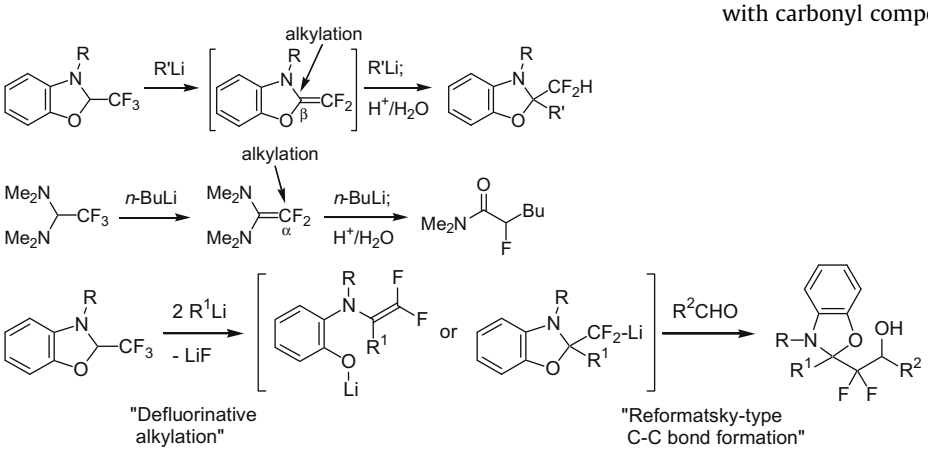
ABSTRACT

Both the defluorinative alkylation reaction of trifluoroacetaldehyde *N*,*O*-acetals using alkyllithiums and the following C–C bond formation with carbonyls as electrophiles were accelerated by a suitable diamine additive such as (−)-sparteine to give α,α-difluoro-β-hydroxyketone *N*,*O*-acetal products in an excellent yield. We also found that *N*-benzyl-*N*,*O*-acetal group of the resultant products can be removed under palladium-catalyzed hydrogenolysis conditions giving rise to the corresponding α,α-difluoro-β-hydroxyketones. The present two-step procedure is a useful and novel synthetic approach for functionalized α,α-difluoroketones.

The chemical transformation of stable carbon–fluorine bond is attracting much attention from organic chemists.[1–3] In particular, selective mono-defluorination of trifluoromethyl compounds is a valuable transformation because the difluoromethylene structure[4,5] in the products is widely used as a key functionality in the field of drug design.[6] For example, difluoromethylene group acts as a biologically isosteric structure for hydroxymethylene group[7] or ethereal oxygen.[8] Since α,α-difluoroketones easily form stable tetrahedral hydrates, these compounds are also used as a transition state mimic toward several proteases such as HIV protease.[9] In addition, trifluoromethyl substrates are easily available from commercial sources or by easy preparation in short steps.

Recently, we reported that the reaction of trifluoroacetaldehyde *N*,*O*-acetals with 2 M equiv of alkyllithium reagent smoothly gives α,α-difluoroketone *N*,*O*-acetal derivatives (Eq. 1).[10] This reaction probably proceeds via the β-elimination of fluoride followed by alkyl transfer at the β-carbon of the resultant ketene *N*,*O*-acetal intermediate.[11] Since the alkyl transfer reaction of $(Me_2N)_2C{=}CF_2$ selectively proceeds at the electronically negative α-carbon (Eq. 2),[12] the regioselectivity of alkyl transfer step observed in the *N*,*O*-acetal substrates is quite unique. Moreover, as a synthetic application of this defluorinative alkylation, we developed the novel and convergent synthetic methodology for α,α-difluoro-β-hydroxyketone derivatives through the one-pot treatment of the reactive intermediate generated by the defluorinative alkylation with carbonyl compounds (Eq. 3):



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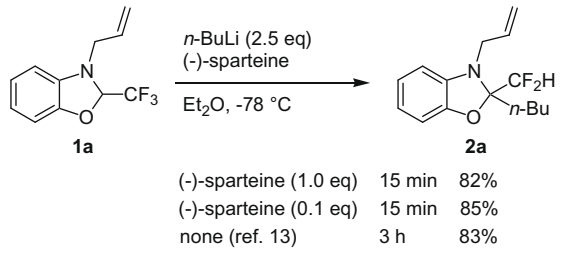
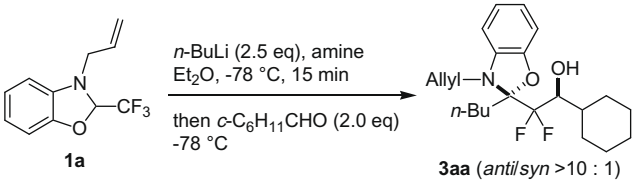


Scheme 1.

However, both the defluorinative alkylation step of *N*,*O*-acetal substrates and the following Reformatsky type C–C bond forming step between the intermediate generated by defluorinative alkylation and less reactive carbonyl compounds such as α-branched aliphatic aldehydes and ketones required relatively long reaction time to obtain the desired products in good yield. In this Letter, we would like to describe that suitable diamine additives such as (−)-sparteine accelerate both the defluorinative alkylation step and the following Reformatsky type C–C bond forming step. Furthermore, although it would be easily predicted that the transformation of cyclic *N*,*O*-acetal group in the product structure to carbonyl group under conventional hydrolytic conditions is extremely difficult due to the stabilization effect of *N*,*O*-acetal group by fluorine di-substitution, we demonstrate that *N*-benzyl-*N*,*O*-acetal group can be easily converted to carbonyl group.

It has been well known that diamine additives such as *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine (TMEDA) and sparteine enhance both basicity and nucleophilicity of alkyllithium reagents through the dissociation of aggregated structure of lithium reagents.[13,14] Therefore, to accelerate the reaction rate in the defluorinative alkylation step, we initially examined the reaction of *N*-allyl-*N*,*O*-acetal **1a** with 2.5 M equiv of *n*-BuLi in the presence of diamine additives (Scheme 1). As shown in the previous Letter,[10] the reaction of **1a** with *n*-BuLi in the absence of any diamine additives requires relatively long reaction time (3 h). On the other hand, we found that, in the presence of 1.0 M equiv of (−)-sparteine, the same reaction at −78 °C is smoothly completed within only 15 min to give difluoroketone *N*,*O*-acetal **2a** in 82% yield. Under similar conditions, the loading of (−)-sparteine could be reduced to 0.1 M equiv without the decrease in product yield.

Table 1
Survey of effective diamine additives in α,α-difluoro-β-hydroxyketone *N*,*O*-acetal synthesis

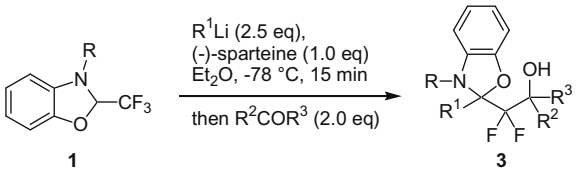


Entry	Diamine (equiv)	Time (h)	Yield[a] (%)
1	(−)-Sparteine (1.0)	1	90
2	(−)-Sparteine (0.2)	7	56
3	TMEDA (1.0)	1	73
4	$Me_2NCH_2CH_2CH_2CH_2NMe_2$ (1.0)	1	78
5	$Me_2NCH_2(CH_2)_4CH_2NMe_2$ (1.0)	1	62
6	Et_3N (2.0)	1	49
7[b]	None	8	81

[a] Isolated yield.
[b] Defluorinative butylation was completed by the reaction at −78 °C for 2 h.
[c] The reaction was carried out at 0 °C, see: Ref. 10a.

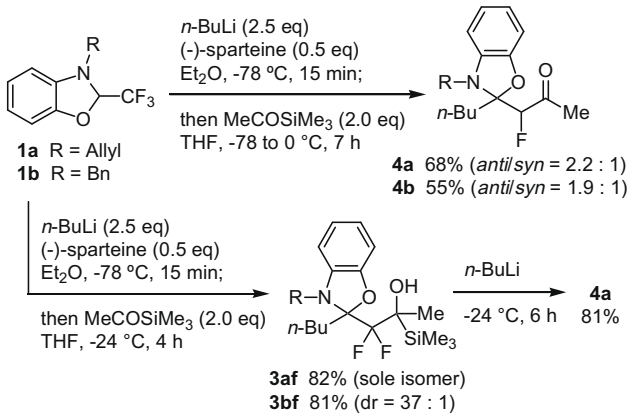
Next, we examined the rate acceleration effect in the Reformatsky type C–C bond formation step between the reactive intermediates and carbonyl substrates by diamine additives (Table 1). That is, after the defluorinative alkylation of **1a** in the presence of 1.0 M equiv of (−)-sparteine, the resultant intermediate was treated with cyclohexanecarbaldehyde in a one-pot manner. In this case, the Reformatsky type C–C bond forming step at −78 °C completed within 1 h to give α,α-difluoro-β-hydroxyketone *N*,*O*-acetal **3aa** in 90% yield with excellent *anti* selectivity (entry 1). Unfortunately, the product was obtained as a racemic mixture and the product yield was sensitive to the amount of (−)-sparteine (entry 2). However, since we have already demonstrated that, in the absence of any diamine additives, this C–C bond forming reaction requires both higher reaction temperature and prolonged reaction time to obtain the product **3aa** in good yield (entry 7, at 0 °C for 8 h),[10] it is obvious that the use of (−)-sparteine accelerates not only the defluorinative alkylation step but also the subsequent C–C bond formation with aldehydes. By using other diamine additives such as TMEDA, carbinol product **3aa** was obtained in moderate yield, while the Reformatsky type C–C bond forming reaction is slower than the reaction in the presence of sparteine (entries 3–5).

Table 2
Sparteine-mediated synthesis of β-hydroxy-α,α-difluoroketone *N*,*O*-acetals



Entry	1	R	R^1	R^2	R^3	Temp. (°C)	Time (h)	3	Yield[a] (%)	Dr[b]
1[c]	**1a**	Allyl	Me	c-C_6H_{11}	H	−24	4	**3aa-Me**	86	5.8:1
2	**1a**	Allyl	*i*-Pr	c-C_6H_{11}	H	−24	4	**3aa-^{i}Pr**	79	Single
3	**1a**	Allyl	*n*-Bu	*t*-Bu	H	−24	4	**3ab**	80	15:1
4	**1a**	Allyl	*n*-Bu	$-CH_2(CH_2)_3CH_2-$		−24	4	**3ac**	81	—
5	**1a**	Allyl	*n*-Bu	Me	Me	0	1	**3ad**	83	—
6	**1a**	Allyl	*n*-Bu	Ph	Me	0	2	**3ae**	82	1.8:1
7	**1b**	Bn	*n*-Bu	c-C_6H_{11}	H	−24	2	**3ba**	91	6.7:1
8	**1b**	Bn	*n*-Bu	$-CH_2(CH_2)_3CH_2-$		0	1	**3bc**	90	—
9	**1b**	Bn	*n*-Bu	Me	Me	0	2	**3bd**	80	—
10	**1c**	n-C_3H_7	*n*-Bu	c-C_6H_{11}	H	−24	2	**3ca**	87	9.6:1

[a] Isolated yield.
[b] Determined by ^{19}F NMR of the crude mixture.
[c] Defluorinative methylation was carried out at −24 °C.

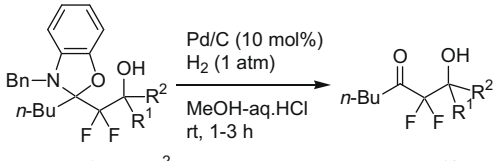


Scheme 2.

Moreover, the use of 2.0 M equiv of triethylamine as a mono amine additive resulted in a poor yield of **3aa** under the reaction at −78 °C (entry 6).

To reveal the scope of the present sparteine-mediated synthesis of α,α-difluoro-β-hydroxyketone *N*,*O*-acetals, we carried out the defluorinative alkylation of trifluoroacetaldehyde *N*,*O*-acetals followed by the Reformatsky type C–C bond formation in the presence of stoichiometric amount of (−)-sparteine (Table 2). In the case of methyllithium, the defluorinative methylation step of **1a** smoothly completed in a mixed solvent of Et_2O and THF at −24 °C within 15 min, then the one-pot treatment of the resultant reaction mixture by cyclohexanecarbaldehyde rapidly gave the carbinol product **3aa-Me** in 86% yield (entry 1). In the presence of sparteine, sterically hindered isopropyllithium could be also used to give isopropyl ketone *N*,*O*-acetal **3aa-*i*Pr** in 79% by the reaction of **1a** for 4 h at −24 °C (entry 2). Interestingly, the diastereoselectivity in these three component syntheses of α,α-difluoro-β-hydroxyketone *N*,*O*-acetals strongly depended on the steric bulkiness of the introduced alkyl group and the improvement of *anti*-selectivity was observed by increasing the steric bulkiness of alkyllithiums (entries 1, 2 and also see Table 1). Furthermore, pivalaldehyde performed as a nice electrophile and the corresponding carbinol product **3ab** was obtained in 80% yield (entry 3). It is worth mentioning that the use of stoichiometric amount of sparteine also resulted in the rate acceleration of the Reformatsky type reaction using relatively low reactive ketones, which had required both higher reaction temperature and prolonged reaction time in the absence of sparteine. For example, the one-pot reaction of the intermediate, which generated by defluorinative alkylation of **1a** with *n*-BuLi, with ketones such as cyclohexanone, acetone and acetophenone smoothly proceeded at −24 °C or at 0 °C to give the corresponding tertiary alcohols **3ac**, **3ad** and **3ae** in excellent yields (entries 4–6). Likewise, this rate acceleration by sparteine was observed in the reactions of *N*-benzyl and *N*-propyl *N*,*O*-acetal substrates **1b** and **1c** (entries 7–10).

Next, to show the useful extension of this sparteine-mediated conditions, we examined the reaction of reactive intermediate with



3ba R_1 = *c*-C_6H_{11}, R^2 = H — **5a** 99%
3bc $R^1 = R^2$ = -$CH_2(CH_2)_3CH_2$- — **5b** 81%
3bg R^1 = Ph, R^2 = H — **5c** 86%

Scheme 3.

acylsilane giving rise to 2-fluoro-1,3-diketone mono-*N*,*O*-acetal **4** or simple adduct **3** (Scheme 2).[15] After numerous attempts, we have established that the desired reaction proceeded nicely by 0.5 M equiv of sparteine and a strict control of the reaction temperature brings about the selective formation of **4** or **3**. For example, after the defluorinative alkylation of **1a** with *n*-BuLi in the presence of 0.5 M equiv of sparteine in Et_2O, the reactive intermediate was treated with a solution of acetyltrimethylsilane in THF. Then, the resultant mixture was warmed to 0 °C over 7 h to give 2-fluoro-1,3-diketone mono-*N*,*O*-acetal **4a** in 68% yield as an *anti*/*syn* mixture in a ratio of 2.2:1.[16] On the other hand, the reaction with acetyltrimethylsilane below −24 °C selectively gave simple adduct **3af** in 82% yield as a sole diastereomer. Moreover, the treatment of **3af** with *n*-BuLi at −24 °C for 6 h in Et_2O/THF mixed solvent resulted in the clean formation of **4a** in 81% yield. Likewise, by one-pot procedure, trifluoroacetaldehyde *N*-benzyl-*N*,*O*-acetal **1b** was converted to the corresponding mono-fluoro product **4b** in 55% yield. The formation of 2-fluoro-1,3-diketone mono-*N*,*O*-acetal **4** can be a consequence of the 1,2-Brook rearrangement[17,18] of lithium alkoxide intermediate followed by mono-defluorination via β-elimination.

Finally, we examined the deprotection of *N*,*O*-acetal group. Since several acetals derived from α,α-difluoroketones or trifluoromethyl ketones are overwhelmingly stable compared to non-fluorinated ketone acetals due to the electronic and stereoelectronic effects by fluoro groups, deprotection of these fluorinated ketone acetals under mild conditions is considerably difficult. However, after several attempts, we found that *N*-benzyl-*N*,*O*-acetal group can be removed by catalytic hydrogenolysis giving rise to α,α-difluoroketones (Scheme 3). Thus, *N*-benzyl-*N*,*O*-acetal **3ba** was converted to the corresponding β-hydroxyketone **5a** by the reaction in a mixed solvent of MeOH and 10% aqueous HCl solution under Pd/C-H_2 conditions. In the absence of any palladium catalysts, the starting material **3ba** could not be converted to the ketone **5a** under such acidic conditions. This deprotecting procedure could be applied to tertiary cyclohexanol **3bc** and benzylic alcohol **3bg** without decomposition of these functionalities to give the corresponding α,α-difluoro-β-hydroxyketones **5b** and **5c** in 81% and 86% yield, respectively.

In conclusion, we found that (−)-sparteine accelerates both the defluorinative alkylation reaction of trifluoroacetaldehyde *N*,*O*-acetals with alkyllithiums and the following Reformatsky type C–C bond formation with carbonyl compounds. *N*-Benzyl-*N*,*O*-acetal group of the obtained products can be removed under palladium-catalyzed hydrogenolysis conditions to give the corresponding α,α-difluoro-β-hydroxyketones. The present two-step procedure is a useful and novel synthetic approach to functionalized α,α-difluoroketones.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.03.018.

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