



Highly Efficient and Stereoselective Access to (*Z*)- α,β -Difluoroallyl Alcohols and (*Z*)- α -Fluoro- α,β -unsaturated Aldehydes Based on the Reaction of 2,3,3-Trifluoro-1-propenyl *p*-Chlorobenzenesulfonate with Grignard Reagents

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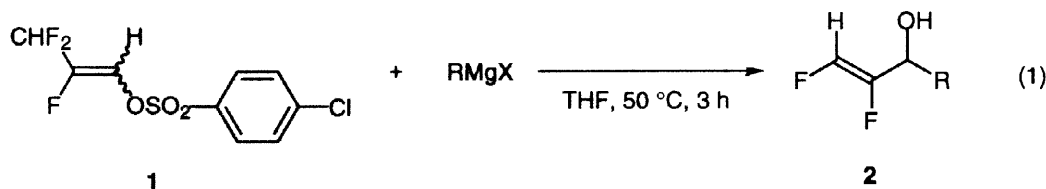
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Abstract: 2,3,3-Trifluoro-1-propenyl *p*-chlorobenzenesulfonate (**1**), readily available from 2,2,3,3-tetrafluoropropanol, reacted smoothly with various Grignard reagents at 50 °C to afford the corresponding (*Z*)- α,β -difluoroallyl alcohols **2** in moderate to excellent yields. These alcohols were smoothly hydrolyzed in the presence of a catalytic amount of montmorillonite K10 (Clay) to provide (*Z*)- α -fluoro- α,β -unsaturated aldehydes **3** in good yields. © 1998 Elsevier Science Ltd. All rights reserved.

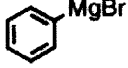

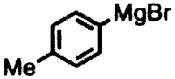
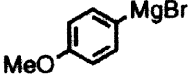
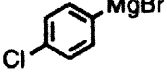
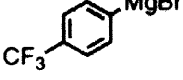
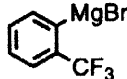
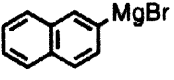
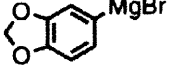
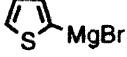
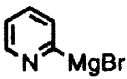
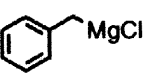

There has been increasing attention to stereo-defined fluoroolefins functionalized with carbonyl, hydroxyl, and amino groups because they frequently bring about unique biological and physiological properties. Especially, allyl alcohols containing fluorine atom(s) onto carbon-carbon double bond, are one of the most important and useful building blocks for the synthesis of organofluorine compounds,¹ since they permit the construction of a variety of fluorine-containing biologically active molecules, such as dipeptide isosteres,² potent enzyme inhibitors,³ and prostaglandins.⁴ Several procedures concerning the preparations and synthetic applications of β,β -difluoroallyl alcohols were known,⁵ however, only few methods dealing with the stereoselective synthesis of α,β -difluoroallyl alcohols have been reported, in which there remain serious disadvantages, such as low stereoselectivity, severe reaction conditions, and low yield of the products.⁶

During the course of our current studies to develop efficient and stereoselective entries to organofluorine compounds using fluorinated enol sulfonate **1**,⁷ we have now attained a novel efficient and general method for the stereoselective synthesis of (*Z*)- α,β -difluoroallyl alcohols **2** by the reaction of **1** with various Grignard reagents, as well as a first example of montmorillonite K10 (Clay)⁸ catalyzed allylic hydrolysis⁹ of **2** affording (*Z*)- α -fluoro- α,β -unsaturated aldehyde **3**¹⁰ in good yields.



The reaction was performed as follows. To a THF (5 ml) solution of PhMgBr, prepared from magnesium (6 mmol) and bromobenzene (6 mmol), was dropwise added a THF (1 ml) solution of the sulfonate **1** (2 mmol) at room temperature under argon atmosphere. After being stirred at 50 °C for 3 h, the reaction mixture was hydrolyzed with a cold saturated NH₄Cl solution (50 ml), followed by extraction with diethyl ether (30 ml X 3). The extracts were washed with a NaHCO₃ solution (40 ml X 2) and brine (40 ml X 2), dried over Na₂SO₄, and concentrated *in vacuo* to give the residue, which was chromatographed on

Table 1. Synthesis of (*Z*)- α,β -Difluoroallyl Alcohols (**2**)

Entry	RMgX	(Equiv.)	Product	Yield ^a /% of 2	(<i>Z/E</i>) ^b of 2
1		(3.0)	2a	75 (72)	(98/2)
2 ^c		(3.0)	2a	67	(98/2)
3 ^d		(3.0)	2a	80	(98/2)
4 ^e		(3.0)	2a	77	(99/1)
5		(3.0)	2b	80 (71)	(98/2)
6		(3.0)	2c	86 (85)	(98/2)
7		(5.0)	2d	71	(98/2)
8		(5.0)	2e	(54)	(>99/<1)
9		(5.0)	2f	trace	–
10		(3.0)	2g	67 (67)	(>99/<1)
11		(3.0)	2h	97 (91)	(>99/<1)
12		(5.0)	2i	56	(>99/<1)
13		(5.0)	2j	26 (26)	(>99/<1)
14 ^f		(5.0)	2k	(15)	(>99/<1)
15 ^g		(5.0)	2l	30 (30)	(>99/<1)
16	MeMgBr	(5.0)	2m	45	(>99/<1)

^a Measured by ¹⁹F NMR. Values in parentheses stand for isolated yields. ^b Determined by ¹⁹F NMR. ^c Carried out in Et₂O at reflux temperature. ^d Only (*Z*)-isomer of **1** was used. ^e Only (*E*)-isomer of **1** was used. ^f Carried out in THF : Et₂O (1 : 5) at reflux temperature. ^g Carried out in THF : Et₂O (1 : 1) at reflux temperature.

silica-gel using chloroform as an eluent to obtain 2,3-difluoro-1-phenyl-2-propen-1-ol (**2a**) ($Z/E = 98/2$) in 72 % yield, together with *p*-chlorophenyl phenyl sulfone in 89% yield.¹¹ (Eq. 1) (Table 1, Entry 1). The reaction at room temperature resulted in a lower yield (48%) of **2a** than that at 50 °C. The use of 1-2 equiv. of PhMgBr gave the only 26-58% yield. Diethyl ether (Et₂O) could be also employed as a solvent (Entry 3). Table 1 also summarizes the results of the reaction of **1** with various Grignard reagents.¹²

Other *p*-substituted phenyl (Entries 5, 6, 7, and 8), 2-naphthyl (Entry 10), 2-piperonyl (Entry 11), 2-thienyl (Entry 12), and methylmagnesium bromide (Entry 16) nicely underwent the reaction to give the corresponding (*Z*)- α,β -difluoroallyl alcohol **2** predominantly in good to excellent yields. Not only 2-pyridylmagnesium bromide (Entry 13) but also benzyl (Entry 14) and *n*-hexylmagnesium chloride (Entry 15), provided fair yields of **2**. The reaction with *o*-trifluoromethylphenylmagnesium bromide did not proceed at all, probably due to the bulkiness of trifluoromethyl group (Entry 9). In these cases, unfortunately, neither elevated temperature, prolonged reaction time, nor the use of excess amount of Grignard reagents, improved the yield of the product.

We assume that the reaction of sulfonate **1** with Grignard reagents is likely to proceed *via* the generation of transient fluorinated enolate¹³ (CHF₂CF=C(H)O⁻ and/or CHF₂C⁻(F)CHO), which converts into α,β -difluoroacrylaldehyde by a loss of a fluorine atom, followed by the simultaneous coupling reaction with Grignard reagents leading to α,β -difluoroallyl alcohols. To be mentioned is that the reaction of **1** with 3 equiv. of PhMgBr in the presence of an equiv. of galvinoxyl (2,6-di-*t*-butyl- α -(3,5-di-*t*-butyl-4-oxo-2,5-cyclohexadien-1-ylidene)-*p*-tosyloxy), took place very sluggishly to give the product **2a** in 22% yield, together with the recovery of **1** in 73% yield. This fact strongly suggests the present reaction would involve electron transfer process, though the exact mechanism is unclear at the present stage.

Significantly, the addition of 3 equiv. of DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone) or TMEDA (*N,N,N',N'*-tetramethylethylenediamine) to the reaction mixture as a co-solvent had no influence on the ratio of stereoisomers of **2a** (DMPU; 45%, $Z/E = 98/2$, TMEDA; 37%, $Z/E = 98/2$). Of much significance, moreover, is that sulfonate **1** reacts with Grignard reagents to provide the corresponding (*Z*)-isomer of **2** exclusively regardless of the configuration of **1** (Entries 3 and 4). According to these results, the predominant formation of (*Z*)-isomer may be attributed to the selective defluorination from the enolate anion. That is, the defluorination seems to proceed *via* the more stable transition state, in which the stabilization of the electron deficient σ^*_{C-F} orbital by the antiperiplanar σ_{C-H} orbital on *vicinal* carbon atom (*gauche* effect)¹⁴(Fig. 1) would play a critical role, giving the (*Z*)-isomer.¹⁵

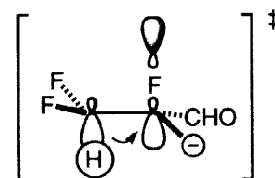
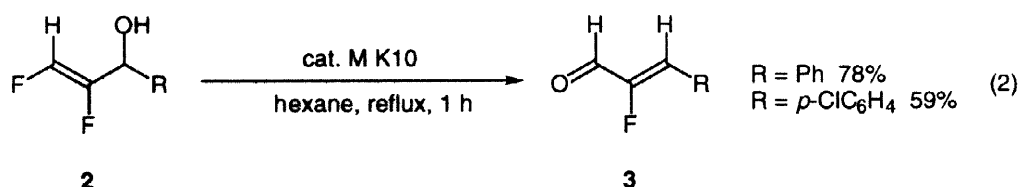


Fig. 1

Furthermore, it was found that treatment of above-obtained alcohols **2** with a catalytic amount of montmorillonite K10 (0.2 g / 1 mmol of **2**) in hexane at reflux temperature afforded predominantly (*Z*)- α -fluoro- α,β -unsaturated aldehydes **3** in good yields (Eq. 2).¹⁶



In conclusion, the reaction of **1** with a number of Grignard reagents smoothly proceeds to give the corresponding (*Z*)- α,β -difluoroallyl alcohols **2** in good yields, which are readily hydrolyzed with a catalytic amount of montmorillonite K10 leading to (*Z*)- α -fluoro- α,β -unsaturated acrylaldehydes. These methods can serve as an efficient and convenient route to (*Z*)- α,β -difluoroallyl alcohols and (*Z*)- α -fluoro- α,β -unsaturated aldehydes, which are very important intermediates for the synthesis of fluorinated biologically active

substances.

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- All compounds gave satisfactorily analytical data. Selected data for **2**: 2,3-Difluoro-1-phenyl-2-propen-1-ol (**2a**): oil; IR (neat) 1721 (C=C), 3362 (OH) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.44 (s, 1H), 5.20 (d, *J* = 12.9 Hz, 1H), 6.42 (ddd, *J* = 72.7, 16.8, 1.0 Hz, 1H), 7.33-7.44 (m, 5H); ¹⁹F NMR (376 MHz, CDCl₃, ext. CF₃COOH) δ -67.73 (ddd, *J* = 16.8, 12.9, 10.3 Hz, 1F), -86.45 (ddd, *J* = 72.7, 10.3, 3.6 Hz, 1F) for (*Z*)-isomer, -97.22 (ddd, *J* = 130.3, 25.9, 3.4 Hz, 1F), -101.05 (ddd, *J* = 130.3, 75.2, 4.2 Hz, 1F) for (*E*)-isomer; MS *m/z* (rel intensity) 170 (M⁺; 73.0), 151 (42.6), 150 (77.8), 149 (100.0), 133 (46.3), 122 (51.2), 109 (50.5), 105 (59.5), 101 (20.1); HRMS Found: *m/z* 170.0537. Calcd for C₉H₈F₂O: M, 170.0543.
- The reaction of **1** with other organometallic reagents, such as Et₂Zn, Et₃Al, DIBAL-H, and Me₄AlLi, did not proceed at all, and the sulfonate **1** was recovered. Treatment of PhLi and Bu₃CuLi resulted in the decomposition of **1**.
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- Detailed results of M K10 catalyzed hydrolysis of **2** will be reported elsewhere.