An Efficient and General Entry to (Z)-α-Fluoro-β-substituted Acrylaldehydes Based on the Coupling Reaction of α-Fluoro-β-amino Acrylaldehydes with Organolithium Reagents

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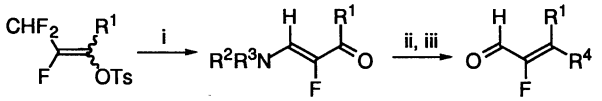
α-Fluoro-β-amino acrylaldehydes (**2**), readily available from the reaction of polyfluoroalkenyl tosylates (**1**) with dialkylamines in the presence of triethylamine and a catalytic amount (10 mol%) of tetrabutylammonium fluoride (TBAF), reacted smoothly with various organolithium reagents at -78 °C for 0.5 h, followed by hydrolysis with 10% hydrochloric acid at room temperture for 1 h to afford the corresponding (Z)-α-fluoro-β-substituted acrylaldehydes (**3**) *via* allylic rearrangement in good to excellent yields.

Considerable attention has been recently focused on the *trans*-fluoroolefinic moiety (-CH=CF-) as a chemically-stable enol mimic[1] or a non-hydrolyzable amide isoster.[2] In close connection with the circumstances, α-fluoro-β-substituted acrylaldehydes are one of the most important and pervasive intermediates in constructing a variety of fluorine-containing bioactive compounds, such as dipeptide isosters,[2] insect sex pheromones,[3] enzyme inhibitors,[4] as well as heteroaromatic compounds.[5]

For the preparation of α-fluoro-β-alkyl or aryl acrylaldehyde,[6] to our best knowledge, there exist only several methods which suffer from a couple of disadvantages, such as variable yields of the product or limitation of the applicable functional groups. It is of great value, therefore, to develop an effective method for the synthesis of functionalized α-fluoro-β-substituted acrylaldehyde bearing a stereodefined olefinic moiety .[7] This communication describes a new highly efficient and stereoselective access to α-fluoro-β-substituted acrylaldehyde based on the coupling reaction of α-fluoro-β-aminoacrylaldehyde with various organolithium reagents.[8]



1a; R^1 = H
1b; R^1 = D
1c; R^1 = Me

2a; R^1 = H, R^2 = R^3 = Et
2b; R^1 = H, R^2, R^3 = -$(CH_2)_4$-
2c; R^1 = D, R^2 = R^3 = Et
2d; R^1 = Me, R^2 = R^3 = Et

3

Scheme 1. *Reagents and conditions*: i, R^2R^3NH, Et_3N, 10 mol% TBAF, MeCN or DMSO, r.t. or 70 °C; ii, R^4Li, THF, -78 °C; iii, 10% HCl aq., r.t.

α-Fluoro-β-(dialkylamino)acrylaldehyde (**2**) was obtained in 78-99% yields from the reaction of fluorinated enol tosylate **1** with the corresponding amine in the presence of triethylamine and a catalytic amount (10 mol%) of TBAF according to our previous report.[7a] The reaction of **1c** with diethylamine was smoothly proceeded by use of dimethyl sulfoxide as a solvent under forced conditions (70 °C, 3 h) to provide the corresponding **2d** in 84% yield.

When α-fluoro-β-(diethylamino)acrylaldehyde (**2a**) was treated with 1.2 equiv of phenyllithium (PhLi) in tetrahydrofuran (THF) at -78 °C for 0.5 h under an argon atmosphere, followed by treatment with 10% hydrochloric acid at ambient temperature for 1 h, (Z)-α-fluoro-β-phenylacrylaldehyde (**3a**) was obtained predominantly in 93% yield, as shown in Table 1 (Entry 1). The results of the reaction are summarized in Table 1.

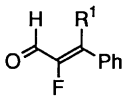
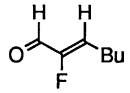
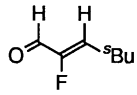
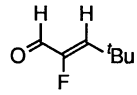
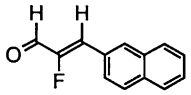
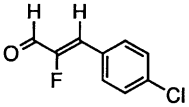
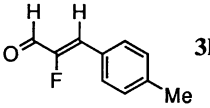
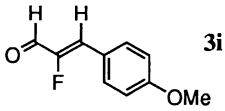
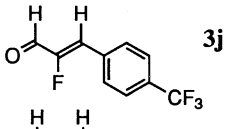
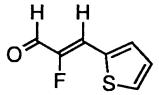
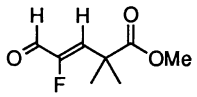
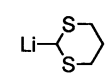
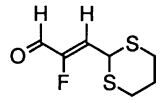
Use of diethyl ether as a solvent led to the formation of **3a** in nearly comparable yield (Entry 2). Substitutions on the nitrogen atom did not have influence upon the yield of product (Entries 1 and 3). Other commercially available alkyllithium, such as *n*-butyllithium (*n*-BuLi) (Entry 5), *s*-butyllithium (Entry 6) and *t*-butyllithium (Entry 7), could participate nicely in the reaction to afford the corresponding α-fluoro-β-substituted acrylaldehyde **3** in moderate to excellent yields. However, the reaction using 2-naphthyllithium, which had been generated from 1.2 equiv each of 2-bromonaphthalene and *n*-BuLi, resulted in a lower yield of the product **3f** than that of commercially available lithium reagents (Entry 8). The employment of 3 equiv of 2-naphthyllithium was found to give the excellent yield (93%) of the product (Entry 9). Similarly, **2a** reacted smoothly with various aryllithiums, prepared by use of halogen–lithium exchange reaction, to provide the corresponding α-fluoro-β-aryl acrylaldehyde **3g-k** in moderate to excellent yields (Entries 10-14). It is very valuable that other lithium reagents[10] participate nicely in the reaction to give the corresponding aldehyde **3** in moderate to good yields (Entries 15 and 16).

It should be noted that the reaction of deuterio-aminoacrylaldehyde (**2c**, R^1 = D) with PhLi under the same conditions provided the only β-deuterio aldehyde **3b**, whose structural assignment was made by ^1H and ^{19}F NMR analyses (Entry 4). We assume that the reaction of **2** with organolithium reagents might proceed as follows. That is, 1,2-addition of various lithium reagents towards **2a** and **2b** is likely to occur through the interaction between lithium metal and oxygen atom as well as a fluorine[11] to give the lithium alkoxide, which is followed by allylic hydrolysis leading to α-fluoro-β-substituted acrylaldehyde.

Of much signifcance is that the present reaction exclusively provides the (Z)-isomer of α-fluoro-β-substituted acrylaldehydes **3**. This result can be attributed to relative stability of allyl cation intermediate, in which 1,3-allylic strain plays a critical part in determining the stereochemical course of the hydrolysis.[12]

At present, the coupling reaction was not applicable for **2d** to give the stereoisomer of 2-fluoro-3-phenyl-2-butenal **3n** (36%, *Z*/*E* = 45/55) and (Z)-3-fluoro-4-phenyl-3-buten-2-one **4** (9%), which were formed *via* 1,2- and 1,4-addition of PhLi, respectively. Further studies on stereoselective synthesis of

Table 1. Preparation of α-fluoro acrylaldehydes (3)

Entry	2	R^4Li (equiv)	Aldehyde 3	Yield[a]/% (Z/E)[b]
1	2a	PhLi (1.2)	 (R^1 = H)	3a 93 (>99/<1)
2[c]	2a		(R^1 = H)	3a 94 (>99/<1)
3	2b		(R^1 = H)	3a 93 (>99/<1)
4	2c		(R^1 = D)	3b 96 (>99/<1)
5	2a	*n*-BuLi (1.2)		3c 86 (>99/<1)
6	2a	*s*-BuLi (1.2)		3d 88 (>99/<1)
7	2a	*t*-BuLi (1.2)		3e 46 (>99/<1)
8[d]	2a	2-NaphthylLi (1.2)		3f 55 (>99/<1)
9[d]	2a	2-NaphthylLi (3.0)		3f 93 (>99/<1)
10[d]	2a	4-ClC_6H_4Li (3.0)		3g 72 (>99/<1)
11[e]	2a	4-MeC_6H_4Li (3.0)		3h 96 (>99/<1)
12[d]	2a	4-$MeOC_6H_4Li$ (3.0)		3i 90 (>99/<1)
13[d]	2a	4-$CF_3C_6H_4Li$ (3.0)		3j 67 (>99/<1)
14[e]	2a	2-thienylLi (3.0)		3k 35 (>99/<1)
15	2a	 (3.0)		3l 75 (>99/<1)
16[f]	2a	 (3.0)		3m 20 (>99/<1)

[a] Isolated yields. [b] Determined by ^{19}F NMR. [c] Performed in diethyl ether. [d] Bromides were used. [e] Iodides were employed. [f] Carried out at 0 °C.

multi-functionalized α-fluoro-α,β-unsaturated carbonyl compounds are now in progress in our laboratory.

In conclusion, the treatment of **2a,b** with various organolithium reagents followed by allylic hydrolysis gave the corresponding (Z)-α-fluoro-β-substituted acrylaldehydes **3** exclusively in good to excellent yields. The present reaction will constitute highly efficient route to (Z)-stereoselective preparation of α-fluoro-β-functionalized acrylaldehydes.

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References and Note

1 M. C. Pirrung, C. P. Holmes, D. M. Horowitz, and D. S. Nunn, *J. Am. Chem. Soc.*, **113**, 1020 (1991); M. C. Pirrung, H.-J. Ha, and C. P. Holmes, *J. Org. Chem.*, **54**, 1543 (1989).

2 T. Allmendinger, P. Furet, and E. Hungerbuhler, *Tetrahedron Lett.*, **31**, 7297 (1990); T. Allmendinger, E. Felder, and E. Hungerbuhler, *Tetrahedron Lett.*, **31**, 7301 (1990).

3 F. Camps, J. Coll, G. Fabrias, and A. Guerrero, *Tetrahedron*, **40**, 2871 (1984).

4 M. C. Pirrung, E. G. Rowley, and C. P. Holmes, *J. Org. Chem.*, **58**, 5683 (1993).

5 D. F. Andres, E. G. Laurent, and B. S. Marquet, *Tetrahedron Lett.*, **38**, 1049 (1997).

6 T. Satoh, Y. Kitoh, K. Onda, K. Takano, and K. Yamakawa, *Tetrahedron*, **50**, 4957 (1994); T. B. Patrick, S. Hosseini, and S. Banis, *Tetrahedron Lett.*, **31**, 179 (1990); Y. Bessiere, D. N.-H. Savary, and M. Schlosser, *Helv. Chim. Acta*, **60**, 1739 (1977); H. Kimoto, H. Muramatsu, and K. Inukai, *Nippon Kagaku Kaishi*, **1975**, 1926.

7 Our contribution for the synthesis of α-fluoro-β-substituted acrylaldehyde, for β-amino-substituted, see: a) K. Funabiki, T. Ohtsuki, T. Ishihara, and H. Yamanaka, *Chem. Lett.*, **1994**, 1075. For β-thio-substituted, see: b) K. Funabiki, C. Ohtake, H. Muramatsu, M. Matsui, and K. Shibata, *Synlett*, **1996**, 444. For other reports on α-fluoroacrylaldehyde, see. For β-amino-substituted, see: c) C. Reichart and K. Halbritter, *Liebigs Ann. Chem.*, **737**, 99 (1970); d) H. Yamanaka, S. Yamashita, and T. Ishihara, *Synlett*, **1993**, 353. For β-thio-substituted, see: Ref. 4.

8 Addition of some organomethallic reagents to α-fluoro-β-substituted α,β-unsaturated aldehydes and/or ketones were reported. For Grignard reagents, see: Ref. 4 and a) P. E. Elkik and M. I. Imbeaux-Oudotte, *Bull. Soc. Chim. Fr.*, **1976**, 439. For dimethylcuprate, see: b) C. Chuit, R. Sâuvetre, D. Masure, J. F. Normant, *Tetrahedron*, **35**, 2645 (1979). For the regioselective addition of some hetero nucleophiles to α-fluoro-β-polyfluoroalkyl-β-substituted α,β-unsaturated carbonyl compounds, see: B. Dondy, P. Doussot, M. Iznaden, M. Muzard, and C. Portella, *Tetrahedron Lett.*, **35**, 4357 (1994).

9 All compounds gave satisfactory analytical data. A selected data for **3**: *2-Fluoro-3-phenyl-2-propenal (3a).* Mp 42.1-42.8°C; IR (CCl_4) 1648.2 (C=C), 1697.5 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.62 (d, *J* = 34.20 Hz, 1H) for (Z)-isomer, 6.85 (d, *J* = 24.88 Hz, 1H) for (E)-isomer, 7.40-7.50 (m, 3H), 7.65-7.75 (m, 2H), 9.36 (d, *J* = 16.12 Hz, 1H) for (Z)-isomer, 9.58 (d, *J* = 17.31 Hz, 1H) for (E)-isomer; ^{19}F NMR (376 MHz, $CDCl_3$, ext. CF_3COOH) δ -48.02 (dd, *J* = 24.88, 17.31 Hz, 1F) for (E)-isomer, -50.81 (dd, *J* = 34.20, 16.12 Hz, 1F) for (Z)-isomer; ^{13}C NMR (100 MHz, $CDCl_3$) δ 126.89, 129.01, 130.61, 130.78 (d, *J* = 19.85 Hz), 130.90, 154.76 (d, *J* = 271.27 Hz), 183.98 (d, *J* = 24.81 Hz); HRMS Found: *m/z* 150.0487. Calcd for C_9H_4FO: M, 150.0481.

10 The reaction of **2a** with 1.2 equiv of PhMgBr at elevated temperature (0 °C) gave **3a** only in 29% yield. The use of other less nucleophilic organomethallic reagents such as Et_3Al and Et_2Zn at 0 °C did not cause the reaction at all to furnish the trace amount of **3a**.

11 For a recent review, see: T. Yamazaki and T. Kitazume, *J. Syn. Org. Chem. Jpn.*, **54**, 665 (1996).

12 K. Funabiki, T. Ohtsuki, T. Ishihara, and H. Yamanaka, *Chem. Lett.*, **1996**, 5.