A Convenient Method for the Synthesis of (*Z*)-α-Fluoroacrylates: Lewis Base-catalyzed Carbonyl Fluoroolefination Using Fluoro(trimethylsilyl)ketene Ethyl Trimethylsilyl Acetal

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A highly useful method is established for the stereoselective synthesis of (*Z*)-α-fluoroacrylates from various aldehydes and fluoro(trimethylsilyl)ketene ethyl trimethylsilyl acetal in the presence of a Lewis base catalyst. The ketene acetal, easily prepared from ethyl fluoroacetate, affords α-fluoroacrylates in high yields with excellent Z stereoselectivities under mild conditions.

Organofluorine compounds are considered as useful building blocks for the preparation of various biologically active compounds.[1] It is well known that a fluoroolefin moiety playing an important role as an amide isostere has unique steric and electronic properties, which exhibits structural similarities to the amide linkage.[2] Whereas peptide bonds exist in cisoid–transoid equilibrium, no isomerization occurs between *E*- and *Z*-fluoroolefins, and they thus behave as an equivalent of amides. Therefore, the stereoselective synthesis of fluoroolefins is important in the area of medicinal chemistry. α-Fluoro-α,β-unsaturated carboxylic esters (α-fluoroacrylates) are frequently used as a building block that has fluoroolefin part.[3] For the stereoselective synthesis of α-fluoroacrylates, various approaches have been investigated. Among the trials, Wittig type,[4] Horner–Wadsworth–Emmons (HWE),[5] Peterson,[6] and Julia type reactions[7] are widely employed even though the yields and stereoselectivities are yet to be solved. Recently the Cr^{II} salt-mediated carbonyl olefination reaction by using trihaloacetate was also reported to afford (*Z*)-α-fluoroacrylates.[8] In those reactions, however, stoichiometric or excess amounts of reagents and costly fluorinated building blocks such as $BrFCHCO_2Et$ or Br_2FCCO_2Et were required. While the use of in situ generated diethyl fluorooxaloacetate derived from ethyl fluoroacetate was also reported, yield and stereoselectivity were still modest.[9] Thus, it is desired to find more practical and inexpensive methods.

It was shown in our previous papers that various acetate salts behaved as effective Lewis base catalysts to activate trimethylsilyl (TMS) derivatives.[10] More recently, trimethylsilylketene ethyl trimethylsilyl acetal was found also as a useful reagent for Lewis base-catalyzed carbonyl olefination in our laboratory.[11] To extend the utility of these reactions, stereoselective synthesis of trisubstituted olefins such as α-fluoroacrylates by using fluoro(trimethylsilyl)ketene ethyl trimethylsilyl acetal (**1**) was studied. That is, the α-fluoroacrylates were formed directly from aldehydes by syn elimination of the formed aldol intermediates via the following Lewis base-catalyzed aldol-type reaction (Figure 1). This reaction proceeds catalytically since the eliminated silanol anion also works as a Lewis base, and the resulted TMS_2O is removed easily by evaporation. It is important to note that ketene acetal **1** was easily prepared from commercially available ethyl fluoroacetate in one step (Scheme 1).[12]

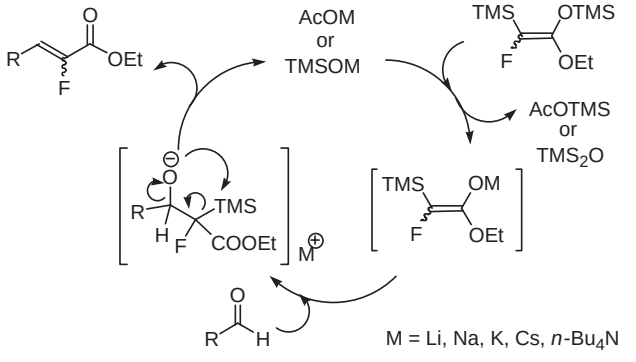
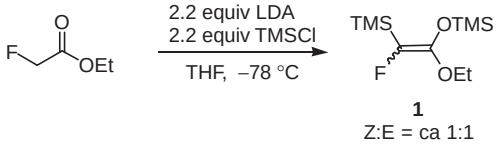


Figure 1. Lewis base-catalyzed synthesis of α-fluoroacrylate.

In this communication, we would like to report a convenient method for the synthesis of (*Z*)-α-fluoroacrylates from carbonyl compounds such as aldehydes and ketene acetal **1** under mild conditions in the presence of a Lewis base catalyst.

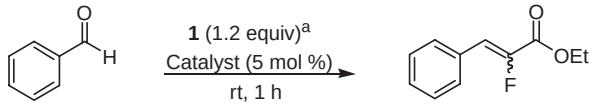
Reactions of benzaldehyde (**2a**) with ketene acetal **1** (Z:E = 1:1) were tried by using 5 mol % each of various Lewis bases (Table 1). This reaction did not take place in the absence of



1
Z:E = ca 1:1

Scheme 1. Preparation of ketene acetal **1**.

Table 1. Optimization of reaction conditions

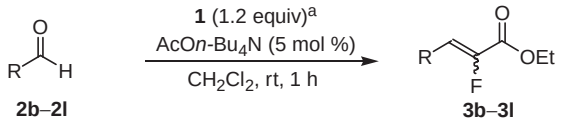


2a **3a**

Entry	Catalyst	Solvent	Yield[b]/%	Z:E[b]
1	None	DMF	N.R.	—
2	AcOLi	DMF	84	83:17
3	AcONa	DMF	84	95:5
4	AcOK	DMF	78	98:2
5	AcOCs	DMF	87	98:2
6	AcO*n*-Bu_4N	DMF	85	98:2
7	AcO*n*-Bu_4N	THF	86	94:6
8	AcO*n*-Bu_4N	Toluene	86	92:8
9	AcO*n*-Bu_4N	CH_2Cl_2	96	99:1

[a]Ketene acetal **1** in a ratio of 1:1 (E/Z) was used. [b]Yields and ratios were determined by GC analysis using internal standard.

Table 2. Fluoroolefination of various aldehydes



2b–2l **3b–3l**

Entry	R	Product	Yield[b]/%	Z:E[c]
1	2-ClC_6H_4	**3b**	94	99:1
2	3-ClC_6H_4	**3c**	81	99:1
3	4-ClC_6H_4	**3d**	93	99:1
4	4-MeC_6H_4	**3e**	87	>99:1
5	4-$MeOC_6H_4$	**3f**	95	99:1
6	4-$MeO_2CC_6H_4$	**3g**	81	99:1
7	4-$Me_2NC_6H_4$	**3h**	93	99:1
8	2-Naphthyl	**3i**	94	99:1
9	(*E*)-PhCH=CH	**3j**	77	83:17
10	(*E*)-PhCH=CMe	**3k**	93	99:1
11	*c*-Hex	**3l**	53	98:2

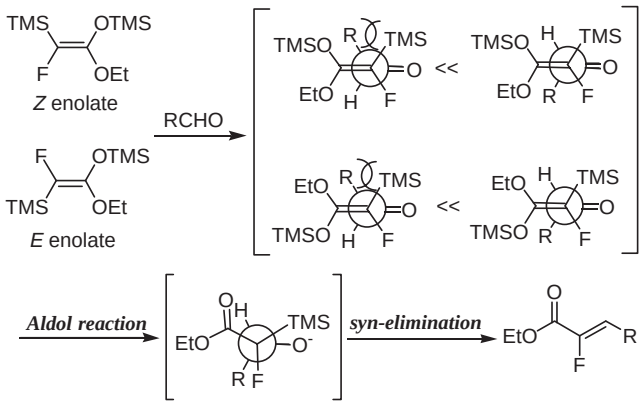
[a]Ketene acetal **1** in a ratio of 1:1 was used. [b]Isolated yield. [c]Diastereomeric ratios were determined by ^{19}F NMR analysis.

the catalyst in DMF (Entry 1) whereas it proceeded smoothly to give an 83:17 mixture of the corresponding Z/E isomers **3a** in 84% yield when AcOLi was used (Entry 2). Effects of the counter cations indicate that Z stereoselectivities of the products improved as the ionic character increased (Entries 3–6). Accordingly, it is noted that the suitable choice of a counter cation was crucial to obtain adducts with high Z stereoselectivity. Then, effect of solvents was examined by using AcO*n*-Bu_4N on the basis of its solubility (Entries 7–9). When CH_2Cl_2 was used, the best result in yield and Z stereoselectivity (Entry 9) was obtained.

Next, reactions of various aldehydes with ketene acetal **1** were examined by using a catalytic amount of AcO*n*-Bu_4N (Table 2). Aromatic aldehydes having electron-donating or -withdrawing groups reacted smoothly to afford the corresponding esters **3b**–**3i** in high yields with almost complete Z selectivity (Entries 1–8). When cinnamaldehyde (**2j**), an α,β-unsaturated aldehyde was used, the stereoselectivity decreased to 83:17 (Entry 9). On the other hand, in the case of α-methylcinnamaldehyde (**2k**), the corresponding diene **3k** was given with excellent Z selectivity (Entry 10). These results indicate that steric effects at an α-position of a carbonyl group has a great influence on the stereoselectivity. Though the yield was moderate, the desired product **3l** was obtained with high stereoselectivity when cyclohexanecarbaldehyde was tried (Entry 11). The above result indicated that a silyl enolate might be formed by partial α-proton abstraction during this aldol reaction.

The observed Z stereoselectivity shows that the first aldol reaction proceeds via acyclic transition states irrespective of the geometry of the ketene silyl acetal **1**. As described in Scheme 2, the reaction proceeds under steric interaction between bulky trimethylsilyl group and R group to generate the corresponding syn intermediate followed by the subsequent syn elimination. In the case when AcOLi was employed, this reaction is considered to proceed under cyclic (Li-chelated) transition state to cause a decrease in the stereoselectivity. Further, it is noted that the observed stereoselectivity of this reaction was opposite to that of HWE reaction.

Thus, a convenient method for the synthesis of (*Z*)-α-fluoroacrylates by using fluoro(trimethylsilyl)ketene ethyl trimethylsilyl acetal was established. In the presence of a catalytic amount of Lewis base, this reaction proceeds smoothly in high yield with Z selectivity. Only TMS_2O was formed as a coproduct which is easily removed by evaporation. In addition, this procedure is useful since inexpensive ethyl fluoroacetate is used as fluorinated building block. Further studies on this type of reaction are now in progress.



Scheme 2. Plausible mechanism of fluoroolefination.

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