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The Stereoselective Construction of Fluoroalkenoates Via the Peterson Olefination Reaction Using *tert*-Butyl α-fluoro-α-(trialkylsilyl)acetates

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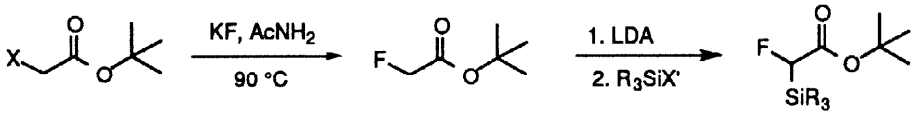
Abstract: A new version of the Peterson fluoroolefination reaction employing *tert*-butyl α-fluoro-α-(trialkylsilyl)acetates was developed to construct various fluoro-alkenoates.

The efficient, stereoselective synthesis of functionalized fluoroolefins became an important transformation with the recognition that this class of compounds has found wide utility in the preparation of biologically active materials like peptide isosteres[1] and enzyme inhibitors.[2] It is known that physical properties and biological activity depend heavily on the configuration of fluoroolefins. However, among those fluoroolefination methods that have been reported,[3-7] many methods are not highly stereoselective and require the use of relatively expensive or difficultly prepared reagents..

Previous studies in our laboratory[1c,4a] showed that the Peterson reaction of 2,4,6-trimethylphenyl α-fluoro-α-(trimethylsilyl)acetate with aryl aldehydes led to highly stereoselective formation of (Z)-fluoroalkenoates in moderate yield. In contrast, olefination reactions with ketones exhibited very low selectivity. We now reported the Peterson fluoroolefination reactions of various carbonyl compounds with new silyl reagents, *tert*-butyl α-fluoro-α-(trialkylsilyl)acetates **1**, which are easily prepared *via* a simple synthetic route from inexpensive reagents as shown in Scheme-1. This new procedure avoids the necessity to use highly toxic and volatile fluoroacetyl chloride.[1c,4a]



2 80% **3** **1**

X= Br, Cl

X' = Me_3SiCl, **1a**: R = Me (71%)
X' = $^iPr_3Si\ SO_3CF_3$, **1b**: R = ^{i}Pr (46%)

Scheme-1

Treatment of commercially available **2** with potassium fluoride easily yielded *tert*-butyl α-fluoroacetate **3** in 80% yield.[1d,8] Direct silylation to give *tert*-butyl α-fluoro-α-(trialkylsilyl)acetate **2a** or **2b**, using chlorotrimethylsilane and triisopropylsilyl triflate followed. The outcome of direct *C*-silylation of **3** is highly dependent upon the molar ratio of the reagents employed, as well as the reaction temperature and time. It was found that *C,C*-bissilylation and Claisen condensation always accompanied the desired *C*-silylation reaction. of

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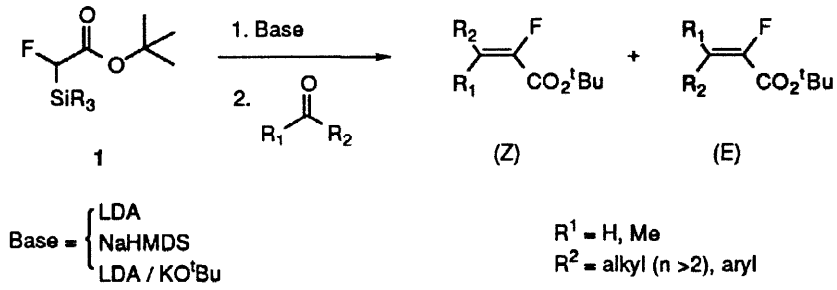
After careful optimization, **1a** was formed in 71% yield by treatment of **3** with four equivalents of LDA and six equivalents chlorotrimethylsilane at -78 °C. Purification of **1a** was achieved by fractional distillation.[9] The higher boiling point by-products such as the *C,C*-bissilylation product and Claisen condensation product were easily separated.

In an attempt to extend the scope of the Peterson olefination reaction for construction of fluoroolefins, we investigated the influence of different cations on the stereochemistry of the reactions. Base-catalyzed Peterson olefination reactions of **1a** and **1b** with aldehydes (Scheme-2)[10] such as acetaldehyde, isobutyraldehyde, 2-ethylbutyraldehyde, heptaldehyde and *o*-tolualdehyde furnished the corresponding fluoroalkenoates **4, 5, 6, 7** and **8** in moderate yield with excellent selectivity (Table 1). Notably, the case of *o*-tolualdehyde showed poor selectivity in the formation of (*Z*)-fluoroalkenoate **8**.



Scheme-2

The Peterson olefination reactions of **1** with ketones such as 2-butanone, 4-methyl-2-pentanone, 2-octanone, and 2-(hydroxymethyl)cyclopentanone were also investigated (Table 1). The fluoroolefination products, **9-12**, were formed with poor selectivity. The preference for formation of the (*Z*)-isomers over (*E*)-isomers was not distinct. Interestingly, (*E*)-fluoroalkenoates were formed as the predominant product by utilizing the more bulky *tert*-butyl α-fluoro-α-(triisopropylsilyl)acetate (**1b**), instead of *tert*-butyl α-fluoro-α-(trimethylsilyl)acetate (**1a**). As shown in Table 1.2, the Peterson olefination of 2-butanone with **1b** yielded the fluoroolefin product as a 2.6:1 ratio of (*E*) : (*Z*) isomer (Entry 7). In the case of 2-(hydroxymethyl)cyclopentanone (Entry 11), the ratio of fluoroolefin product (*E*)-**12** to (*Z*)-**12** was enhanced further, reaching 19.5:1.

As indicated in Table 1, the selectivity in the Peterson olefination was not obviously cation and/or base dependent. In all cases, LDA seemed to be a better base system than NaHMDS and LDA/KO^{t}Bu in terms of the reactivity and stereoselectivity of the reactions. It appeared that the stereoselectivity of the fluoroolefin forming reaction is mainly dependent on the structural features of carbonyl compounds, and on the steric effect of the trialkylsilyl groups.

This new silyl reagent, *tert*-butyl α-fluoro-α-(trialkylsilyl)acetate **1**, has been employed in the base-catalyzed Peterson olefination reactions with a variety of aldehydes and ketones to yield a series of new fluoroolefin compounds in moderate yields. The (*Z*)-stereoselectivity of these transformations is complimentary to the typical (*E*)-selectivity obtained with fluorinated Horner-Emmons reagents, e.g., the reaction of isobutyraldehyde with **1** can be highly (*Z*) selective (entry 2) while ethyl diethylphosphonofluoroacetate is highly (*E*) selective.[3e] The yields of fluoroolefin are quite comparable with either method, however Peterson reagents similar to **1**, have previously been found to be less basic than the Horner-Emmons reagent and therefore more effective in compounds with especially sensitive substituents (entries 10 and 11).

Acknowledgments

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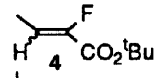
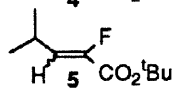
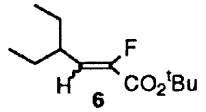
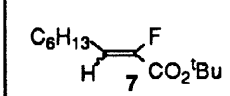
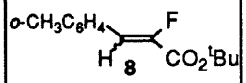
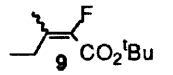
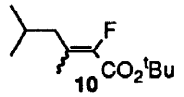
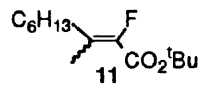
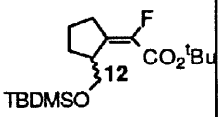
Table 1 Synthesis of α-fluoroolefin esters **4-12**

Entry	Carbonyl compound	Product	Base	Isolated [a] yield %	Ratio of [b] isomer *Z/E*
1	acetaldehyde	 **4**	LDA LDA / KO^{t}Bu	43 51	13.7 / 1.0 Z only
2	isobutyraldehyde	 **5**	LDA NaHMDS	56 23	39.1 / 1.0 Z only
3	2-ethylbutyraldehyde	 **6**	LDA NaHMDS LDA / KO^{t}Bu	37 41 81	Z only 11.9 / 1.0 8.2 / 1.0
4	heptaldehyde	 **7**	LDA LDA / KO^{t}Bu	58 49	9.0 / 1.0 5.0 / 1.0
5	*o*-tolualdehyde	 **8**	LDA LDA / KO^{t}Bu	76 88	1.4 / 1.0 1.2 / 1.0
6	2- butanone	 **9**	LDA LDA / KO^{t}Bu	72 47	1.0 / 1.1 1.0 / 1.3
7	2- butanone	**9**	LDA[c]	*d*	1.0 / 2.6
8	4-methyl-2-pentanone	 **10**	LDA	53	1.4 / 1.0
9	2-octanone	 **11**	LDA LDA / KO^{t}Bu	69 46	1.4 / 1.0 1.5 / 1.0
10	2-(hydroxymethyl)-cyclopentanone	 **12**	LDA	78	1.2 / 1.0
11	2-(hydroxymethyl)-cyclopentanone	**12**	LDA[c]	*d*	1.0 / 19.5

[a] determined by column chromatography; [b] estimated by ^{19}F NMR spectroscopy; [c] compound **1b** was used, instead of **1a**; [d] the yield was not determined.

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9. Compound **1a**, colorless oil: bp 62-64 °C (3 mm Hg); IR (neat) 2956, 1749, 1253, 821 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ -225.70 (d, J = 47.5Hz); ^{1}H NMR ($CDCl_3$) δ 4.53 (d, J = 47.9 Hz, 1H), 1.47 (s, 9H), 0.15 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 170.07 (d, J =19.2 Hz), 87.87 (d, J = 181.2 Hz), 81.74, 28.30, 2.92, 1.10, -3.71; Anal. Calcd for $C_9H_{19}FO_2Si$: C, 52.39; H, 9.28. Found: C, 52.16; H, 9.08.

10. General procedure for the Peterson olefination reactions: To a solution of diisopropylamine (0.32 mL, 2.3 mmol) in THF (10 mL), was added dropwise *n*-butyllithium (0.90 mL, 2.3 mmol, 2.5 *M* solution in hexane) at -30 °C. The solution was stirred for 15 min at -30 °C, then allowed to cool to -90 °C. *tert*-Butyl α-fluoro-α-trialkylsilyl acetate **1** (1.5 mmol) was dissolved in THF (3 mL), and added to LDA solution, stirred for 10 min at -90 °C, followed by addition of a particular aldehyde and ketone (2.3 mmol). The reaction mixture was stirred for additional 10 min at -90 °C, and the cooling bath was removed. The reaction mixture was quenched with a saturated NH_4Cl solution (10 mL) at 0 °C. The separated aqueous layer was extracted with hexanes (3 x 10 mL). The combined organic layers were dried with $MgSO_4$, filtered and evaporated. The crude product was purified by columm chromatography (hexanes: CH_2Cl_2; 6:4).