The First Synthesis and Reaction of β-Ethoxy-α-fluoro-α-(phenylselanyl)ethene: Scandium or Lanthanum Triflate Catalyzed α-Fluoroformylalkenylation of Aldehydes

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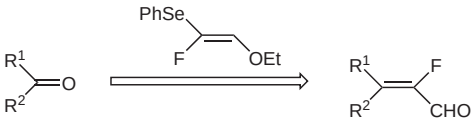
Received 17 May 2005

Abstract: We describe the first preparation of the hitherto unknown β-ethoxy-α-fluoro-α-(phenylselanyl)ethenes and the successful Lewis acid catalyzed α-fluoroformylalkenylation of non-enolizable aldehyde acetals to provide α,β-unsaturated aldehydes or acetals exclusively.

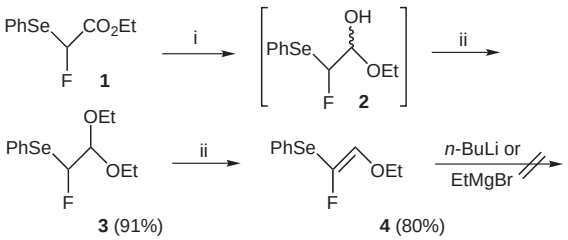
Key words: (phenylselanyl)ethane, scandium triflate, lanthanum triflate, double bond formation, fluorine, α,β-unsaturated aldehydes

α-Fluoro-α,β-unsaturated carbonyl compounds have recently attracted considerable attention as novel starting materials for the synthesis of a wide variety of fluorine containing alkenes or polyenes.[1] Although many synthetic methods have been developed for the preparation of α-fluoro-α,β-unsaturated esters and ketones,[2] there are very few methods for the preparation of α-fluoro-α,β-unsaturated aldehydes (fluoroacrolein). Furthermore, they have the following disadvantages: the usual methods by Horner–Wadsworth–Emmons reactions involves the successive transformation of functional groups such as α,β-unsaturated esters and nitriles to the corresponding aldehydes;[3] direct synthesis from carbonyl compounds using 1,1,2-trifluorovinyl lithium, which could be generated by transmetalation of chlorotrifluoroethene with BuLi at –135 °C, is efficient for the preparation of α,β-unsaturated acid fluorides, however, they cannot be converted to the corresponding aldehydes;[4] the acid-mediated or solvolytic ring-opening of alkoxychlorofluorocyclopropanes is the most popular route,[5] however, the chlorofluorocyclopropanation of enol ethers requires longer reaction times;[6] 2,3,3-trifluoro-1-propenyl ammonium iodides[7] or tosylates[8] are good precursors for β-amino and β-organosulfanylfluoroacrolein derivatives, however, these are also multi-step-procedures.[9] We previously investigated the two-step alkenylation using alkenyl lithiums bearing a β-alkoxy group,[10] which gave the expected α,β-unsaturated aldehydes. In order to explore new synthetic methods for the synthesis of α-fluoro-α,β-unsaturated aldehydes using β-alkoxy-α-fluoroethenes, we investigated and report here the preparation and Lewis acid catalyzed direct α-fluoro-α-formylalkenylation of aldehydes using the hitherto unknown β-ethoxy-α-fluoro-α-(phenylselanyl)ethene (Scheme 1).



Scheme 1 α-Fluoroformylalkenylation using β-ethoxy-α-fluoro-α-organoselanylalkene

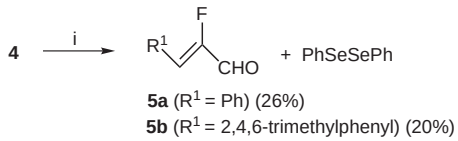
First, we prepared the new β-ethoxy-α-fluoro-α-(phenylselanyl)ethene (**4**) by our original method as shown in Scheme 2.[11] The α-fluoro-α-(phenylselanyl)acetic acid ethyl ester (**1**), which was prepared from ethyl chlorofluoroacetate and diphenyl diselenide, was converted to the hemiacetal **2** by DIBAL-H reduction in toluene at –70 °C. Successive acetalization by the usual method (triethyl orthoformate and a catalytic amount of *p*-toluenesulfonic acid) afforded α-fluoro-α-(phenylselanyl)acetaldehyde diethyl acetal (**3**) in good yield. The deethanolysis of **3** was accomplished by treatment with lithium isopropylcyclohexylamide at –60 to –40 °C in diethyl ether. The reactions in THF gave rise to a low yield of **4**. Next, we attempted the generation of β-ethoxyalkenyl metals and their reaction with electrophiles. Although the transmetalation of **4** with BuLi or ethylmagnesium bromide in THF at –78 °C proceeded and gave the butyl or ethyl phenyl selenide, the reactions with electrophiles was not successful. This result showed that the β-ethoxy-α-(phenylselanyl)ethene (**4**) is not a suitable precursor of β-ethoxy-α-fluoroethenyl metals; therefore, we modified the course of the reaction to employ a new α-formylalkenylation using β-ethoxy-α-(phenylselanyl)ethenes, thus avoiding the alkenyllithium intermediates.



Scheme 2 *Conditions and reagents:* i) DIBAL-H (1.2 equiv, toluene, –70 °C, 30 min; ii) $CH(OEt)_3$ (3.0 equiv), *p*-TsOH (0.1 equiv), EtOH, r.t., 12 h; lithium isopropylcyclohexylamide (1.5 equiv), Et_2O, –60 to –40 °C, 10 min.

SYNLETT 2005, No. 14, pp 2191–2194
Advanced online publication: 13.07.2005
DOI: 10.1055/s-2005-871961; Art ID: U15305ST

In order to explore new areas in the organic chemistry of the alkenylations using enol ethers, we examined the Lewis acid catalyzed reactions using β-ethoxy-α-fluoroethene **4**. When hafnium triflate was used as a catalyst, the corresponding α-fluorocinnamaldehydes **5a**,**b** were obtained in low yields (Scheme 3). We optimized both the reaction conditions and the electrophiles, and found that the acetals are effective electrophiles for the Lewis acid catalyzed α-fluoroformylalkenylation. These results are shown in Table 1.



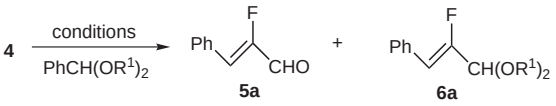
Scheme 3 *Conditions and reagents:* R^1CHO, $Hf(OTf)_3$ (5 mol%), $ClCH_2CH_2Cl$, r.t.

We examined the reaction of **4** with benzaldehyde dimethyl acetal in the presence of $BF_3{\cdot}Et_2O$ (5 mol%) and obtained **5a** in 56% yield (Table 1, entry 1). Scandium or lanthanum triflate gave satisfactory results (Table 1, entries 7 and 11). Next, we examined the reactions in other solvents (Table 1, entries 8–10), however, the yields of products were almost the same. When the reaction was quenched by triethylamine, acetal was obtained exclusively (Table 1, entry 13).

Next, we performed the alkenylations with a range of aldehydes as shown in Table 2.[12] *p*-Methoxybenzaldehyde gave satisfactory results; however, *p*-chlorobenzaldehyde produced a low yield of **5c** or **6c** (Table 2, entries 4 and 5). α-Fluoropenta-2,4-dienal (**5f**) was obtained in good yield; however, the enynal **6g** was afforded in low yield (Table 2, entries 9 and 10). We further investigated the α-fluoroalkenylation of ketone acetals such as 4-phenylcyclohexanone; however, the coupling products were not observed.

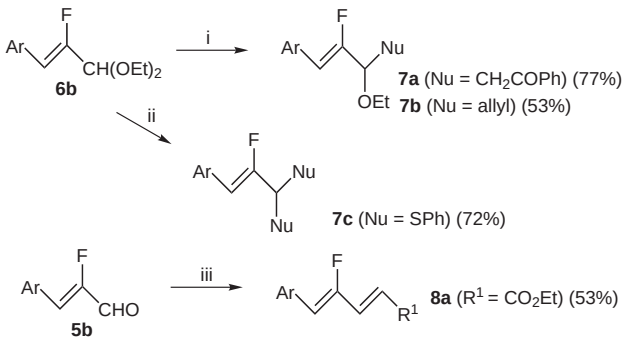
α-Fluoro-α,β-unsaturated aldehydes could be converted to useful 3-fluoropyridines,[13] fluoro-2-cyclohexenol, fluoro-2,5-dihydropyranols, fluoro-3,6-dihydro-1,2-oxadines,[14] fluorothiophenes,[15] 3-fluoro-1,3-butadienes,[6] and 3-fluorovinylglycines, which are efficient irreversible inhibitors of *E. coli* Alanine Racemase,[16] and fluorinated analogues of insect sex pheromones.[6] The new catalytic α-fluoroalkenylation of aldehydes is much better in producing products such as aldehydes or acetals than the usual methods. Some useful transformations of α-fluoro-α,β-unsaturated aldehyde **5b** or acetal **6b** were examined (Scheme 4). The Lewis acid mediated or catalyzed nucleophilic substitution reactions of **6b** with allyltrimethylsilane or 1-phenyl-1-(trimethylsilyloxy)ethylene occurred regioselectively at the acetal carbon to give the alkylated products **7a**,**b**, respectively. The phenylsulanyltrimethylsilane gave exclusively the disulfanyl acetal **7c** in good yield. The usual transformations to the fluorobuta-1,3-dienes using Wittig reagents were mostly satisfactory.

Table 1 Lewis Acid Catalyzed α-Fluoroformylalkenylation of Benzaldehyde Dimethyl or Diethyl Acetals



Entry	Acetal R^1	Conditions[a]	Yields (%)[b] **5a**	**6a**
1	Me	$BF_3{\cdot}Et_2O$, $Cl(CH_2)_2Cl$, 83 °C, 12 h	56	–
2	Me	$SnCl_4$, $Cl(CH_2)_2Cl$, r.t., 12 h	46	–
3	Me	$Zn(OTf)_2$, $Cl(CH_2)_2Cl$, r.t.,12 h	–	–
4	Me	$Yb(OTf)_3$, $Cl(CH_2)_2Cl$, r.t., 12 h	42	–
5	Me	$Yb(OTf)_3$, $Cl(CH_2)_2Cl$, 83 °C, 10 min	52	–
6	Me	$Hf(OTf)_4$, $Cl(CH_2)_2Cl$, r.t., 12 h	28	–
7	Me	$Sc(OTf)_3$, $Cl(CH_2)_2Cl$, r.t., 12 h	36	–
8	Me	$Sc(OTf)_3$, $MeNO_2$, r.t., 12 h	39	25
9	Me	$Sc(OTf)_3$, THF, 65 °C, 5 min	10	52
10	Me	$Sc(OTf)_3$, MeCN, r.t., 45min	3	54
11	Me	$La(OTf)_3$, $Cl(CH_2)_2Cl$, r.t., 12 h	59	–
12	Et	$La(OTf)_3$, $Cl(CH_2)_2Cl$, r.t., 25 h	48	46
13	Et	$La(OTf)_3$, $Cl(CH_2)_2Cl$, r.t., 25 h	–	85[c]

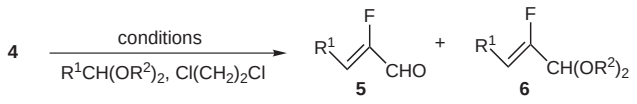
[a] Lewis acid (5 mol%).
[b] Diphenyl diselenide was obtained in each case in 72–100% yield.
[c] The reaction was quenched with Et_3N.



Scheme 4 *Conditions and reagents:* i) $CH_2{=}C(OTMS)Ph$ (3 equiv), TMSOTf (1.5 equiv), CH_2Cl_2, –78 °C, 10 min or $Me_3SiCH_2CH{=}CH_2$ (5 equiv), $Sc(OTf)_3$ (5 mol%), $ClCH_2CH_2Cl$, r.t., 1 h; ii) TMSSPh, $ClCH_2CH_2Cl$, r.t., 1 h; iii) $R^1CH_2PPh_3Br$ (1.5 equiv), LDA, THF, –78 °C.

In summary, we prepared β-ethoxy-α-fluoro-α-(phenylselanyl)ethenes for the first time and successfully utilized them in the Lewis acid catalyzed α-fluoroalkenylation of the non-enolizable aldehydes. However, the reactivity and scope of β-ethoxy-α-fluoro-α-(organoselanyl)ethenes in organic chemistry has not been fully determined; this is

Table 2 Lewis Acid Catalyzed α-Fluoroformylalkenylation of Aldehyde Acetals



Entry	Acetal		Conditions[a]	Yields (%)[b]	
	R^1	R^2		**5**	**6**
1	*p*-$MeOC_6H_4$	Et	$La(OTf)_3$, 83 °C, 15 min	**5b** (58)	**6b** (19)
2	*p*-$MeOC_6H_4$	Me	$La(OTf)_3$, 83 °C, 15 min	**5b** (57)	**6b** (7)
3	*p*-$MeOC_6H_4$	Me	$La(OTf)_3$, 83 °C, 15 min	–	**6b** (85)
4	*p*-ClC_6H_4	Me	$La(OTf)_3$, 83 °C, 10 min	**5c** (26)	–
5	*p*-ClC_6H_4	Me	$Sc(OTf)_3$, 83 °C, 10 min	**5c** (16)	**6c** (2)[c]
6	2,4,6-$Me_3C_6H_2$	Me	$La(OTf)_3$, 83 °C, 15 min	**5d** (54)	–
7	*p*-HOC_6H_4	Me	$Sc(OTf)_3$, 83 °C, 10 min[d]	**5e** (12)	–
8	(*E*)-Cinnamyl	Et	$La(OTf)_3$, r.t., 12 h	**5f** (47)	–
9	(*E*)-Cinnamyl	Et	$Hf(OTf)_4$, r.t., 12 h[d]	**5f** (70)	–
10	Phenylethynyl	Et	$La(OTf)_3$, 83 °C, 1 min	–	**6g** (12)

[a] Lewis acid (5 mol%).
[b] Diphenyl diselenide was obtained in each entry in 79–100% yield.
[c] Acetal **6c** was obtained as ethyl methyl acetal.
[d] Lewis acid (20 mol%).

currently under investigation and results will be reported elsewhere.

Acknowledgment

The support of part of this work by the Endo Seijiro Memorial Foundation is gratefully acknowledged.

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(11) Preparation of β-ethoxy-α-fluoro-α-(phenylselanyl)ethene(**4**). To a toluene (80 mL) solution of ethyl 2-fluoro-2-(phenylselanyl)acetate (**1**; 4.00 g, 15.3 mmol) was added DIBAL-H (18.4 mL, 1 M toluene solution, 18.4 mmol) at –78 °C under an Ar atmosphere. After the reaction mixture was stirred for 30 min, 1 M HCl solution (16 mL) was added to the mixture. The resulting mixture was

stirred for 10 min and then poured into H_2O (200 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure. To the residue in EtOH (23 mL) was added ethyl orthoformate (11.4 g, 76.6 mmol) and *p*-TsOH (0.26 g, 1.53 mmol). The mixture was stirred for 12 h at 20 °C and poured into a sat. soln of $NaHCO_3$ (200 mL). Work-up and purification by column chromatography on silica gel eluting with EtOAc–hexane (1:50) gave 2-fluoro-2-(phenylselanyl)acetaldehyde diethyl acetal(**3**) (14.1 g, 91%) as a yellow oil. IR: 2978, 2929, 2884, 2362, 2344, 1579, 1478, 1372, 1340, 1301, 1118, 1067, 1023, 999, 891, 741, 691, 470 cm^{-1}; ^1H NMR: δ = 1.25 (3 H, t, *J* = 7 Hz, Me), 1.26 (3 H, t, *J* = 7 Hz, Me), 3.62–3.68 (2 H, m, OCH_2), 3.76–3.82 (2 H, m, OCH_2), 4.71 (1 H, dd, *J* = 4, 9 Hz, acetal H), 6.02 (1 H, dd, *J* = 4, 52 Hz, CHF), 7.24–7.33 (3 H, m, ArH), 7.64–7.66 (2 H, m, ArH); ^{19}F NMR (referenced to CF_3CO_2H): δ = –87.05 (dd, *J* = 9, 53 Hz); MS: *m*/*z* = 292 (M^+). Anal. Calcd for $C_{12}H_{17}FO_2Se$: C, 49.49; H, 5.88. Found: C, 49.27; H, 5.79

An ethereal (5.0 mL) solution of **3** (3.0 g, 10.3 mmol)was added to lithium isopropylcyclohexylamide (prepared from isopropylcyclohexylamine (2.90 g, 20.6 mmol) and BuLi (6.0 mL, 15.4 mmol) in Et_2O (60 mL)) at –60 °C. The reaction mixture was warmed to –40 °C and then stirred for 10 min. The mixture was poured into H_2O (200 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:100) to give **4** (2.02 g, 80%) as a yellow oil. IR: 3444, 2980, 2357, 1658, 1577, 1477, 1439, 1395, 1313, 1194, 1130, 1061, 1000, 902, 737, 689, 535, 515, 466, 441, 425, 406 cm^{-1}; ^1H NMR: δ = 1.33 (3 H, t, *J* = 7 Hz, Me), 3.97 (2 H, q, *J* = 7 Hz, OCH_2), 6.24 (1 H, d, *J* = 19 Hz, olefinic H), 7.24–7.30 (3 H, m, ArH), 7.48 (2 H, d, *J* = 8 Hz, ArH); ^{19}F NMR: δ = –39.67 (d, *J* = 18 Hz); MS: *m*/*z* = 246 (weak M^+). Compound **4** was too volatile to measure the elemental analysis.

(12) A typical procedure for the preparation of 2-fluoro-4′-methoxycinnamaldehyde dimethyl acetal(**6a**): Lanthanum triflate (60 mg, 0.10 mmol) was added to a $ClCH_2CH_2Cl$ (5.0 mL) solution of **4** (0.50 g, 2.04 mmol) and *p*-methoxybenzaldehyde dimethyl acetal (0.80 g, 4.07 mmol) under an Ar atmosphere. The reaction mixture was refluxed for 10 min, cooled, and treated with Et_3N (2 drops). Work-up afforded 2-fluoro-4′-methoxycinnamaldehyde dimethyl acetal (**6a**, 0.77 g, 85%).

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