Z-Selective or Stereospecific Alkenylation Reaction: A Novel Synthetic Method for α-Fluoro-α,β-unsaturated Esters

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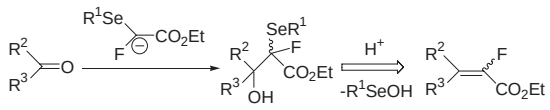
The *Z*-selective formation of α-fluoro-α,β-unsaturated esters was achieved using the deselenenic acid of the *syn*- and/or *anti*-3-aryl-2-fluoro-3-hydroxy-2-organoselanylacetates **3** and **4** with trifluoromethanesulfonic acid. In contrast, the 3-alkyl-substituted propanoates **3f** and **4b** stereospecifically underwent alkenylation to give the (*E*)- or (*Z*)-α-fluoro-α,β-unstaurated esters **5f**. We were also successful in the one-pot alkenylation reactions.

α-Fluoro-α,β-unsaturated esters are novel building blocks for biologically active compounds, agrochemicals, and polymers.[1] The main synthetic routes for the α-fluoro-α,β-unsaturated esters are the Wittig and Horner–Wadsworth–Emmons (HWE) reactions. However, the *Z*-selective HWE reactions are quite limited.[2] Nagao et al. reported a modified method for the α-fluoro-α,β-unsaturated esters as an alternative route.[3]

While the α-organosulfanyl, sulfinyl, and sulfonyl α-fluoroacetic acid esters are widely used for the synthesis of α-fluoro-α,β-unsaturated esters,[4] α-fluoroalkenes,[5] α,α-difluoroacetic acid esters,[6] and 2-fluoroallylic alcohols,[7] in contrast, the α-organoselanylacetic esters are quite limited.[8,9] Previously, we have explored a new field in synthetic organic chemistry using β-alkoxyalkenyl lithiums.[10] The addition reactions of alkenyl lithiums with aldehydes and ketones, and the successive hydrolysis afford the corresponding types of alkenes. This two-step procedure using the carbanion of the α-fluoro-α-organoselanylacetic acid esters would be expected to give the α-fluoro-α,β-unsaturated esters because the treatment of the β-hydroxy-α-organoselanylalkanes with acids is well-known to afford the alkenes by removal of the organoselenenic acid (RSeOH).[11] We have investigated the synthetic utilization using α-fluoro-α-organoselanylacetic acid esters, and the transformation of the α-fluoro-β-hydroxy-α-organoselanylalkanes was found to form the corresponding α-fluoroalkenes. Herein, we report the *Z*-selective synthetic methods of the α-fluoro-α,β-unsaturated esters (Scheme 1).

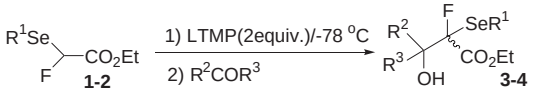
We first prepared the α-fluoro-α-phenylselanyl and α-butylselanylacetic acid ethyl esters **1** (82%) and **2** (54%) by the usual method from the commercially available chlorofluoroacetic acid ethyl ester and the corresponding diorganyl diselenides/$NaBH_4$ in EtOH. Next, we performed the lithiation and reaction with benzaldehyde with the normal amide bases such as LDA or lithium 2,2,6,6-tetramethylpiperidide (LTMP). The corresponding alcohol **3a** was obtained in almost the same yields as both the syn and anti diastereomers (syn:anti = 64:36).[12] The relative configuration of each isomer was determined by X-ray analysis (Figure 1).[13] The reactions with some aldehydes and ketones provided the alcohols **3b**–**3j** and **4a** and **4b** as shown in Table 1.



Scheme 1. α-Fluoroalkenylation using α-fluoro-α-organoselanylacetates.

The treatment of **3a** with trifluoromethanesulfonic acid in 1,2-dichloroethane gave the α,β-unsaturated ester **5a**, accompanied by diphenyl diselenide. The stereochemistry of the ethyl (*Z*)-2-fluorocinnamate (**5a**) was confirmed on the basis of the coupling constant of the product.[14] When *p*-toluenesulfonic acid was used as the acid, the product was obtained in 53% yield as a mixture of the diastereomers (*E*:*Z* = 47:53). We reexamined the formation of the double bond in each isomer; however, the same product **5a** was obtained from the *syn*- or *anti*-alcohols **3a**. The dehydration reactions of some alcohols were examined using almost the same procedure, and these results are shown in Table 2. The reactions of the 3-aryl-**3b**–**3d** and 3-styryl-3-hydroxyacetates **3e** exclusively provided the (*Z*)-α-fluoro-α,β-unsaturated esters **5b**–**5e** (Entries 3–8). The reaction of **3c** with

Table 1. Synthesis of ethyl 2-fluoro-3-hydroxy-2-(organoselanyl)alkanoates **3**–**4**



Entry	R^1	R^2	R^3	Yield (syn:anti)
1	Ph	Ph	H	**3a** (69; 64:36)
2	Ph	2,4,6-$Me_3C_6H_2$	H	**3b** (60; 72:16)
3	Ph	4-$MeOC_6H_4$	H	**3c** (66; 58:42)
4	Ph	4-ClC_6H_4	H	**3d** (63; 41:59)
5	Ph	(*E*)-PhCH=CH	H	**3e** (53; 55:45)
6	Ph	$PhCH_2CH_2$	H	**3f** (36; 58:42)
7	Ph	$(CH_2)_5$		**3g** (68)
8	Ph	$(CH_2)_4$		**3h** (61)
9	Ph	$(CH_2)_2CHPh(CH_2)_2$		**3i** (99)
10	Ph	$CH=CH(CH_2)_3$		**3j** (50; 68:32)
11	*n*-Bu	4-$MeOC_6H_4$	H	**4a** (51; 57:43)
12	*n*-Bu	$PhCH_2CH_2$	H	**4b** (72; 64:36)

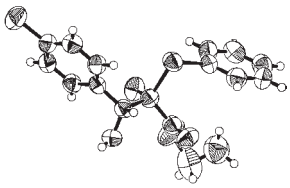
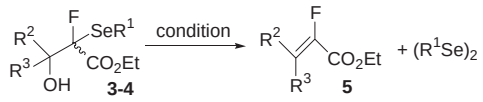


Figure 1.

Table 2. Synthesis of ethyl 2-fluoroalkanoates with acids

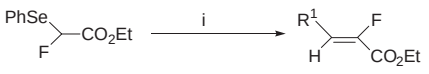


Entry	Alcohol	Condition	Yield/%	Yield/%
		Method/temp and time	**5** (*Z*:*E*)	$(R^1Se)_2$[a]
1	***s*-3a**	A/rt/10 min	**5a** (74)(99:1)	(71)
2	***a*-3a**	A/rt/10 min	**5a** (85)(99:1)	(71)
3	***s*- and *a*-3b**	A/rt/10 min	**5b** (99)(99:1)	(31)
4	***s*- and *a*-3c**	B	**5c** (75)(99:1)	(46)
5	***s*-3d**	A/rt/10 min	**5d** (63)(99:1)	(49)
6	***a*-3d**	A/rt/10 min	**5d** (84)(99:1)	(54)
7	***s*-3d**	C	**5d** (70)(99:1)	(17)
8	**3e**	A/0 °C/10 min	**5e** (35)(99:1)	(50)
9	***s*-3f**	A/83 °C/10 min	**5f** (71)(1:99)	(93)
10	***a*-3f**	A/83 °C/10 min	**5f** (99)(99:1)	(13)
11	**3g**	A/0 °C/50 min	**5g** (77)	(—)
12	**3h**	A/0 °C/10 min	**5h** (59)	(70)
13	**3i**	A/rt/10 min	**5i** (47)	(45)
14	**3j**	A/0 °C/10 min	**5j** (18)	(32)
15	***s*- and *a*-4a**	A/0 °C/10 min	**5c** (51)	(—)
16	***s*-4b**	A/83 °C/10 min	**5f** (42)(1:99)	(—)
17	***a*-4b**	A/83 °C/10 min	**5f** (42)(99:1)	(—)

Method A: CF_3SO_3H(2.0 equiv.)/$Cl(CH_2)_2Cl$; Method B: CF_3SO_3Me(2 equiv.)/NEt_3(3 equiv.)/DMF/rt/10 min; Method C: $Sc(OTf)_3$/(0.05 equiv.)/$Cl(CH_2)_2Cl$/rt/5 min; [a]The yield of diphenyl diselenide was confirmed by the starting alcohol **3** or **4**.

methyl trifluoromethanesulfonate/triethylamine (Method B) also afforded the alkene **5c** in good yield (Entry 4). The yield of diphenyl diselenide was found to be lower than that of the α,β-unsaturated esters; however, we could not understand the reasons for it. The reaction of the alkyl ($R^2 = CH_2CH_2Ph$; $R^3 = H$) substituted alcohol **3f** did not proceed at room temperature; however, the reaction at 83 °C stereospecifically proceeded to give the (*E*)- or (*Z*)-alkene **5f** in high yields (Entries 9 and 10). The alkenylation of the butylselanyl derivative **4b** also succeeded (Entries 16 and 17). We also examined the Lewis acid-catalyzed alkenylation of the 3-hydroxy-2-phenylselanylpropanoate **3d** which succeeded under the following conditions: scandium triflate (0.05 mol) in $ClCH_2CH_2Cl$ at room temperature (Method C, Entry 7). Overall, the stereoselectivities of the α,β-unsaturated esters were excellent; however, the yields of the products were not satisfactory because the alkenylation process consisted of stepwise procedures. We then examined the one-pot reaction as a modified method of the alkenylation step including the addition reaction of the carbanion with aldehydes or ketones and the removal of the benzeneselenenic acid (Scheme 2).

After the addition of the corresponding aldehyde or ketone,



Reagent: i, LTMP/THF/R^1CHO/ −78 °C/$MeSO_2Cl$

5a (R^1 = Ph)(68%)(*Z*:*E* = 99:1)

5b (R^1 = 2,4,6-$Me_3C_6H_2$)(99%)(*Z*:*E* = 99:1)

Scheme 2. One pot synthesis of α-fluoro-β-hydroxy-α-organoselenanylalkanoates.

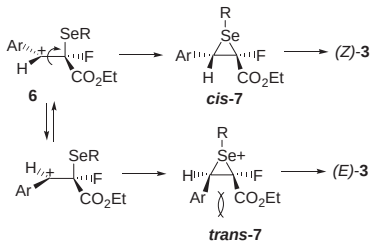


Figure 2.

the reaction mixture was treated with some acids. Excellent yields and stereoselectivities were obtained using methanesulfonyl chloride at −78 °C. Especially, the 2,4,6-trimethylphenyl derivative was obtained in excellent yield. The excellent *Z*-selectivity of the reactions would be considered as shown in Figure 2. The dehydration of the 3-aryl-3-hydroxypropanoate with acid gives the cationic intermediate **6**, which is stabilized by the organoselanyl group through a bridged intermediate **7**. The 3-aryl intermediate **6** should be further stabilized by the aryl group, therefore, the extrusion of the selanyl moiety would be very slow and proceed via the preferred *cis*-**7**, which minimizes the steric interactions. On the other hand, the stereospecificity during the formation of the double bond in the reactions of the 3-alkyl derivatives **3f** and **4b** would proceed with retention of its stereochemistry without the equilibrium like **6** because the corresponding cationic intermediates would be less stable than the aromatic **6**.

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12 Each diastereomer was easily purified by preparative TLC or column chromatography on silica gel. In all cases, the 2,3-*syn* derivatives are less polar compounds similar to the corresponding sulfur analogs.

13 Crystal data for *syn*-**3d**. Orthorombic, space group $P2_1/a$, $a = 6.203(7)$, $b = 22.74(3)$, $c = 12.29(2)$ Å, $\beta = 98.21(5)°$, $V = 1715(3)$ Å^3, $Z = 4$, $D_c = 1.556$ g/cm^3, crystal dimensions: $0.10 \times 0.12 \times 0.20$ mm^3. Total reflections (Mo Kα radiation, ω-2θ scan technique, $2\theta_{max} = 55.0°$): 16189. Unique reflections with $I > 0\sigma(I)$: 15942 ($R_{int} = 0.055$). Final R and R_w values, based on F^2, were 0.108 and 0.155, respectively. Deposition number at Cambridge Crystallog. Data Centre: CCDC 270027.

14 The coupling constant of (*Z*)-**5a** was obtained from the reference 8: δ_H: 6.92 (d, $J_{H-F} = 35$ Hz, olefinic H), δ_F: −47.6 ppm ($J = 35$ Hz). *Z*-**5a**: δ_H: 6.91 ppm (d, $J_{H-F} = 22$ Hz, olefinic H), δ_F: −39.5 ppm ($J = 22$ Hz).

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