First Lewis Acid Catalyzed Generation and Reaction of α-Organylsulfanyl and α-Organylselanyl Carbenium Ions Using Ethyl α-Fluoroacetate Derivatives

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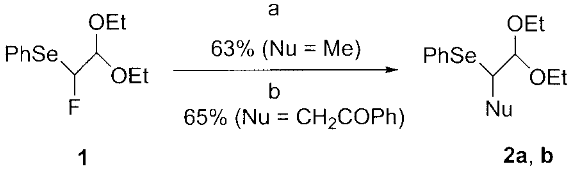
Lewis acid catalyzed generation and reactions of α-organylsulfanyl and α-organylselanyl carbenium ions with nucleophiles proceeded in high yields using α-fluoro-α-organylsulfanyl- and α-fluoro-α-organylselanylacetate and 5 mol-% scandium triflate.

Introduction

Carbenium ions stabilized by α-organylsulfanyl and α-organylselanyl substituents are useful for the C–C and C–heteroatom bond-forming reactions with intra- and intermolecular nucleophiles including cyclization reactions in organic synthesis.

Usually, we use sulfoxides[1] (Pummerer reaction), α-chloro-α-organylsulfanyl alkanes,[2] bis(organylsulfanyl)alkanes (*S*,*S*-acetals),[3,4] bis(organylselanyl)alkanes (*Se*,*Se*-acetals),[5] α-bromo-α-organylselanyl alkanes[6], and selenoxides[7] as precursors for the organylsulfanyl and organylselanyl carbenium ions; however, these starting materials have some disadvantages. α-Chloro-α-organylsulfanyl alkanes can be obtained by the reactions of organylsulfanyl alkanes with *N*-chlorosuccinimide, which is the most popular reagent for the chlorination of the α-position to the sulfur atom of organylsulfanyl alkanes; however, it is difficult to completely remove the resultant succinimide, and further purification is not possible because of the lability of the α-chloro-α-organylsulfanyl alkanes. It is also difficult to prepare α-bromo-α-organylselanyl alkanes, which are contaminated by the corresponding bis(organylselanyl)alkanes.[6] The bis(organylselanyl)alkanes are highly reactive to moisture. Furthermore, it is necessary to use a stoichiometric amount of Lewis acid to generate and complete the reactions of α-organylsulfanyl and α-organylselanyl carbenium ions with the nucleophiles. Usually, tin(IV) chloride or titanium(IV) chloride is used as the effective Lewis acid in the stoichiometric reactions; however, the complexation between the bis(organylselanyl)alkanes or α-chloro-α-organylselanyl alkanes slows down the reaction with nucleophiles or does not complete the reactions. Recently, we demonstrated a preliminary investigation of the nucleophilic addition reaction of 2-fluoro-2-(phenylselanyl)acetaldehyde diethyl acetal (**1**) (Scheme 1). The reaction of **1** with trimethylaluminum in 1,2-dichloroethane at 20 °C provided the unprecedented product 2-(phenylselanyl)propanal diethyl acetal (**2a**) exclusively. The reaction with phenyl(trimethylsilyloxy)ethylene gave the corresponding compound **2b**. These experimental data show that the Lewis acid mediated reactions of 2-fluoro-2-(phenylselanyl)acetaldehyde diethyl acetal (**1**) with nucleophiles occur at the α-carbon of the fluorine atom, not at the acetal carbon. The α-fluoro-α-organylselanyl alkanes were found to be surprisingly more reactive toward Lewis acids than the *O*,*O*-acetals. Although the α-fluoro-α-organylsulfanyl and organylselanyl alkanes are not common precursors of carbenium ions, they are expected to become novel precursors of organylsulfanyl and organylselanyl carbenium ions. Furthermore, since the Lewis acid catalyzed generation and reactions of the organylsulfanyl and organylselanyl carbenium ions have not been reported, the α-fluoro-α-organylselanyl alkanes could utilize the Lewis acid catalyzed reactions of carbenium ions (Scheme 2). Here we report the first Lewis acid catalyzed generation and nucleophilic addition reactions of α-organylsulfanyl and organylselanyl carbenium ions.



Scheme 1. Regioselective reactions of 2-fluoro-2-(phenylselanyl)acetaldehyde diethyl acetal with nucleophiles. a) Me_3Al (2 equiv.), $ClCH_2CH_2Cl$, 20 °C, 10 min. b) $CH_2=C(OTMS)Ph$ (3 equiv.), Et_3Al (1 equiv.), $ClCH_2CH_2Cl$, 83 °C, 20 min.

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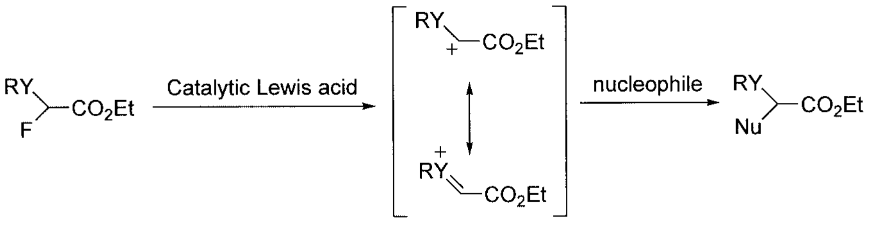
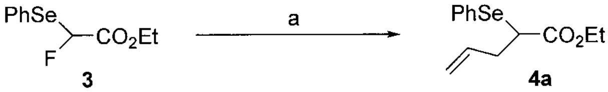


Scheme 2. Lewis acid catalyzed generation and reactions of α-organylsulfanyl and α-organylselanyl carbenium ions with nucleophiles (RY = PhSe, BuSe, PhS).

Results and Discussion

In the initial phase of the work, we selected ethyl 2-fluoro-2-(phenylselanyl)acetate (**3**), which is easily prepared by the usual method using diphenyl diselenide,[8] sodium borohydride, and ethyl chlorofluoroacetate in ethanol and used it as a substrate for the catalytic reactions as shown in Scheme 3. We first carried out the allylation of **3** with allyltrimethylsilane in the presence of 5 mol-% of boron trifluoride–diethyl ether at 20 °C. The allylated ester **4a** was obtained accompanied by the starting ester **3** (Table 1, entry 1). Some Lewis acid catalyzed allylation reactions were carried out; however, satisfactory results were not obtained (Table 1, entries 2–5). During the course of the investigations, we found that the trifluoromethanesulfonic acid lanthanoids were effective in Lewis acid catalyzed allylation. Scandium triflate was found to be the best in all respects (Table 1, entry 10).[9] Next, we performed the allylations with 5 mol-% of scandium triflate in various solvents. The reactions in the chlorinated solvents such as dichloromethane and 1,2-dichloroethane gave satisfactory results (Table 1, entries 10 and 11), while THF was found to deactivate the Lewis acids (Table 1, entry 12). Next, we investigated some nucleophiles using the phenylselanyl (**3**), butylselanyl (**5**), and phenylsulfanyl (**8**) derivatives. The results are shown in Table 2. The ester **3** reacted with phenyltrimethylsilyloxyethene in the presence of 5 mol-% of scandium triflate to give the adduct **4b** (Table 2, entry 1). Commasetto *et al.* reported the Friedel–Crafts reactions of ethyl α-bromo-α-(phenylselanyl)- and α,α-diorganylselanylacetate with $TiCl_4$;[6] however, 1.1 equiv. of $TiCl_4$ was needed to complete the reactions. The reaction of 1,2,3-trimethoxybenzene proceeded cleanly with 5 mol-% of scandium triflate at 20 °C (Table 2, entry 2). The butylselanyl derivative **5** also reacted with almost the same nucleophiles; however, the Friedel–Crafts reaction of **5** with 1,2,3-trimethoxybenzene provided ethyl 2,2-bis(2,3,4-trimethoxyphenyl)acetate (**7**) in 20% yield accompanied by the normal adduct (Table 2, entry 7). This method provided the *S,Se*-heteroacetals **4d** and **6c** (Table 2, entries 3 and 6). On the other hand, the phenylsulfanyl derivative **8** gave better results in terms of the yields of products **9a–g** and the regioselectivities of the Friedel–Crafts reactions (Table 2, entries 7–13).



Scheme 3. Scandium-catalyzed allylation of ethyl-2-fluoro-2-(phenylselanyl)acetate. a) allyltrimethylsilane, $Sc(OTf)_3$ (5 mol-%), CH_2Cl_2.

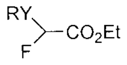
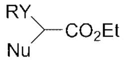
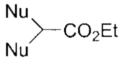
Table 1. Lewis acid catalyzed allylation of ethyl-fluoro(phenylselanyl)acetate **3**.

Entry	Conditions	Product (% yield)
1	BF_3-Et_2O (5 mol-%), CH_2Cl_2, 20 °C, 3 h	**4a** (53), **3** (32)
2	$TiCl_4$ (5 mol-%), CH_2Cl_2, r.t., 1 h	complex mixture
3	$Ti(OiPr)_4$ (5 mol-%), CH_2Cl_2, 40 °C, 2 h	**4a** (7), **3** (26)
4	$SnCl_4$ (5 mol-%), CH_2Cl_2, 40 °C, 2 h	**3** (48)
5	$Zn(OTf)_2$ (5 mol-%), CH_2Cl_2, 40 °C, 3 h	**3** (82)
6	$Yb(OTf)_3$ (5 mol-%), CH_2Cl_2, 40 °C, 2 h	**4a** (80)
7	$La(OTf)_3$ (5 mol-%), CH_2Cl_2, 40 °C, 3 h	**4a** (15), **3** (11)
8	$HfCl_4$ (5 mol-%), CH_2Cl_2, 40 °C, 2 h	**4a** (11), **3** (76)
9	$Hf(OTf)_4$ (5 mol-%), CH_2Cl_2, r.t., 4 h	**4a** (79)
10	$Sc(OTf)_3$ (5 mol-%), CH_2Cl_2, r.t., 1.5 h	**4a** (87)
11	$Sc(OTf)_3$ (5 mol-%), $ClCH_2CH_2Cl$, r.t., 2.5 h	**4a** (74)
12	$Sc(OTf)_3$ (5 mol-%), THF, 65 °C, 2 h	**3** (100)
13	$Sc(OTf)_3$ (5 mol-%), Et_2O, r.t., 12 h	**4a** (68)
14	$Sc(OTf)_3$ (5 mol-%), MeCN, r.t., 12 h	**4a** (81)
15	$Y(OTf)_3$ (5 mol-%), 40 °C, 2 h	**4a** (44), **3** (37)

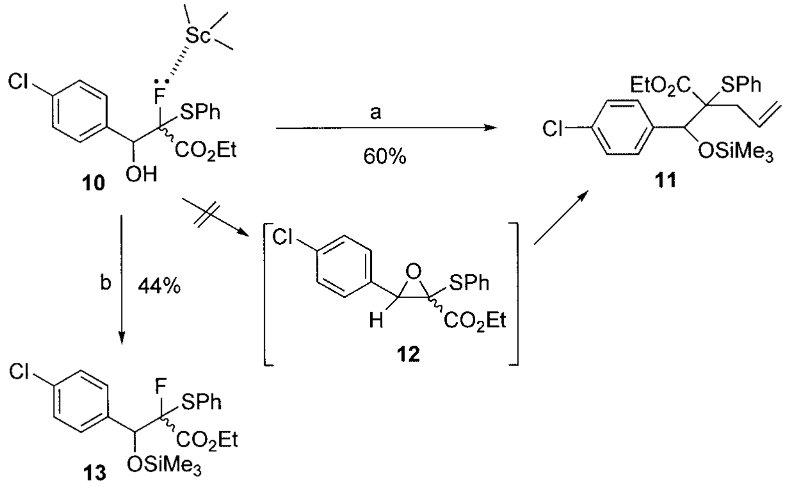
Next, we performed the scandium-catalyzed allylation of 3-hydroxy-2-fluoro-2-(phenylsulfanyl)propionate **10** with allyltrimethylsilane, as shown in Scheme 4. It required 0.3 equiv. of the Lewis acid to complete the reaction where the product is ethyl 2-(4′-chlorophenyltrimethylsilyloxymethyl)-2-(phenylsulfanyl)pent-5-enoate (**11**). It was observed that the reaction proceeded via the oxirane intermediate **12**. Therefore, we examined the allylations of each diastereomer under the same conditions; however, each isomer gave one diastereomer of **11**. Therefore, the allylation and the *O*-trimethylsilylation reaction of **10** in the presence of 0.3 equiv. of scandium triflate was found to be nonstereospecific in the defluorination, epoxidation, and ring-opening processes. In contrast, the reaction of **10** in the presence of 5 mol-% scandium triflate provided the *O*-trimethylsilylated product **13**, not **11**. The proposed mechanism of the scandium-catalyzed reactions with nucleophiles is depicted in Scheme 5.

The proposed catalytic cycle comes from the observations of the experiments. Since scandium metal has a high

Table 2. Scandium triflate catalyzed reactions of α-organylsulfanyl and α-organylselanyl carbenium ions with soft nucleophiles.

Entry	 (RY)	Conditions[a]	 4,6,9 Product (Nu) (% yield)	 7
1	**3** (PhSe)	$CH_2=C(OSiMe_3)Ph$ (2 equiv.), 40 °C, 7 h	**4b** (CH_2COPh) (78)	
2	**3**	1,2,3-trimethoxybenzene (3 equiv.), 20 °C, 40 min	**4c** (3,4,5-$(MeO)_3C_6H_2$) (20) (2,3,4-$(MeO)_3C_6H_2$) (36)	
3	**3**	$PhSSiMe_3$ (2 equiv.), 20 °C, 10 min	**4d** (SPh) (41)	
4	**5** (BuSe)	$CH_2=CHCH_2SiMe_3$ (3 equiv.), 83 °C, 10 min	**6a** (allyl) (72)	
5	**5**	$CH_2=C(OSiMe_3)Ph$, 0 °C, 40 min	**6b** (CH_2COPh) (57)	
6	**5**	$PhSSiMe_3$ (2 equiv.), 20 °C, 1 h	**6c** (SPh) (69)	
7	**5**	1,2,3-trimethoxybenzene (3 equiv.), 20 °C, 40 min	**6d** (3,4,5-$(MeO)_3C_6H_2$) (9) (2,3,4-$(MeO)_3C_6H_2$) (20); **7** (20)	
8	**8** (PhS)	$CH_2=CHCH_2SiMe_3$ (3 equiv.), 20 °C, 10 min	**9a** (allyl) (86)	
9	**8**	$CH_2=C(OSiMe_3)Ph$ (2 equiv.), 0 °C, 20 min	**9b** (CH_2COPh) (89)	
10	**8**	$PhSSiMe_3$ (2 equiv.), 20 °C, 10 min	**9c** (SPh) (89)	
11	**8**	1,2,3-trimethoxybenzene (3 equiv.), 20 °C, 40 min	**9d** (3,4,5-$(MeO)_3C_6H_2$) (26) (2,3,4-$(MeO)_3C_6H_2$) (42)	
12	**8**	1,2-dimethoxybenzene (3 equiv.), 20 °C, 40 min	**9e** (3,4-$(MeO)_2C_6H_3$) (99)	
13	**8**	anisole (3 equiv.), 20 °C, 2.5 h	**9f** (*o*- and *p*-$MeOC_6H_4$) (67)[b]	
14	**8**	toluene, 20 °C, 0.5 h[c]	**9g** (*o*- and *p*-$MeOC_6H_4$) (62)[d]	

[a] Most reactions were carried out with 5 mol-% of scandium triflate in $ClCH_2CH_2Cl$. [b] *o*/*p* = 77:23. [c] $Sc(OTf)_3$ (10 mol-%) was used. [d] *o*/*p* = 84:16.

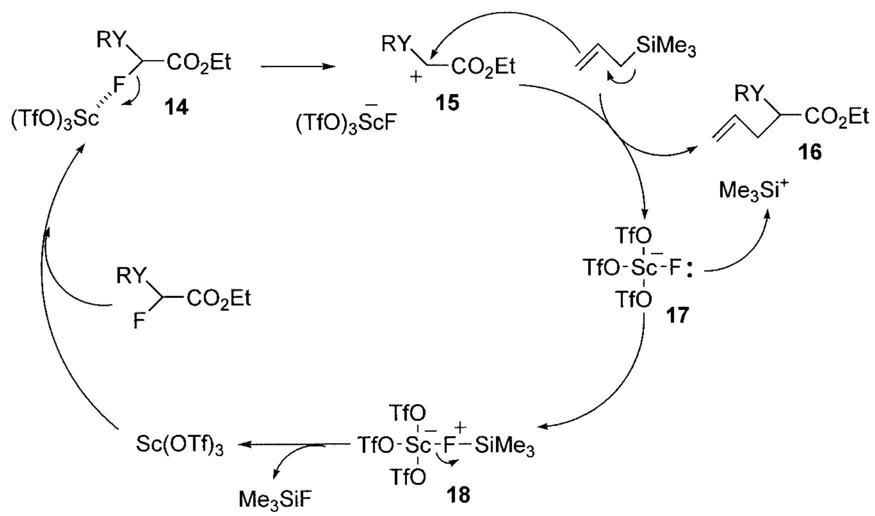


Scheme 4. Scandium triflate-catalyzed allylation of ethyl-3-hydroxy-2-fluoro-2-(phenylsulfanyl)propionate. a) allyltrimethylsilane (3 equiv.), scandium triflate (0.3 equiv.), $MeNO_2$, room temp., 10 min. b) Allyltrimethylsilane (3 equiv.), scandium triflate (0.05 equiv.), $MeNO_2$, room temp., 10 min.

affinity for the fluorine atom in chlorinated solvents, the scandium-coordinated intermediate **14** undergoes C–F bond cleavage to give the α-organylsulfanyl or α-organylselanyl carbenium ion **15**. The nucleophilic addition of allyltrimethylsilane affords the product **16** and the trimethylsilyl cation. The fluorine atom of the counter anion **17** attacks the silyl cation to give the intermediate **18**, which regenerates the scandium triflate accompanied by trimethylsilyl fluoride. The products with the silylated soft nucleophiles are mostly obtained in high yield and the reaction time is very short because the resultant trimethylsilyl fluoride activates the cleavage of the C–Si bond of the nucleophile.

Conclusion

In summary, we have uncovered the first Lewis acid catalyzed generation and reactions of α-organylsulfanyl and α-organylselanyl carbenium ions using ethyl-α-fluoro-α-organylsulfanyl- and organylselanylacetate. The catalytic reac-



Scheme 5. Catalytic cycle of nucleophilic addition reaction of α-organylsulfanyl and α-organylselanyl carbenium ions.

tions are very clean and proceed under milder conditions than previous stoichiometric methods. High regioselectivity of the reactions between the α-fluoro-α-organylsulfanyl or α-fluoro-α-organylselanyl moieties and Lewis acids was successfully achieved; therefore, the new reaction can be applied to the synthesis of more complicated compounds. Planned future work in this area includes scandium-catalyzed intramolecular or intermolecular cyclization via α-organylsulfanyl or α-organylselanyl carbenium ions. These results will be reported elsewhere.

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[8] Preparation of ethyl 2-fluoro-2-(phenylselanyl)acetate (**3**): To ethanol (120 mL) and diphenyl diselenide (8.00 g, 25.6 mmol) was added sodium borohydride (1.94 g, 51.3 mmol). When the yellow solution changed color to colorless, ethyl chlorofluoroacetate (7.20 g, 51.3 mmol) was added to the reaction mixture. The whole mixture was stirred for 1 h at room temperature and poured into water (300 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried with $MgSO_4$. The solvent was then removed under reduced pressure. The residue was purified by column chromatography on silica gel, being eluted with AcOEt/*n*-hexane (1:20) to give ethyl 2-fluoro-2-(phenylselanyl)acetate (**3**)[10] (11.0 g, 82%) as a yellow oil. IR (KBr): = 1752 cm^{-1} (CO). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.65–7.67 (m, 2 H, ArH), 7.32–7.41 (m, 3 H, ArH), 6.38 [d, ^3J(H,F) = 52 Hz, 1 H, CHF], 4.08–4.13 (m, 2 H, OCH_2), 1.17 [t, ^3J(H,H) = 7 Hz, 3 H, Me] ppm. ^{19}F NMR ($CDCl_3$, CF_3CO_2H): δ = –88.85 [d, ^3J(H,F) = 52 Hz, 1 F] ppm. MS (70 eV): *m*/*z* (%) = 262 (7) [M$^+$]. $C_{10}H_{11}FO_2Se$: calcd. C 45.99, H 4.25; found C 45.92, H 4.24. The compound **3** can be stored in the refrigerator for one year.

[9] Typical experimental procedure: Under argon, scandium triflate (9.0 mg, 0.02 mmol) was added to a dichloromethane (1.0 mL) solution of **3** (0.10 g, 0.38 mmol) and allyltrimethylsilane (0.13 g, 1.2 mmol) at room temperature. The reaction mixture was stirred for 1.5 h and poured into a saturated $NaHCO_3$ solution (100 mL). The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel, being eluted with AcOEt/*n*-hexane (1:50) to give ethyl 2-(phenylselanyl)pent-4-enoate (**4a**) (94.0 mg, 87%) as a pale yellow oil. **4a**: IR (KBr): = 1727 cm^{-1} (CO). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.60 [d, ^3J(H,H) = 7 Hz, 2 H, ArH], 7.26–7.35 (m, 3 H, ArH), 5.75–5.83 (m, 1 H, olefinic H], 5.07–5.12 (m, 2 H, olefinic H), 4.08 [q, ^3J(H,H) = 7 Hz, 2 H, OCH_2], 3.66 [dd, ^3J(H,H) = 6 and 9 Hz, 1 H, SeCH], 2.63–2.69 (m, 1 H, CH_2), 2.49–2.55 (m, 1 H, CH_2), 1.16 [t, ^3J(H,H) = 7 Hz, 3 H, Me) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ = 172.5 (s), 135.8 (2 d), 134.8 (d), 129.1 (2 d), 128.6 (d), 127.8 (s), 117.7 (t), 61.1 (t), 42.6 (d), 36.1 (t), 14.1 (q) ppm. MS (70 eV): *m*/*z* (%) = 284 (2.5) [M$^+$]. $C_{13}H_{16}O_2Se$: calcd. C 55.13, H 5.69; found C 55.27, H 5.72.

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