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Regioselective Synthesis of α-Fluorinated Cyclopentenones via Organocatalytic Difluorocyclopropanation and Fluorine-Directed and -Activated Nazarov Cyclization

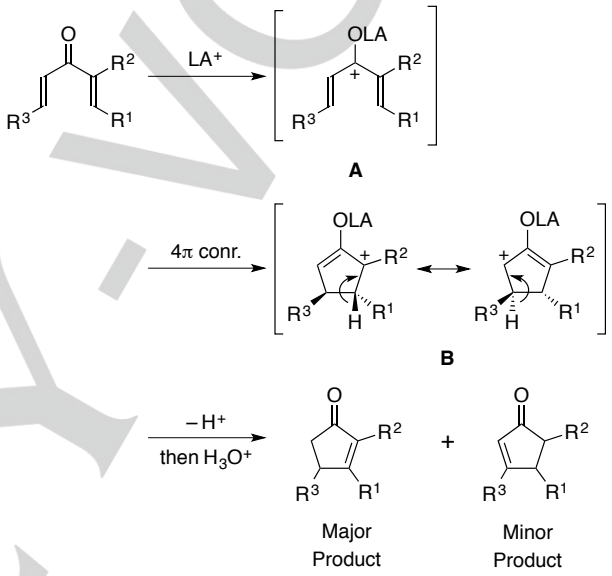
Kohei Fuchibe,[a] Ryo Takayama,[a] Takaharu Yokoyama,[b] and Junji Ichikawa[a]*

Abstract: Silyl dienol ethers, prepared from α,β-unsaturated ketones, underwent proton sponge-catalyzed difluorocyclopropanation with trimethylsilyl 2,2-difluoro-2-fluorosulfonylacetate (TFDA) in a regioselective manner, leading to 1,1-difluoro-2-siloxy-2-vinylcyclopropanes in good yields. The cyclopropanes thus obtained were in turn subjected to fluoride ion-catalyzed ring opening to afford 1-fluorovinyl vinyl ketones (i.e., Nazarov precursors). Treatment of the precursors with Me_3Si^+ $B(OTf)_4^-$ regioselectively promoted the Nazarov cyclization, whose rate and regioselectivity were drastically enhanced by the fluorine substituent, thereby facilitating efficient synthesis of biologically promising α-fluorocyclopentenone derivatives.

Introduction

The Nazarov cyclization[1] is one of the most versatile methods for the construction of cyclopentenone frameworks. Because cyclopentanoids are ubiquitously encountered in natural products,[2] the Nazarov cyclization have been extensively studied within the last decades.[3] However, the Nazarov cyclization suffers from the lack of control in the position of the double bond introduced to products. In the Nazarov cyclization, treatment of divinyl ketones with Lewis or Brønstead acids forms pentadienyl cation intermediates **A** (Scheme 1). Subsequent electrocyclization of **A** proceeds to generate cyclic oxyallyl cation intermediates **B**. Deprotonation of **B** typically proceeds to afford the more substituted (thermodynamically more stable) isomers of cyclopentenone derivatives. With the aim to overcome the issue of substrate dependency, stabilizing charge localization of **B** by silicon,[4] tin,[5] or oxygen[6] functionalities have been conducted.

Fluorine has a number of characteristic electronic effects and properties (Figure 1):[7] (i) a fluorine substituent inductively destabilizes β-cation because of its high electronegativity (–I effect, Figure 1a), (ii) a fluorine substituent *stabilizes* α-cation via donation of its unshared electron pair to a vacant 2p orbital (+R effect, Figure 1b),[8] (iii) a fluorine substituent acts as a leaving group because of the stability of the fluoride ion (leaving group ability, Figure 1c).



Scheme 1. Pathway of the Nazarov Cyclization.

We have previously reported two types of fluorine-directed Nazarov cyclizations, in which the position of the introduced double bond was governed by the β-cation destabilizing effect of fluorine.[9] Thus, 2,2-difluorovinyl vinyl ketone **1** and 1-(trifluoromethyl)vinyl vinyl ketone **2** were treated with trimethylsilyl trifluoromethanesulfonate (TMSOTf) in 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP)[10]/dichloromethane (Eqs 1 and 2). The Nazarov cyclization proceeded in a regioselective manner to afford 3-fluorocyclopent-2-en-1-one **3** and 5-(trifluoromethyl)cyclopent-2-en-1-one **4** in high yields, respectively. In the case of intermediary oxyallyl cations **B1** and **B2**, positive charges are localized mainly on the carbon δ to the fluorine substituents owing to the β-cation destabilizing effect of fluorine. Elimination of a proton adjacent to the less destabilized δ cation proceeded with the subsequent regioselective formation of the products. However, rate enhancement is not expected in these systems because cationic **B1** and **B2** are destabilized by inductive effect of fluorine.

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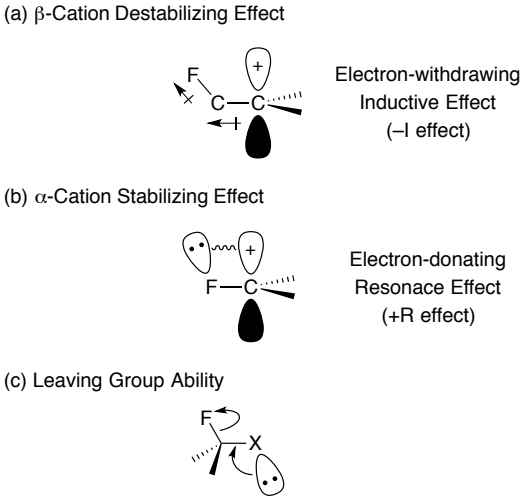
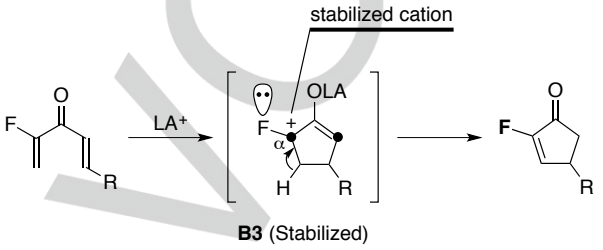


Figure 1. Properties of Fluorine Substituents.

We revisited the fluorine-directed Nazarov cyclization, in which a fluorine substituent would act not only as a controller but also as an activator (Scheme 2). In the case of this fluorine-directed and -activated Nazarov cyclization, we used 1-fluorovinyl vinyl ketones as substrates. The predicted oxyallyl cation intermediates **B3** would be stabilized by the α-cation stabilizing effect of fluorine, thereby promoting the rate-determining ring closure and enhancing the reactivity of the substrates (i.e., fluorine substituent acting as an activator). Their positive charge localized at the carbon α to the fluorine substituent in **B3** would cause regioselective formation of 2-fluorocyclopent-2-en-1-ones (i.e., fluorine substituent acting as a controller).[11] Thus, the fluorine-directed and -activated Nazarov cyclization has potential to provide the 2-fluorocyclopentenones as new candidates and intermediates for pharmaceuticals and agrochemicals.[12–14]

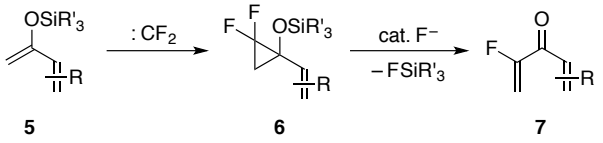


Scheme 2. Strategy for Fluorine-Directed and -Activated Nazarov Cyclization.

Results and Discussion

Preparation of 1-Fluorovinyl Vinyl Ketones: Organocatalytic Difluorocyclopropanation of Silyl Dienol Ethers

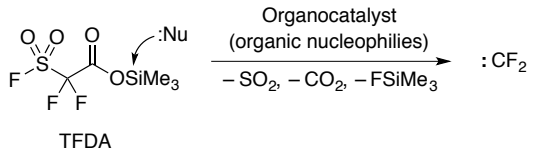
We envisioned that the synthesis of the required Nazarov precursors (i.e., 1-fluorovinyl vinyl ketones) would be facilitated by the following difluorocyclopropanation/ring opening sequence of silyl dienol ethers (Scheme 3):[15] silyl dienol ethers **5**, readily prepared from α,β-unsaturated ketones, would be subjected to difluorocarbene to give 1,1-difluoro-2-siloxy-2-vinylcyclopropanes **6**. Ring opening of the siloxy cyclopropanes (i.e., elimination of a fluorosilane) catalyzed by a fluoride ion might afford the desired fluorovinyl ketones **7**.[16]



Scheme 3. Approach to the Nazarov Precursors.

However, difluorocyclopropanation of silyl enol ethers has been quite limited until recently[17] because of the instability of these substrates under the harsh conditions required for conventional difluorocarbene generation.[18] In particular, difluorocyclopropanation of silyl dienol ethers has remained largely unexplored.[14a,c] Meanwhile, we have developed methods for the organocatalytic generation of difluorocarbene under mild conditions and the *O*- and *S*-difluoromethylation of aliphatic ketones, secondary amides, and thioamides.[19] We thus used the generation of difluorocarbene from trimethylsilyl

2,2-difluoro-2-fluorosulfonylacetate (TFDA)[20] for the cyclopropanation of silyl dienol ethers (Scheme 4). Treatment of TFDA with a suitable organic nucleophile as an organocatalyst would release difluorocarbene at the rates required for difluorocyclopropanation of silyl dienol ethers **5** under mild conditions. This leads to efficient formation of 1,1-difluoro-2-siloxy-2-vinylcyclopropanes **6**.

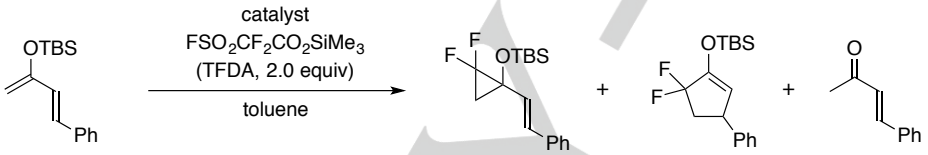


Scheme 4. Organocatalytic Generation of Difluorocarbene.

In order to achieve the required difluorocyclopropanation of silyl dienol ethers, the organocatalyst was optimized (Table 1). TFDA was originally designed to generate difluorocarbene upon treatment with fluoride ion at 105 °C. Silyl dienol ether **5a**, prepared from methyl styryl ketone, was thus treated with TFDA (2.0 equiv) in the presence of sodium fluoride in toluene at 80 °C. However, the desired difluorocyclopropane **6a** was obtained in 9% yield presumably because of the lower temperature (i.e., lower than the original conditions, entry 1). NHC catalysts **10a** and **10b** afforded cyclopropane **6a** in higher yields (17% and 49%, respectively, entries 2 and 3).

The catalytic activity of nitrogen nucleophiles was examined to improve the yield of **6a**. Although pyridine and benzo[*h*]quinoline were not effective as catalysts for the production of **6a** (20% and 0% yields, respectively, entries 4 and 5), 1,10-phenanthroline (10 mol%) exhibited high catalytic efficiency, affording **6a** in 58% yield (entry 6). Aliphatic amines such as triethylamine and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine

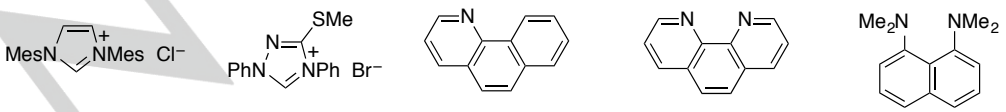
Table 1. Catalyst Optimization.[a]



5a **6a** **8** **9**

Entry	Catalyst [mol%]	Temp [°C]	*t* [min]	**6a** [%]	**8** [%]	**9** [%]	**5a** [%] [b]	Recovery of TFDA [equiv] [b]
1	NaF (20)	80	30	9	nd	40	37	0.91
2	**10a**·HCl (10) + Na_2CO_3 (20)	80	30	17	nd	40	9	nd
3	**10b**·HBr (10) + Na_2CO_3 (20)	80	30	49	8	20	26	nd
4	pyridine (20)	80	30	20	nd	62	7	0.75
5	benzo[*h*]quinoline (10)	80	60	nd	nd	55	35	0.96
6	1,10-phenanthroline (10)	80	10	58	5	16	1	0.02
7	NEt_3 (20)	80	30	47	11	5	21	trace
8	TMEDA (16)	80	120	38	22	20	nd	nd
9	**11** (5)	80	30	75	11	16	nd	trace
10 [c]	**11** (5)	70	10	75	2	1	nd	trace
11 [c]	**11** (5)	60	10	77 (76)	trace	5	nd	trace
12 [c]	**11** (5)	50	10	74	trace	7	nd	trace

[a] ^{19}F NMR yield based on an internal standard $(CF_3)_2C(C_6H_4p\text{-}Me)_2$ (for **6a**, **8**, and TFDA) or ^1H NMR yield based on **6a** (for **5a** and **9**). Isolated yield is shown in parentheses. TBS = Si*t*-BuMe_2. TMEDA = *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine. nd = Not detected by ^{19}F NMR spectroscopy (for **6a**, **8**, and TFDA) or ^1H NMR spectroscopy (for **5a**). [b] Recovery. [c] TFDA 1.5 equiv.



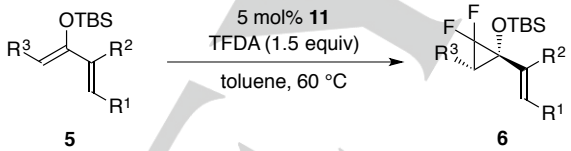
10a·HCl **10b**·HBr benzo[*h*]quinoline 1,10-phenanthroline **11**

(TMEDA) were found to be less effective (47% and 38% yields of **6a**, respectively, entries 7 and 8). Finally, silyl dienol ether **5a** afforded difluorocyclopropane **6a** in the presence of 5 mol% of 1,8-bis(dimethylamino)naphthalene (i.e., proton sponge, **11**) in 75% yield (entry 9).[20b] It was also found that the proton sponge catalyst **11** was active even at low temperatures (entries 10–12). When TFDA (1.5 equiv) was added to a toluene solution of silyl dienol ether **5a** and 5 mol% of **11**, the reaction was completed within 10 min at 60 °C to afford difluorocyclopropane **6a** in 76% isolated yield (entry 11).

^{19}F NMR analysis revealed that TFDA used for the experiments contained 2 mol% (at maximum) of inseparable free carboxylic acid $FSO_2CF_2CO_2H$ (not shown). Proton sponge **11** likely promoted removal of a proton from the free acid, followed by elimination of CO_2, difluorocarbene, and SO_2, to generate the HF salt of **11**. The formed fluoride ion bearing a stable ammonium ion exerted high nucleophilicity, thereby allowing catalytic generation of difluorocarbene from TFDA even at low temperatures.[21]

Under the optimized conditions, additional 1,1-difluoro-2-siloxy-2-vinylcyclopropanes were synthesized in a similar manner (Table 2). Electron-donating and -withdrawing groups installed on the aromatic ring at the terminal position (R^1) did not affect the reaction, leading to the corresponding products **6b** and **6c** in 79% and 83% yields, respectively (entries 2 and 3). Substrate **5d** bearing an alkyl substituent (i.e., isopropyl group) on the reacting alkene moiety (R^3) afforded the corresponding cyclopropane **6d** in 78% yield (entry 4). The silyl dienol ether bearing a butyl group as a R^1 substituent also reacted smoothly (75% yield of **6e**, entry 5). Difluorocyclopropanation of these silyl dienol ethers proceeded in a diastereospecific manner, with **5d** and **5e** (91:9 and 92:8 *Z*/*E* ratios, respectively) leading to **6d** and **6e** (82:18 and 92:8 diastereomer ratios, respectively).[22] Substrates bearing a methyl group (**5f**) and a bromine substituent (**5g**) at the internal position (R^2) afforded **6f** and **6g** in 92% and 96% yields (entries 6 and 7), respectively. Apart from silyl dienol ethers, silyl enol ethers also underwent organocatalytic difluorocyclopropanation. Silyl enol ether **5h**, derived from acetophenone, afforded the corresponding cyclopropane **6h** in 80% yield (entry 8). Thus, the required difluorocyclopropanation of silyl dienol ethers **5** was successfully achieved by the organocatalytic difluorocarbene generation with proton sponge **11**.

Table 2. Difluorocyclopropanation of Silyl Dienol Ethers.[a]



5 **6**

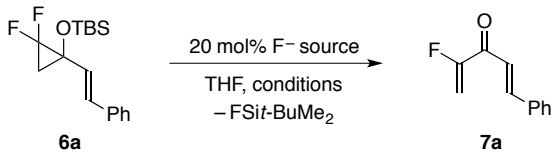
Entry	**5**	R^1	R^2	R^3 (*Z*/*E*) [b]	*t* [min]	Yield [%] (dr), **6**
1	**5a**	Ph	H	H	10	76, **6a**
2	**5b**	C_6H_4*p*-Me	H	H	15	79, **6b**
3	**5c**	C_6H_4*p*-Cl	H	H	15	83, **6c**
4	**5d**	Ph	H	*i*-Pr (91:9)	25	78 (82:18), **6d**
5	**5e**	*n*-Bu	H	*n*-Bu (92:8)	15	75 (92:8), **6e**
6	**5f**	Ph	Me	H	15	92, **6f**
7	**5g**	Ph	Br	H	15	96, **6g**
8	**5h**	–(CH=CH)$_2$– [c]		H	15	80, **6h**

[a] Isolated yield, unless otherwise noted. TBS = Si*t*-BuMe_2. [b] Geometry of siloxyalkene moiety. [c] 1-(*tert*-butyldimethylsilyloxy)styrene.

The Nazarov precursors (i.e., 1-fluorovinyl vinyl ketones **7**) were prepared by ring opening of 1,1-difluoro-2-siloxy-2-vinylcyclopropanes **6** (Table 3). Treatment of the obtained difluoro(vinyl)cyclopropane **6a** with cesium fluoride at 60 °C in THF did not afford the desired **7a** (72% recovery of **6a**, entry 1). In contrast, utilization of tetrabutylammonium fluoride (TBAF, 20 mol%) led to the formation of **7a** at room temperature in 70% yield (entry 2). Utilization of tetrabutylammonium difluorotriphenylsilicate (TBAT, n-Bu_4N^+ $SiF_2Ph_3^-$) instead of TBAF at room temperature resulted in a higher yield of **7a** (94%, entry 3). While tris(dimethylamino)sulfonium difluorotrimethylsilicate afforded a complex mixture (entry 4), tetrabutylammonium difluorotriphenylstannate was inactive even at 60 °C (97% recovery of **6a**, entry 5).

Several 1-fluorovinyl vinyl ketones **7** were prepared by the abovementioned method (Table 4). Cyclopropanes bearing phenyl (**6a**), *p*-methylphenyl (**6b**) and *p*-chlorophenyl (**6c**) groups underwent ring opening to afford the corresponding Nazarov precursors **7a**–**c** in 53–76% yields, respectively (entries 1–3). Substrates **6d** and **6e** bearing an alkyl group on the cyclo-

Table 3. Catalyst Optimization.[a]

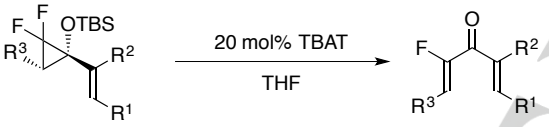


6a **7a**

Entry	F^- Source	Conditions	**7a** [%]	Recovery of **6a** [%] [b]
1	CsF [c]	60 °C, 30 min	nd	72
2	*n*-Bu_4N^+ F^- (TBAF)	rt, 15 min,	70	nd
3	*n*-Bu_4N^+ $SiF_2Ph_3^-$ (TBAT)	rt, 20 min	94	nd
4	$(Me_2N)_3S^+$ $SiF_2Me_3^-$	60 °C, 20 min	nd [d]	nd [d]
5	*n*-Bu_4N^+ $SnF_2Ph_3^-$	60 °C, 20 min	nd	97

[a] ^{19}F NMR yield based on an internal standard $(CF_3)_2C(C_6H_4p\text{-}Me)_2$. TBS = Si*t*-$BuMe_2$. nd = not detected by ^{19}F NMR spectroscopy. [b] Recovery. [c] 45 mol%. [d] Complex mixture.

Table 4. Preparation of 1-Fluorovinyl Vinyl Ketones.[a]



6 **7**

Entry	**6a** (dr) [b]	Conditions	Yield [%] (*Z*/*E*),[c] **7**
1	**6a**	rt, 1 h	76, **7a**
2	**6b**	rt, 20 min	53, **7b**
3	**6c**	rt, 20 min	59, **7c**
4 [d]	**6d** (82:18)	–78 °C to rt, 82 h	74 (97:3), **7d**
5 [e]	**6e** (91:9)	–78 to –5 °C, 17 h	61 (62:38), **7e** [f]
6	**6f**	50 °C, 1 h	77, **7f**
7	**6g**	50 °C, 1 h	75, **7g**

[a] Isotated yield, unless otherwise noted. TBS = Si*t*-$BuMe_2$, TBAT = *n*-Bu_4N^+ $SiF_2Ph_3^-$. [b] Diastereomer ratio of cyclopropane moiety. [c] Geometry of fluoroalkene moiety. [d] 60 mol% TBAF, H_2O 4 equiv. [e] 20 mol% TBAF, H_2O 7 equiv. [f] ^{19}F NMR yield based on an internal standard $C_6H_5CF_3$.

propane moiety were stable under the TBAT system at room temperature and decomposed at elevated temperatures (not shown). Ring opening of **6d** and **6e** was conducted with water-deactivated TBAF at controlled temperatures to give **7d** and **7e** in 74% and 61% yields, respectively (entries 4 and 5). Methylated and brominated vinylcyclopropanes **6f** and **6g** afforded divinyl ketones **7f** and **7g** in 77% and 75% yields, respectively (entries 6 and 7).

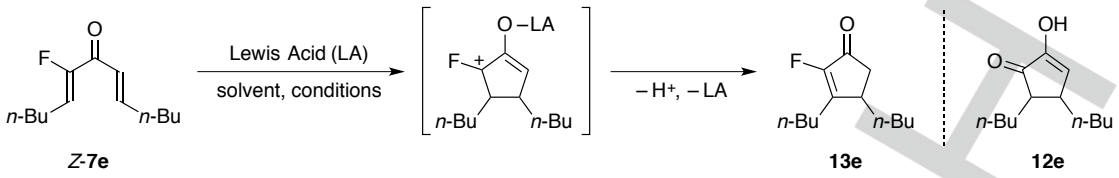
Fluorine-Directed and -Activated Nazarov Cyclization: Regioselective Synthesis of α-Fluorocyclopentenones

The Nazarov cyclization of 1-fluorovinyl vinyl ketones was examined using *Z*-**7e** as a model substrate (Table 5). Treatment of *Z*-**7e** with 3 equiv of trimethylsilyl trifluoromethanesulfonate (TMSOTf) in HFIP/dichloromethane (1:1) led to hydroxycyclopentenone **12e** (i.e., a hydrolyzed product of the desired 2-fluorocyclopent-2-en-1-one **13e**) in 57% yield (entry 1). We assumed that the hydrolysis was caused by trace amounts of water present in HFIP. Although the reaction was conducted in dichloromethane, no reaction was observed even under reflux presumably because of the lack of cation-stabilizing effect of HFIP (entry 2). Thus, we examined other Lewis acids to efficiently generate pentadienyl cations. Utilization of $BF_3{\cdot}OEt_2$ in dichloromethane was fruitless (entry 3), whereas $SnCl_4$ afforded the desired **13e** in 41% yield (entry 4). Eventually, a strong silylation reagent Me_3Si^+ $B(OTf)_4^-$ [23] successfully induced the desired Nazarov cyclization to afford **13e** in 89% yield within 15 min (entry 5).

As expected, the Nazarov cyclization proceeded in a regioselective manner (Table 6). 1-Fluorovinyl vinyl ketone **7a** bearing a phenyl group at the terminal carbon (R^1) afforded the corresponding **13a** in 51% yield (entry 1). It must be emphasized that the undesired isomer concerning the position of the double bond was not observed by ^{19}F NMR and GC-MS analyses. Electron-donating (**7b**) and -withdrawing (**7c**) groups installed on the aromatic ring at the terminal position (R^1) did not affect the reaction, leading to **13b** and **13c** in 57% and 74% yields, respectively (entries 2 and 3). Divinyl ketones **7d**, *Z*-**7e**, and *E*-**7e** bearing an alkyl substituent (i.e., isopropyl or butyl group) on the fluoroalkene moiety readily underwent cyclization upon increasing loadings of the Lewis acid to afford the products **13d** (88%, entry 4) and **13e** (79% and 70% yields, entries 5 and 6), respectively. The Nazarov cyclization of cyclohexenyl ketone **7i**[11a] allowed the construction of a bicyclic structure, leading to **13i** in 79% yield (entry 7).

The oxygenated cyclopentenone skeleton of **12e** is found in cyclotenes, which are used as food additives with a caramel-like flavor.[24] Fluorovinyl ketone **7f** bearing a methyl group at

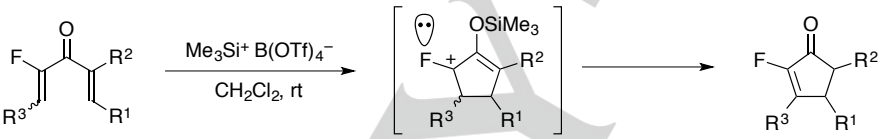
Table 5. Optimization of Lewis Acid for Regioselective Nazarov Cyclization.[a]



Entry	LA	Equiv	Solvent	Conditions	**13e** [%]	**12e** [%]
1	Me_3SiOTf	3	HFIP/CH_2Cl_2 (1:1)	rt, 5 h	nd	57
2	Me_3SiOTf	3	CH_2Cl_2	reflux, 3 h	no reaction	
3	$BF_3{\cdot}OEt_2$	1	CH_2Cl_2	reflux, 3 h	nd	nd
4	$SnCl_4$	3	CH_2Cl_2	reflux, 1 h	41	nd
5	Me_3Si^+ $B(OTf)_4^-$	1	CH_2Cl_2	rt, 15 min	89	nd

[a] ^{19}F NMR yield based on an internal standard $(CF_3)_2C(C_6H_4p\text{-}Me)_2$. Tf = trifluoromethanesulfonyl. HFIP = 1,1,1,3,3,3-hexafluoropropan-2-ol. nd = Not detected by ^{19}F NMR spectroscopy (for **13e**) or ^1H NMR spectroscopy (for **12e**).

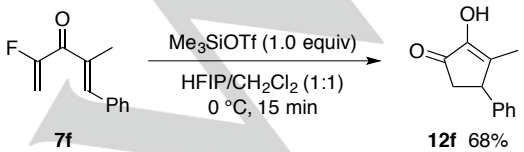
Table 6. Regioselective Synthesis of α-Fluorocyclopentenones.[a]



Entry	**7**	R^1	R^2	R^3	Me_3Si^+ $B(OTf)_4^-$ [equiv]	*t* [h]	Yield [%], **13**
1	**7a**	Ph	H	H	1.0	1	51, **13a**
2	**7b**	C_6H_4p-Me	H	H	1.0	1	57, **13b**
3	**7c**	C_6H_4p-Cl	H	H	1.0	0.5	74, **13c**
4	*Z*-**7d**	Ph	H	*Z*-*i*-Pr [b]	1.2	1	88, **13d**
5	*Z*-**7e**	*n*-Bu	H	*Z*-*n*-Bu [c]	2.0	2	79, **13e**
6	*E*-**7e**	*n*-Bu	H	*E*-*n*-Bu [c]	2.0	2	70, **13e**
7	**7i**	–$(CH_2)_4$– [d]		Et	1.0	0.25	79, **13i**

[a] Isolated yield. TBS = Si*t*-BuMe_2. [b] *Z*/*E* = 98:2. [c] Single diastereomer. [d] Cyclohexenyl 1-fluorobut-1-en-1-yl ketone.

an internal position (R^2) also underwent defluorinative Nazarov cyclization (Eq 3). When methylated ketone **7f** was treated with TMSOTf (1.0 equiv) in HFIP/dichloromethane (1:1) at 0 °C, 2-hydroxycyclopent-2-en-1-one **12f** was obtained in 68% yield. Thus, the fluorine-directed and -activated Nazarov cyclization is a useful synthetic method to fluorinated cyclopentanone derivatives and their fluorine-free analogues.



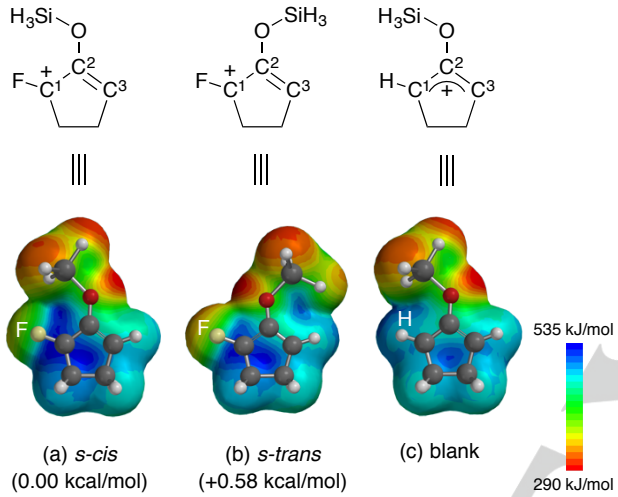
(3)

Effect of Fluorine Substituent on Reactivity and Regioselectivity

In order to elucidate the regioselectivity of the fluorine-directed Nazarov cyclization, the structures of key oxyallyl cation intermediates were analyzed by theoretical calculation. Figure 2 shows the calculated electrostatic potential maps and selected charge values of the optimized model structures of oxyallyl cation intermediates [(a) *s-cis* and (b) *s-trans* forms] and their fluorine-free counterpart [(c) blank].

The theoretical calculation indicated that the carbons α to the fluorine substituent (C^1) present strongly positive charges [i.e., +0.362 (*s-cis*) and +0.354 (*s-trans*)], whereas the C^3 carbons have slightly negative charges [–0.032 (*s-cis*) and –0.064 (*s-trans*)]. These charge distributions were not found in

the blank structure, where the C^1 and C^3 carbons showed slightly negative and positive charges (–0.015 and +0.027, respectively). Thus, positive charge was localized mainly on the carbon α to the fluorine substituent. Differences in bond orders were also observed. The Lowdin bond orders for C^1–C^2 bonds in *s-cis* and *s-trans* forms (1.28 and 1.26) were significantly lower than those for C^2–C^3 bonds (1.58 and 1.45), respectively. On the other hand, the bond orders of C^1–C^2 and C^2–C^3 bonds in the blank structure were nearly equal (1.39 and 1.38). These electronic and structural perturbations suggested that the fluorinated oxyallyl cations have a localized allyl cation structure, thereby leading to regioselective deprotonation and selective formation of 2-fluorocyclopent-2-ene-1-ones.



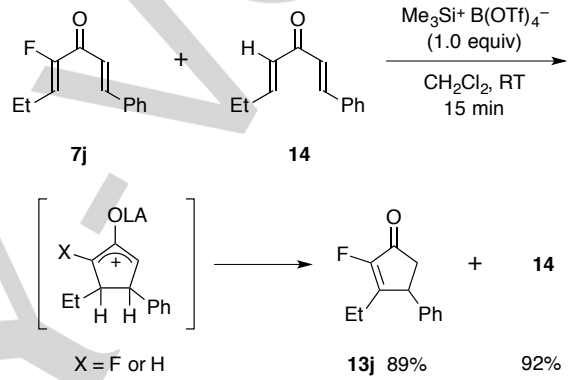
(a) *s-cis* (0.00 kcal/mol) (b) *s-trans* (+0.58 kcal/mol) (c) blank

electrostatic charge	*s-cis*	*s-trans*	blank
C^1	+0.362	+0.354	–0.015
C^2	+0.250	+0.264	+0.348
C^3	–0.032	–0.064	+0.027
Lowdin bond order	*s-cis*	*s-trans*	blank
C^1–C^2	1.28	1.26	1.39
C^2–C^3	1.58	1.45	1.38

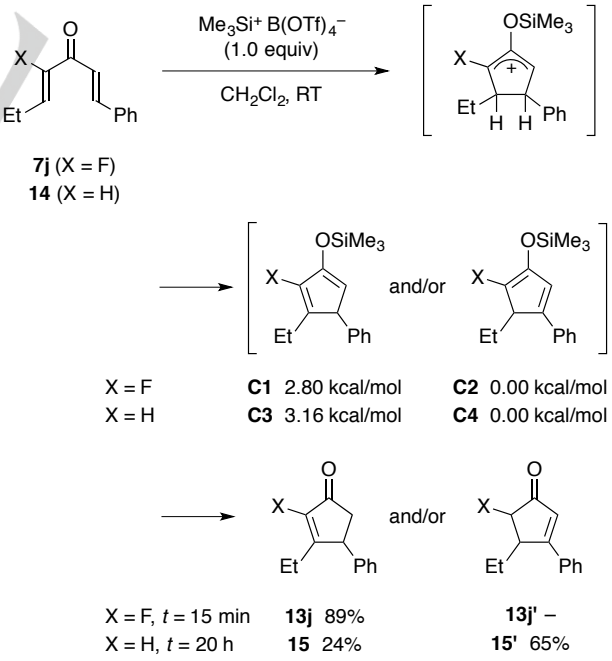
Figure 2. Calculated Electronic and Structural Properties of Oxyallyl Cation Intermediates (DFT, B3LYP/6-31G**).

The effect of fluorine substituents on the reactivity and selectivity of the Nazarov cyclization was experimentally investigated by using fluorinated (**7j**,[11a] X = F, Scheme 5) and fluorine-free (**14**, X = H) substrates. Competition experiment demonstrated the rate enhancement effect of the fluorine substituent. A 1:1 mixture of **7j** and **14** was treated with 1.0 equiv of Me_3Si^+ $B(OTf)_4^-$ in dichloromethane at room temperature. Fluorinated **7j** exclusively underwent the Nazarov cyclization to afford the corresponding product **13j** in 89% yield as a single product, whereas fluorine-free counterpart **14** remained unreacted. Thus, the fluorine substituent activated the substrates in the Nazarov cyclization via fluorine-stabilized oxyallyl cation intermediates.

When fluorine-free divinyl ketone **14** was separately treated with Me_3Si^+ $B(OTf)_4^-$ (1.0 equiv), the Nazarov cyclization proceeded, although very slowly (Scheme 6). It required 20 h for completion (i.e., 80 times slower than **7j**) to give a regioisomeric mixture concerning the position of the double bond (**15** and **15'** in 24% and 65% yields, respectively). Theoretical calculation suggested that phenyl-non-conjugated cyclic intermediate **C1**, leading to **13j,** is less stable as compared to phenyl-conjugated **C2** by 2.80 kcal/mol (DFT, B3LYP/6-31G**). Thus, the fluorine substituent governed the cyclization to exclusively afford the non-conjugated cyclopentenone **13j** as a kinetic product, whereas fluorine-free substrate **14** afforded **15'** as a major product under the influence of the higher stability of phenyl-conjugated **C4** by 3.16 kcal/mol.



Scheme 5. Effects of Fluorine Substituent (1): Activation.



Scheme 6. Effects of Fluorine Substituent (2): Direction.

Conclusions

We developed a synthetic sequence for 2-fluorocyclopent-2-ene-1-ones (α-flurocyclopentenones) via (i) organocatalyzed difluorocyclopropanation of silyl dienol ethers and (ii) fluorine-directed and -activated Nazarov cyclization. The synthesis of the Nazarov precursors (i.e., 1-fluorovinyl vinyl ketones) was facilitated via proton sponge-catalyzed generation of difluorocarbene. The mild reaction conditions allowed efficient preparation of 1,1-difluoro-2-siloxy-2-vinylcyclopropanes, whose ring opening afforded the required precursors in good yields. Regioselective synthesis of 2-fluorocyclopent-2-en-1-ones was achieved by the Nazarov cyclization enhanced and directed through α-cation stabilizing effect of fluorine. The treatment of the precursors with Me_3Si^+ $B(OTf)_4^-$ readily induced the Nazarov cyclization allowing the efficient synthesis of biologically promising α-fluorocyclopentenone derivatives.

Experimental Section

General Statements. Tetrahydrofuran (THF), toluene, and CH_2Cl_2 were dried by passing through a column of activated alumina followed by a column of Q-5 scavenger (Engelhard). HFIP supplied by Central Glass Co., Ltd (purity 99.9%) was distilled from and stored over molecular sieves 3A. HFIP can be also purchased from commercial suppliers such as Sigma–Aldrich Co. LLC. TFDA was prepared according to the literature.[20c] TBAT was purchased from Sigma–Aldrich Co. LLC. and used as received. Me_3Si^+ $B(OTf)_4^-$ was prepared according to the literature.[23] 1,1,1,3,3,3-Hexafluoro-2,2-di(*p*-tolyl)propane, an internal standard for ^{19}F NMR yields, were purchased from Tokyo Chemical Industry Co., Ltd. and used as received.

Column chromatography and preparative thin layer chromatography (PTLC) were conducted on silica gel (Silica Gel 60 N, Kanto Chemical Co., Inc. for column chromatography and Wakogel B-5F, Wako Pure Chemical Industries, Ltd. for PTLC) or alumina (Aluminium Oxide 90 Active Basic, Merck KGaA for column chromatography).

IR spectra were recorded on a Horiba FT-300S spectrometer by the attenuated total reflectance (ATR method). NMR spectra were recorded on Bruker Avance 500, Jeol Alpha 500, or Jeol JNM ECS-400 spectrometers in $CDCl_3$ at 500, 500, or 400 MHz (^1H NMR), at 126, 126, or 101 MHz (^{13}C NMR), and at 470, 470, or 376 MHz (^{19}F NMR), respectively. Chemical shifts were given in ppm relative to internal Me_4Si (for ^1H NMR: δ = 0.00), $CDCl_3$ (for ^{13}C NMR: δ = 77.0), and C_6F_6 (for ^{19}F NMR: δ = 0.0). High-resolution mass spectroscopy (HRMS) was conducted with a Jeol JMS-T100GCV spectrometer (EI, TOF). Elemental analyses (EA) were performed with a Yanako MT-3 CHN Corder apparatus.

Organocatalytic Difluorocyclopropanation of Silyl Dienol Ethers: to a toluene solution (4 mL) of proton sponge (**11**, 3.7 mg, 0.017 mmol) and $(CF_3)_2C(C_6H_4p\text{-}Me)_2$ (21 mg, 0.063 mmol) as a standard was added silyl dienol ether **5a** (104 mg, 0.398 mmol) at rt. The reaction mixture was stirred and heated at 60 °C. After TFDA (120 μL, 0.609 mmol) was added to the solution of **11** and **5a** dropwise over 10 min, hexane (5 mL) and aqueous $NaHCO_3$ (10 mL) were added to quench the reaction at rt. Organic materials were extracted with hexane four times. Combined extracts were dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane) to give difluoro(vinyl)cyclopropane **6a** (94 mg, 76% yield) as a colorless oil.

TBAT-Catalyzed Ring Opening of Difluoro(vinyl)cyclopropanes: to a solid TBAT (83 mg, 0.15 mmol) was added a THF solution (5 mL) of difluoro(vinyl)cyclopropane **6a** (240 mg, 0.774 mmol) at rt. After the reaction mixture was stirred for 1 h, CH_2Cl_2 (5 mL) and aqueous $NaHCO_3$ (5 mL) were added to quench the reaction at rt. Organic materials were extracted with CH_2Cl_2 four times. Combined extracts were dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane/AcOEt 100:1 to 50:1) to give fluorovinyl viny ketone **7a** (104 mg, 76% yield) as colorless crystals.

The Nazarov Cyclization of 1-Fluorovinyl Vinyl Ketones: to a CH_2Cl_2 solution (2 mL) of Me_3Si^+ $B(OTf)_4^-$ (0.29 mol/L, 0.57 mmol) was added a CH_2Cl_2 solution (4 mL) of fluorovinyl vinyl ketone **7a** (101 mg, 0.573 mmol) at rt. After the reaction mixture was stirred for 1 h, aqueous $NaHCO_3$ (4 mL) was added to quench the reaction at rt. Organic materials were extracted with CH_2Cl_2 three times. Combined extracts were washed with aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. The residue was purified by preparative thin layer chromatography (SiO_2, hexane/AcOEt 5:1) to give fluorocyclopentenone **13a** (52 mg, 51% yield) as a colorless oil.

The Defluorinative Nazarov Cyclization of 1-Fluorovinyl Vinyl Ketones: to a HFIP/CH_2Cl_2 solution (4 mL, 1:1) of fluorovinyl vinyl ketone **7f** (55 mg, 0.30 mmol) was added TMSOTf (54.0 μL, 0.30 mmol) at 0 °C. After the reaction mixture was stirred for 15 min, aqueous $NaHCO_3$ (3 mL) was added to quench the reaction at 0 °C. Organic materials were extracted with CH_2Cl_2 three times. Combined extracts were washed with aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. The residue was purified by preparative thin layer chromatography (SiO_2, hexane/AcOEt 5:1 to 1:1) to give hydroxycyclopentenone **12f** (38 mg, 68% yield) as a pale yellow oil.

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Keywords: carbenes • cations • fluorine • Nazarov • organocatalysis

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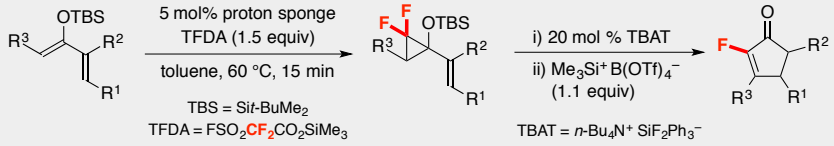

Silyl dienol ethers, prepared from α,β-unsaturated ketones, underwent proton sponge-catalyzed difluorocyclopropanation with trimethylsilyl 2,2-difluoro-2-fluorosulfonylacetate (TFDA) in a regioselective manner, leading to 1,1-difluoro-2-siloxy-2-vinylcyclopropanes in good yields. The cyclopropanes thus obtained were in turn subjected to fluoride ion-catalyzed ring opening to afford 1-fluorovinyl vinyl ketones (i.e., Nazarov precursors). Treatment of the precursors with Me_3Si^+ $B(OTf)_4^-$ regioselectively promoted the Nazarov cyclization, whose rate and regioselectivity were drastically enhanced by the fluorine substituent, thereby facilitating efficient synthesis of biologically promising α-fluorocyclopentenone derivatives.

Kohei Fuchibe, Ryo Takayama, Takaharu Yokoyama, and Junji Ichikawa*

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Regioselective Synthesis of α-Fluorinated Cyclopentenones via Organocatalytic Difluorocyclopropanation and Fluorine-Directed and -Activated Nazarov Cyclization